FISCAL YEARS 2011-2012

Report of the Advisory Committee on Research on Women's Health

Office of Research on Women's Health

and

NIH Support for Research on Women's Health

Report of the Advisory Committee on Research on Women's Health

---

Fiscal Years 2011–2012

Office of Research on Women's Health

and

NIH Support for Research on Women's Health

National Institutes of Health
Office of Research on Women's Health

Office of Research on Women's Health. (2013). *Report of the Advisory Committee on Research on Women's Health, Fiscal Years 2011–2012: Office of Research on Women's Health and NIH Support for Research on Women's Health.* Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

NIH Publication No. 13-7995

Copies of this report and other publications of the Office of Research on Women's Health are available:

Office of Research on Women's Health
National Institutes of Health
6707 Democracy Blvd., Suite 400, MSC 5484
Bethesda, Maryland 20892-5484
Voice: 301-402-1770
http://orwh.od.nih.gov

Preface

The Advisory Committee on Research on Women's Health (ACRWH), in collaboration with the Office of Research on Women's Health (ORWH) and the National Institutes of Health (NIH) Coordinating Committee on Research on Women's Health (CCRWH), submits to the Director of NIH this biennial report for fiscal years (FYs) 2011 and 2012, which details NIH activities carried out in fulfillment of the core mission of ORWH, as defined in the NIH Revitalization Act of 1993. That mission is to strengthen and enhance NIH basic, translational, and clinical research:

- **To increase the understanding of the diseases and conditions that affect women, including investigation and elucidation of the role of sex and gender factors in health and disease;**
- **To build NIH programs to develop a cadre of researchers, both women and men, who are trained to conduct interdisciplinary research in these areas;**
- **To ensure the appropriate representation of women in NIH research; and**
- **To support the advancement of women in biomedical careers.**

The ACRWH has reviewed the information contained in this biennial report, and finds that it reflects the breadth and depth of research and related activities through which ORWH has achieved its mission in FY 2011 and FY 2012. The report also provides highlights from women's health and sex/gender research supported by NIH Institutes, Centers (ICs), and Offices in the Office of the NIH Director (OD). In addition, the report presents information on NIH budget allocations for women's health research during FY 2011 and FY 2012 using criteria supplied by the NIH Office of Financial Management and the U.S. Department of Health and Human Services (HHS) Office on Women's Health. Finally, the report contains information documenting the inclusion of women and minorities in NIH-funded clinical research during the same time period.

The ACRWH wishes to acknowledge the work of the CCRWH representatives, whose efforts ensured the timely preparation of reports from the ICs and Offices they represent. The ACRWH also wishes to acknowledge the work of the NIH staff members who assisted in the continued implementation and analysis of the inclusion of women and minorities in NIH-funded research, and the work of staff who collected and tabulated the budgetary data presented in this report.

Finally, the ACRWH wishes to acknowledge the work of ORWH staff in meeting the mandates underlying the establishment of ORWH by providing leadership, both within NIH and with the extramural research community, to accomplish the many outstanding and important advances in NIH-funded science and in career support that are described herein.

Advisory Committee on Research on Women's Health, FY 2013

Janine A. Clayton, M.D., *Chair*
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health

Susan E. Maier, Ph.D., *Executive Secretary*
Deputy Director
Office of Research on Women's Health
National Institutes of Health

Richard Besdine, M.D. *(2015)*
Director, Center for Gerontology and Healthcare Research
Director of the Division of Geriatrics, Department of Medicine
Greer Professor of Geriatric Medicine
Alpert Medical School
Brown University

John O. DeLancey, M.D. *(2015)*
Norman F. Miller Professor
Obstetrics and Gynecology
University of Michigan

Francisco Garcia, M.D., M.P.H. *(2014)*
Distinguished Outreach Professor of Obstetrics and Gynecology and Public Health
Director, Center of Excellence in Women's Health
The University of Arizona

Ronda S. Henry-Tillman, M.D. *(2014)*
Practice Director, Ladies' Oncology Clinic
Director, Cancer Control
Winthrop P. Rockefeller Cancer Institute
University of Arkansas for Medical Sciences

Karen Kim, M.D., M.S. *(2014)*
Associate Professor of Medicine
The University of Chicago

Susan Kornstein, M.D. *(2015)*
Director and Professor of Psychiatry and Obstetrics-Gynecology
Institute for Women's Health
Virginia Commonwealth University

Valerie Latona *(2015)*
Health & Fitness Writer/Editor
New York, NY

Jon Levine, Ph.D. *(2015)*
Director
Wisconsin National Primate Research Center

Afaf I. Meleis, Ph.D., Dr.P.S. (hon.), F.A.A.N., F.R.C.N. *(2016)*
Margaret Bond Simon Dean of Nursing
Professor of Nursing and Sociology
University of Pennsylvania School of Nursing

Heidi D. Nelson, M.D., M.P.H. *(2016)*
Research Professor, Departments of Medical Informatics & Clinical Epidemiology, and Medicine
Medical Director, Providence Women and Children's Program and Research Center
Co-Director, V.A. Women's Health Fellowship
Oregon Health & Science University

Claire Pomeroy, M.D., M.B.A. *(2014)*
Vice Chancellor, Human Health Sciences
Dean, School of Medicine
Professor of Internal Medicine and Microbiology/Immunology
University of California, Davis

Judith G. Regensteiner, Ph.D. *(2017)*
Professor of Medicine
Division of General Internal Medicine
Denver School of Medicine
University of Colorado

Paul F. Terranova, Ph.D. *(2014)*
Vice Chancellor for Research
Senior Associate Dean for Research and Graduate Education, University of Kansas School of Medicine
The University of Kansas Medical Center

Gerson Weiss, M.D. *(2016)*
Professor and Chair
Department of Obstetrics, Gynecology and Women's Health
University of Medicine & Dentistry of New Jersey—New Jersey Medical School

Table of Contents

Introduction

This report of the Advisory Committee on Research on Women's Health (ACRWH) for FYs 2011 and 2012 provides a summary of the accomplishments of NIH to address women's health over the past 2 years. The report documents the expansive growth of women's health and sex differences research, along with many other significant programs and activities across the NIH. As requested in the NIH Revitalization Act of 1993, the ACRWH, a chartered group composed of non-Federal experts, submits a report to the NIH Director every 2 years, describing its findings related to the mandates for ORWH and NIH support of women's health research. This document fulfills that directive.

In 2010, ORWH introduced a new strategic plan and research agenda for the NIH, "Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research" (NIH Publication No. 10-7606), which provided a blueprint for future NIH women's health and sex differences research and career advancement in biomedical sciences for the coming decade. This "NIH Strategic Plan for Women's Health Research" identified six major goals for new research and other funding initiatives. In 2011 and 2012, the NIH community took steps to further these goals and to track the progress toward their achievement. These efforts are described in the ORWH section, as well as in the women's health and sex/gender differences research initiatives reported on by NIH ICs and Program Offices, also contained in this report.

Organization of the FY 2011–FY 2012 Biennial Report of the ACRWH

This FY 2011–FY 2012 biennial report bears witness to the phenomenal growth in women's health research and related programs that has occurred since the formation of the Office in 1990. It reflects major ORWH research programs, initiatives, activities, and highlights that were reported from the NIH ICs and Program Offices. This report is not a comprehensive listing of all NIH research on women's health, which would necessarily be encyclopedic; the report does serve, however, to summarize, under a single cover, examples of the wealth of NIH advances in women's health research. This report also provides information on and analyses of support for women's health research and related activities. The budget figures for NIH expenditures on women's health research and programs during FY 2011–FY 2012 are included as well.

This biennial report is divided into two major parts: Part 1 presents ORWH programs, and part 2 provides individual reports on women's health research from the NIH ICs and Program Offices in the Office of the NIH Director. Information about ORWH programs in part 1 is organized into the following seven sections:

I. ORWH Research

II. ORWH Interdisciplinary Research and Career Development Programs

III. ORWH Biomedical Career Development Activities

IV. ORWH Research Dissemination and Outreach Activities

V. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

VI. NIH Budget for Women's Health Research

VII. Committee Members, FY 2011–FY 2012

Section I. This section offers tables of ORWH-funded projects, examples of special ORWH research initiatives, and highlights of other trans-NIH women's health scientific activities. The research that has occurred because of ORWH support or with ORWH cofunding is documented in this section, representing an investment in basic and clinical scientific investigations into 1) newly recognized conditions that may affect the wellness or morbidity of women across their lifespan; and 2) ongoing gaps in knowledge about normal aspects of women's health and disease processes that may be unique to women, or affect both men and women, with potential differences yet to be defined.

Section II. ORWH has long recognized that women's health research is an inherently broad interdisciplinary endeavor, encompassing a full range of scientific activities. Since 1999, ORWH has been working to provide individual and institutional support for interdisciplinary research and career development. ORWH-introduced interdisciplinary initiatives have evolved into signature programs of new and exciting efforts in women's health research that are changing institutional approaches; these efforts and programs are described in detail in section II.

Section III. This section provides information on a number of other programs through which ORWH works to promote women's biomedical careers and the development of careers in research on women's health and sex/gender factors. This section also describes the activities of the NIH Director's Working Group on Women in Biomedical Careers to provide a comprehensive, action-oriented NIH response to the Federal agencies' challenges posed in the 2007 National Academies report "Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering."

Section IV. This section on research dissemination and outreach describes ORWH's Internet-based health information initiatives, including an ongoing collaborative effort with the NIH National Library of Medicine as part of the Office's online resources for information on women's health research; a Web-based series of courses, "The Science of Sex and Gender in Human Health," cosponsored with the U.S. Food and Drug Administration (FDA); a multimedia approach to communicate advances being made from past and current women's health research; and other efforts to ensure that information generated from the NIH investment in research on women's health informs future research efforts and improves women's health and health care. The section also provides a description of ORWH-cofunded conferences and workshops.

Section V. This section details NIH's strides to monitor the inclusion of women and minorities in NIH-funded clinical research, including aggregate data on the numbers of women, men, and minorities who participated as volunteers in the research.

Section VI. This section provides information on NIH expenditures on women's health research, including a breakdown of the expenditures by disease category and other major categories of interest.

Part 2 of the biennial report consists of individual reports from 24 NIH Institutes, Centers, and Program Offices located within the Office of the NIH Director. These reports summarize their major initiatives and activities and provide highlights of the research each has funded related to women's health and sex differences research, consistent with their specific missions. This information is presented as submitted by the ICs, most often by their Coordinating Committee on Research on Women's Health (CCRWH) representatives, and is impressive as well as fascinating in its scope and dimensions.

During FY 2011 and FY 2012, major transitions occurred in the NIH women's health program. After nearly 20 years of NIH women's health leadership, Dr. Vivian Pinn retired as Associate Director for Research on Women's Health and Director of ORWH in November 2011. In September 2012, I was appointed to these positions after serving in an acting capacity following Dr. Pinn's departure.

The field of women's health research is greatly indebted to Dr. Pinn for her tireless efforts and inspirational leadership. I owe a personal debt of gratitude to her for serving me as a valued mentor and as a model for leadership. It is in grateful acknowledgment of her influence that, over the past 2 years, I have continued to push new efforts to increase the reach and influence of ORWH programs and to enhance its trans-NIH collaborative role in developing initiatives to build the scientific foundations of women's health and an innovative future in research.

I intend to also continue to implement and to further augment the 2010 comprehensive research agenda in order to inform sex-based, personalized medicine and to link basic research to public health by highlighting the importance of studying sex and gender factors and sex differences in health and illness, including the potential application of such research to health care delivery.

As I lead ORWH and serve the research community, I am confident that the Office will remain a focal point and catalyst for women's health research and career programs, including those that are interdisciplinary in nature, include women and minorities in clinical research, and ensure that efforts addressing sex differences in basic investigation are firmly secured into the fabric of NIH. And I expect the ideals that led to the establishment of the Office will only become strengthened and more fully appreciated for their importance to the scientific mission of NIH and the health and health care of women and their families.

You are invited to read this in-depth report to become acquainted with the tremendous advances related to women's health, which have taken place during this 2-year period. I further hope that this report enhances your appreciation of the value of studying the role of sex/gender factors in health and disease for improvements in the health of both women and men.

Janine A. Clayton, M.D.
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health
August 2013

Report of the Office of Research on Women's Health

A Historical Perspective: The Development of the Office of Research on Women's Health

In 1983, the Assistant Secretary for Health, Dr. Edward N. Brandt, established the U.S. Public Health Service Task Force on Women's Health Issues in recognition of the paucity of data related to women's health. In 1985, the task force produced a report, "Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, Volume I," calling for an expansion of biomedical and behavioral research on conditions and diseases unique to, or more prevalent in, women in all age groups (U.S. Public Health Service, 1985). In 1986, NIH published a policy that "urged" the inclusion of women in NIH clinical research (NIH, 1986, vol. 15, p. 1; NIH, 1986, vol. 16, p. 2). Shortly thereafter, in recognition of the need to promote the inclusion of minority populations, NIH published another policy in 1987, this time encouraging the inclusion of minorities in clinical studies (NIH, 1987, vol. 16, p. 3–4).

In 1990, the Congressional Caucus for Women's Issues requested that the General Accounting Office (GAO), now known as the Government Accountability Office, conduct an investigation into the implementation of the guidelines for the inclusion of women in NIH-funded clinical research. This report, included in congressional testimony, indicated that the policy's implementation was slow and not well communicated, that gender analysis was not performed routinely, and that the impact of the policy could not be determined (National Institutes of Health: Problems in Implementing Policy, 1990). These findings catalyzed the 1990 establishment of ORWH within the NIH OD; the NIH Revitalization Act of 1993 established the Office in statute. In that act, Congress assigned a far-reaching leadership role for ORWH by mandating that its Director:

(1) Advise the NIH Director and staff on matters relating to research on women's health;

(2) Strengthen and enhance research related to diseases, disorders, and conditions that affect women;

(3) Ensure that research conducted and supported by NIH adequately addresses issues regarding women's health;

(4) Ensure that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH;

(5) Develop opportunities and support for recruitment, retention, reentry, and advancement of women in biomedical careers; and

(6) Support research on women's health issues.

The Revitalization Act also established two committees to assist ORWH in fulfilling its mission. An Advisory Committee on Research on Women's Health (ACRWH), composed of non-Federal members, was established to provide the ORWH Director with a ready source of expert, outside advice and recommendations on women's health research issues. ACRWH members are chosen from among leading research scientists, health practitioners, advocates, educators, and other professionals.

A trans-NIH committee, the Coordinating Committee on Research on Women's Health (CCRWH), was also established in statute in the 1993 NIH Revitalization Act. The Committee is composed of Directors, or their designees, from NIH ICs and Offices in the OD to act as direct liaisons for ORWH with the ICs. CCRWH also provides advice and recommendations to the ORWH Director.

In 2006, the NIH Reform Act called for a reorganization of the OD. ORWH was placed in a new division whose responsibilities included developing and guiding major trans-NIH initiatives. This placement of ORWH within the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) highlighted and facilitated the ORWH role as NIH's focal point for women's health research. In addition, the ORWH Director started reporting to the Director of DPCPSI. However, the 2006 legislation did not change the Office's statutory responsibilities.

The 2011 mission statement of ORWH continues to emphasize its historic role in improving women's health through research, the inclusion of women in clinical research, and the promotion of women in biomedical careers. The mission statement also places new emphasis on the contribution of research on sex and gender factors in health and disease, especially as findings contribute to achieving a goal of personalized medicine. ORWH is also focusing on other key areas of significance, including interdisciplinary research and training, and research to understand the causes of health disparities among different subgroups of women, defined by factors such as age, socioeconomic, and racial and ethnic group membership.

Within DPCPSI, ORWH has worked to increase its NIH coordinating role by continuing to forge new partnerships with ICs to ensure that women's health and sex differences research is incorporated into the broad NIH scientific framework. To this end, ORWH is guided by the goals, objectives, and crosscutting themes within the NIH Strategic Plan "Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research," (HHS, NIH, ORWH, 2010) to implement a trans-NIH approach to research priorities.

References

National Institutes of Health. (1986). Inclusion of women in study populations. *NIH Guide for Grants and Contracts, 15*(22), 1.

National Institutes of Health. (1986). Inclusion of women in study populations. *NIH Guide for Grants and Contracts, 16*(3), 2.

National Institutes of Health. (1987). Inclusion of minorities in study populations. *NIH Guide for Grants and Contracts, 16*(32), 3–4.

National Institutes of Health: Problems in implementing policy on women study populations: Hearings before the Subcommittee on Health and the Environment, of the House Committee on Energy and Commerce, 101st Cong., (1990) (testimony of Mark V. Nadel).

NIH Reform Act of 2006, H.R. 6164, 109th Cong. (2007).

NIH Revitalization Act of 1993, Public Law No. 103-43, § 141, 107 Stat. 22 (1993), amending the Public Health Service Act to add Section 486(d)(5)(A), 42 U.S.C. § 287d-2.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Strategic plan—Executive summary* (NIH Publication No. 10-7606). Bethesda, MD: National Institutes of Health.

U.S. Public Health Service. (1985). Women's health: Report of the Public Health Service Task Force on Women's Health Issues, volume I. *Public Health Reports, 100*(1), 73–106.

NIH Strategic Plan for Women's Health Research

Introduction

In September 2010, ORWH released the third NIH scientific agenda for women's health, titled "Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research" (HHS, NIH, ORWH, 2010a). This research agenda was the culmination of a highly interactive scientific and public partnership that encompassed both looking back for historical perspectives and looking forward to new research opportunities on the horizon. The resulting three volumes represent the NIH Strategic Plan for Research on Women's Health for the coming decade and serve as a framework for research investigations galvanized by cutting-edge technologies and catalyzed by nascent scientific concepts to advance women's health research through interdisciplinary and multidisciplinary collaborations across the entire research spectrum, from basic to clinical and translational (Pinn, Clayton, Begg, & Sass, 2010).

The Strategic Plan resulted from five regional public hearings and scientific workshops held in 2009 and 2010. Thirty-seven scientific and career development working groups were jointly cochaired by leading extramural and NIH scientists, representing 44 academic institutions, 19 ICs, and the Office of the NIH Director. Reports of all the working groups were compiled in volume II of the Strategic Plan (HHS, NIH, ORWH, 2010b).

Identifying the Goals for the New NIH Agenda for Women's Health Research

Each workshop served as a dynamic forum for a collaborative process of setting the research agenda. The resulting working group reports put forward 400 recommendations, from which 6 crosscutting goals and 44 specific objectives were distilled. Central to the six goals is the importance of evaluating sex and gender factors and sex differences across the research spectrum, with an explicit emphasis on interdisciplinary approaches. The goals of the Strategic Plan are as follows:

(1) Increase the study of sex differences in basic biomedical and behavioral research.

(2) Incorporate findings of sex differences in the design of new technologies, medical devices, and therapeutic drugs.

(3) Actualize personalized prevention, diagnostics, and therapeutics for women and girls.

(4) Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research.

(5) Achieve a clearer and wider understanding of women's health issues through strategic communications of research findings to diverse audiences.

(6) Employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce.

Research on Sex and Gender Factors and Their Role in Health and Disease

The agenda outlined in the Strategic Plan challenges the boundaries of women's health by calling for an increased focus on basic scientific research on sex and gender factors and sex differences and their significance in health and disease. To provide a foundation for research to improve health and accelerate research advances into clinical care, the Strategic Plan calls for a comprehensive conceptual framework that explores variation due to sex as critical to advancing many fields of study (such as genetics, immunology, endocrinology, developmental biology, cell biology, microbiology, biochemistry, and toxicology, as well as other areas in basic biological and behavioral sciences). New technologies, such as high-throughput sequencing, data acquisition, bioengineering, bioinformatics, and new modeling and data analytical techniques can contribute to innovative and effective approaches to advance emerging areas of science. Research conducted with both female and male cells,

tissues, and animal model systems is paramount for developing strategies to improve sex- and gender-appropriate medicine, including clinical diagnosis and therapy. In addition, research designed to delineate the effects of age and aging is critical for age-appropriate health care. The study of biological, behavioral, and social variables and how they interact with environmental, age, sex, and other differences should be integral to the development of a new and expanded multidimensional scientific knowledge base.

Since its inception, ORWH has challenged historically limited concepts of women's health and has advanced an understanding of women's health and research that encompasses the full lifespan, not just the traditional age periods of interest. This expanded view provides an integrated framework that can mitigate fragmented approaches to health and health care. The increasing emphasis on researching differences by sex continues to broaden the perspectives and value of women's health to benefit women and men as well as girls and boys. In addition, ORWH continues to address the distinction between biological sex and socially derived gender and works to ensure the expansion and translation of research on both sex differences and gender identity.

Health Disparities and Women's Health

The research agenda illuminates knowledge gaps in women's and girls' health. It includes a call for biomedical and behavioral research to understand how race, ethnicity, poverty, environment, gender identity, disability, immigrant status, occupation, sexual orientation, and other differences influence the causes, diagnoses, progression, treatment, and outcome of disease among different populations of women and girls. These concepts serve as catalysts to propel the research continuum toward the goals of prevention and individualized treatment and the translation of such findings to promote the health and well-being of all women and girls. Efforts to improve their health may also benefit the health of others; women comprise a disproportionate number of the world's caretakers and are thus often in a position to make healthy choices for themselves, their families, and their communities, both internationally and nationally.

Moving into the Future by Implementation of the NIH Strategic Plan for Women's Health Research

The mission of NIH is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. As ORWH moves into its third decade, it is important to reaffirm its role within the NIH mission as a catalyst for integrating the study of males and females within areas from basic to applied research. In FY 2011–FY 2012, in partnership with the NIH ICs and OD, ORWH has led efforts to meet the NIH mission and expand upon it, particularly as it relates to women's health.

Developing Success Metrics and a Toolkit to Collect and Visualize Data for the Strategic Plan Implementation Evaluation

Collection and Assimilation of SPIE Data

An evaluation of the way the NIH Strategic Plan for Women's Health Research is implemented requires data not previously collected by any existing system or database. ORWH has developed a new data collection system in order to gather data on the full spectrum of ORWH program activities, from personnel-attended activities to research projects cofunded by the Office. The electronic Strategic Plan Implementation Evaluation (SPIE) form was devised to allow the coding of each relevant ORWH activity by the Strategic Plan goals and objective(s) that it fulfills. Figure 1 provides a complete listing of the goals and objectives.

Figure 1. NIH Strategic Plan for Women's Health Research Goals and Objectives

GOAL 1: Increase sex differences research in basic science studies

1.1 Encourage genetic and epigenetic studies to identify sex differences in gene expression.

1.2 Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

1.3 Study sex differences using a systems biology-based approach. This will include research based on new technology platforms such as microbiomics, genomics, phenomics, proteomics, and metabolomics.

1.4 Include sex parameters in the design of experiments using animal models.

1.5 Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.

1.6 Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases including HIV/AIDS, urinary tract, and sexually transmitted infections.

1.7 Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs. Apply this knowledge to sex differences in disease prevalence, symptoms, management, and outcomes in conditions such as lupus and cardiovascular diseases and to predominantly sex-specific diseases such as breast cancer and uterine fibroids.

1.8 Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.

1.9 Incorporate sex/gender considerations into discussions in scientific conferences and meetings.

GOAL 2: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs

2.1 Encourage the development of technologies that will address sex-based differences at all scales of detail, from the nanometer to the whole person.

2.2 Develop novel animal, in vitro, and computational (virtual) models to study sex differences in diseases and conditions.

2.3 Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women and girls.

2.4 Develop computational models that will utilize multiple levels of analyses to address both qualitative and quantitative outcomes of clinical research related to women.

2.5 Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.

2.6 Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery.

2.7 Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

2.8 Consider the sex and age of the patient in the development of engineered medical products, cell-based therapeutics, and regenerative procedures.

2.9 Encourage collaborative interactions among clinicians, bioethicists, and technologists regarding accessibility of new technologies, drugs, and other interventions relevant to women's health.

GOAL 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women

3.1 Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan.

3.2 Study sex/gender differences in embryonic development, including epigenetic changes.

3.3 Encourage research on safe and effective interventions for conditions affecting pregnant women.

3.4 Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

3.5 Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

3.6 Study sex/gender differences in the aging process.

3.7 Explore differences in response to therapeutic interventions among samples of elderly women, including those with comorbid conditions.

3.8 Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

3.9 Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

Figure 1 (continued)

GOAL 4: Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research

4.1 Convene futuristic thinkers from many fields of science, engineering, business, and the humanities to assist in devising implementation strategies for women's health research.

4.2 Establish new ventures and initiatives with a wide cross-section of partners, including NIH institutes, centers, and offices; academia; other Federal agencies; international organizations; private foundations; and industry.

4.3 Promote an environment that uses multiple avenues and technologies to facilitate continuing input from partners committed to improving women's health and promoting research.

4.4 Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups.

4.5 Partner with professional societies to include women's health research issues in national scientific meetings and conferences, including issues involving career training and development.

4.6 Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries.

GOAL 5: Develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health and wellness research

5.1 Serve as a key informational resource for Federal and State agencies, elected representatives, the media, health and advocacy organizations, and the public on women's health research issues.

5.2 Expand collaboration with other NIH institutes and centers and Federal agencies in outreach activities on issues related to women's health.

5.3 Expand strategic alliances and partnerships with key national and international organizations to maximize the communication and impact of women's health research.

5.4 Convene leaders in communication sciences to explore and identify optimum messages and messaging to benefit women's health research.

5.5 Support research to explore and evaluate the ability of women and men of different ages to access, process, and act on health-related information.

5.6 Build a central portal of information for women's health research findings suitable for the specific needs of researchers, health care practitioners, patients, and their families.

GOAL 6: Employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce

6.1 Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH.

6.2 Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs; encourage evaluation of mentoring practices.

6.3 Address the organizational, institutional, and systemic factors that impede recruitment, retention, and advancement of women in science, and modify practices that impede the careers of biomedical scientists.

6.4 Evaluate the challenges and successes of part-time research careers and explore strategies to allow part-time faculty to remain involved in their fields of science.

6.5 Promote recognition and understanding of women's health among future health professionals and scientists by informing the design of curricula with up-to-date research findings for use in educational materials for medical, dental, nursing, and other professional training.

Figure 1. A comprehensive list of the six goals and their corresponding objectives from the NIH Strategic Plan for Women's Health Research.

In addition to coding program activities by Strategic Plan goals and objectives fulfilled, the electronic SPIE form also collects other relevant data such as type of activity, ORWH role in the activity, and any IC or HHS partners in the activity. Using a single click, staff can send the form to the staff members responsible for SPIE data collection, where assimilation is automated using free Adobe software and reviewed for standardization across all staff. Further, a weighting score is coded into each activity, based on a weighting scheme created by ORWH (from 1 to 100, spanning activities such as "attended meeting," "research supported," or "cosponsored a program announcement"). This process, implemented by ORWH, gathers a breadth of information not collected elsewhere, in a way that is systematic, efficient, and highly effective.

Visualization of SPIE Data

The creation of the SPIE toolkit by ORWH culminated in the design and implementation of a data visualization technique that allows all 44 objectives of the Strategic Plan to be presented in a single aesthetic and accessible model (Figure 2). This type of tool is dynamic, in that the radius of the circle can be any relevant success metric, from the number of activities that meet each objective to the amount of funding put toward each objective. Figure 2, specifically, illustrates the number of ORWH activities fulfilling each objective as of March 2012. The longer the bar, the more that success metric has been achieved for that objective. The relative width of the bars is not meant to convey any information about the activities within that objective. The number at the end of each bar corresponds to the number of an objective within that goal. For example, Objective 1.3 is labeled "3" within Goal 1; however, in the figure below, only some bars are labeled for image simplicity.

This visual conveys the successes in implementation of the Strategic Plan across specific objectives, and identifies those objectives in which there are opportunities for increased focus.

Prioritization of the Strategic Plan's Objectives

The goal of having all new ORWH funding, activities, and initiatives be guided by the Strategic Plan required that all 44 objectives

Figure 2. Success Measurement of Strategic Plan Objectives by Goal and Specific Objective

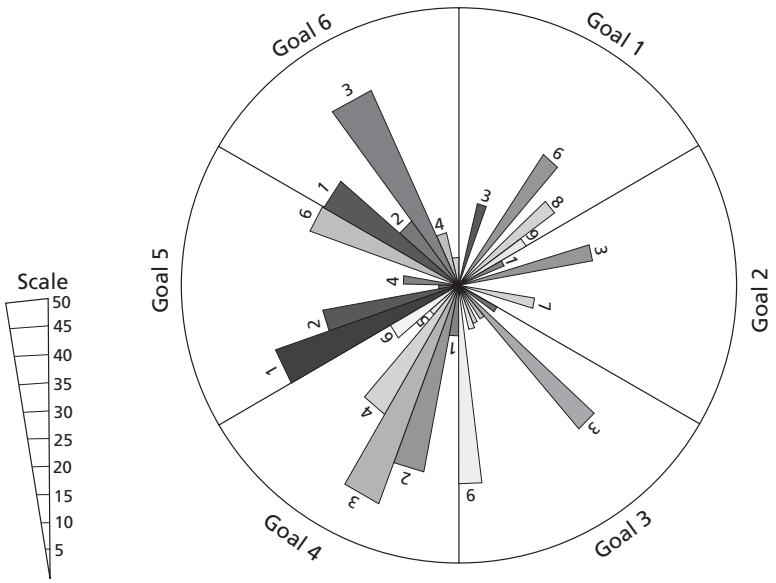


Figure 2. Data visualization tool, conceived and developed at ORWH, allows all 44 objectives in the Strategic Plan to be seen at once, across a dynamic set of metrics. Shown in the figure is the number of activities fulfilling each objective as of March 2012.

under each of the 6 goals be prioritized and targeted in a manner that took into consideration the costs (financial, feasibility, or other) and the time required to complete each. As another way to identify areas of opportunity, an "action matrix" was developed to represent estimated time and cost/difficulty for NIH to complete each strategic objective. (This is in contrast to the SPIE data, which specifically track ORWH staff efforts.) The action matrix not only includes estimates of difficulty and time but it also identifies strategic objectives in terms of their priority. For example, Objective 1.9, "Incorporate sex/gender considerations into discussions in scientific conferences and meetings," was designated as low-cost and short-term because it may only require staff time to accomplish, whereas Objective 2.2, "Develop novel animal, in vitro, and computational (virtual) models to study sex differences in diseases and conditions," was designated as highest cost and longest term because the science necessary to accomplish the goal will require significant time and funding. However, both objectives were selected as being among the highest priority for ORWH. The matrix was created with input from the Advisory Committee on Research on Women's Health (ACRWH) and the Coordinating Committee on Research on Women's Health (CCRWH).

Summary: Guiding Tomorrow's Research on Women's Health

The research agenda in the Strategic Plan was developed as a way of moving toward further innovative and promising science important to women's health. It is of critical importance that ORWH continue to devise and refine methods and metrics, such as the ones described in this section, to track and quantify the implementation of the Strategic Plan, to consider the opportunities for progress in identified priority areas in terms of time and expense; and to use the information thus obtained to monitor overall progress toward the goals. In this way, the Strategic Plan can serve an integral role in NIH efforts to harness the exciting potential of biomedical research to enhance health, lengthen life, and reduce the burdens of illness and disability.

References

Pinn, V. W., Clayton, J. A., Begg, L., & Sass, S. E. (2010). Public partnerships for a vision for women's health research in 2020. *Journal of Women's Health*, 19(9), 1603–1607.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010a). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Strategic plan—Executive summary* (NIH Publication No. 10-7606). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010b). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Regional scientific report—Volume II: Working group reports* (NIH Publication No. 10-7606B). Bethesda, MD: National Institutes of Health.

I. ORWH Research

ORWH and NIH Priorities for Women's Health Research

The mission of ORWH is to encourage and support meritorious research on women's health, including investigations of the role of sex and gender factors in health and disease. ORWH works in partnership with NIH ICs to ensure that such research is part of the scientific framework of NIH. Since its publication in 2010, the NIH Strategic Plan for Women's Health Research has guided ORWH research priorities and initiatives. Since that time also, ORWH has taken the trans-NIH lead role in efforts to implement the Strategic Plan in collaboration with NIH ICs and with ongoing input from ORWH external and internal advisory committees.

To advance women's health research, the Strategic Plan identified 6 major goals and 44 specific objectives. The Strategic Plan also identified three crosscutting themes to provide additional context for the goals and objectives. The first theme emphasizes the value of research that explores biological sex differences to contribute important new knowledge of the sources of variability in human health and disease. The second theme stresses the need to ensure that new basic and applied scientific fields consider biological sex as a potentially significant source of variability to be taken into account in the design of new techniques and technologies. Finally, the third theme stresses the importance of new public-private and interdisciplinary partnerships to increase the impact of biomedical women's health research by disseminating findings to ever wider clinical, community, and policy audiences. Taken together, these goals, objectives and crosscutting themes provided a major orienting framework for ORWH research and related activities in FY 2011 and FY 2012.

Overview of ORWH-Cofunded Research

During FY 2011 and FY 2012, ORWH worked to implement the Strategic Plan across NIH. The results of these efforts can be seen throughout this biennial report, in the other ORWH sections, and in the IC reports, which highlight how IC specific research activities map to the goals and objectives of the Strategic Plan. This section details ORWH research cofunding for that time period.

ORWH works with NIH ICs to cofund research because the Office does not have direct grant-making authority. ORWH may support research in two ways. First, it cosponsors funding opportunity announcements (FOAs) or otherwise partners with NIC ICs to cofund meritorious projects relevant to women's health. Second, to stimulate research in specific areas of women's health, ORWH may develop and release FOAs. Two ORWH "signature" programs, Advancing Novel Science in Women's Health Research (ANSWHR) and the Research Enhancement Awards Program (REAP), are described below. ANSWHR is a program that involves the competitive review of applications. REAP uses an administrative review of research that has already been peer-reviewed. Additionally, in FY 2011 and FY 2012, ORWH initiated and provided major support for two other ORWH signature FOAs, the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health interdisciplinary research program and the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program, which supports interdisciplinary research training. These ORWH programs are described in Section II of this report. Table 1 (page 18) lists FY 2011 and FY 2012 FOAs in which ORWH participated. These FOAs reflect a wide range of science areas.

Tables 2 and 3 (pages 19–27) list the research grants and contracts that ORWH, along with the NIH ICs, supported in FY 2011 and FY 2012. In both FYs, there were more than 150 funded initiatives. The majority of funding used NIH Research Project Grant (RPG) mechanisms, but funding may also have been provided through research contracts. As illustrated by the 2 tables, ORWH has cofunded 1 or more research projects with 19 ICs. The "top three" Institutes for FY 2011–FY 2012 were the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the

National Cancer Institute (NCI), and the National Institute of Allergy and Infectious Diseases (NIAID), followed by the Fogarty International Center; the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); and the National Institute on Aging (NIA). ORWH also collaborated with the HHS Agency for Healthcare Research and Quality (AHRQ), the Food and Drug Administration (FDA), and the Indian Health Service (IHS) to support relevant research activities. Research summaries for FY 2011 and FY 2012 are found in Appendices A and B, respectively. In this report, Tables 2 and 3 list the titles of the research projects grouped by the primary NIH IC.

Trans-NIH Research Initiatives

In FY 2011 and FY 2012, ORWH used the ANSWHR program to fund competitively reviewed R21s and the REAP to support meritorious research on women's health that just missed an IC pay line. ORWH also coordinated the trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group. These initiatives are described below.

Advancing Novel Science in Women's Health Research Program

The Advancing Novel Science in Women's Health Research (ANSWHR) program was developed by ORWH to stimulate and support innovative research to advance new concepts in women's health research and the study of sex/gender factors in health and disease. The R21 mechanism is used by ANSWHR to support exploratory and developmental projects. Because of the complexity of working with up to 21 ICs on the ANSWHR program, in both FY 2011 and FY 2012, ORWH continued to have only 1 submission date (October 16). In both FYs, ORWH funds were augmented by funds from several ICs, thereby expanding the reach of this program. ORWH provided ANSWHR funding of $1.96 million in FY 2011 and $1.64 million in FY 2012. A total of 14 ICs had 1 or more ANSWHR applications funded during these 2 FYs. The areas of science covered included breast cancer; reproductive health, especially relating to conditions such as preeclampsia and hypertension and intrauterine growth restriction of the fetus; diabetes; urinary incontinence; urinary tract infections; obesity; human papillomavirus (HPV); cardiovascular disease; chronic pain; microbial exposures across the life span of women; violence prevention on college campuses; depression relapse during in vitro fertilization; and gender-specific prevalence of infectious diseases.

Research Enhancement Awards Program

In 1997, ORWH created the Research Enhancement Awards Program (REAP). Offered annually, REAP is a trans-NIH initiative through which ORWH partners with NIH ICs to offer funding to meritorious research on women's health that has just missed the IC pay line. REAP funding is open to all NIH research mechanisms. ORWH's policy is to fund 1 year only, and so all "out year" funds are provided by the primary IC.

In FY 2011, ORWH partnered with 7 ICs to fund 16 grants under REAP for a total of $2.65 million. The areas of science that were funded included colorectal cancer in women; hip fracture risk prediction; cervical cancer health gap for women in jail; gene expression in mammalian oocytes; telemedicine; sex differences in brain; breast reconstruction; phospholipid-reactive T cells in pregnancy; FAK/Pyk2 signaling pathway and bone formation; acupuncture for aromatase inhibitor-related arthralgias in breast cancer patients; fatigue and lifestyle physical activity in SLE (systemic lupus erythematosus); a biopsychosocial investigation of women's health at midlife; vitamin D status, gene polymorphisms, and breast cancer progression/prognosis; survivorship care planning and communication for rural breast cancer survivors; and mechanisms for estrogen-dependent myocardial depressant effects of ethanol.

In FY 2012, ORWH partnered with 7 ICs to fund 11 grants under REAP for a total of $1.73 million. The FY 2012 REAP-funded grants included the following topics: international pooling project of mammographic density; molecular basis of *E. coli* adhesions in bladder disorder; premenstrual syndrome and risk

of subsequent hypertension; glycated CD59 as a novel biomarker of gestational diabetes mellitus; feasibility of virtual-agent cervical cancer education for Hispanic farmworkers; unintended birth, fetal and infant loss, and maternal depressive symptoms; feasibility of community-based tampon self-sampling to prevent cervical cancer; pharmacotherapy evaluation tools for improving breast cancer outcomes in rural Appalachia; brain-centered therapy versus medication for urgency urinary incontinence; trajectories of reward sensitivity and depression across adolescence; and role of B cells in lupus pathogenesis.

Trans-NIH Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Activities

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating illness that lacks a universally accepted case definition, etiological agent, diagnosis, or treatment. It is characterized by 6 months or more of incapacitating fatigue and problems with concentration and short-term memory. The condition may be preceded by flu-like symptoms that are followed by pain in the joints and muscles, sleep disturbances, tender lymph nodes, sore throat, and headache. ME/CFS is characterized by a worsening of symptoms following physical or mental exertion that requires an extended recovery period. Roughly 17 million people worldwide are estimated to have ME/CFS, and women are disproportionately affected by an estimated ratio of 4:1.

Trans-NIH ME/CFS Research Working Group

In partnership with NIH ICs, in FY 2011 and FY 2012, ORWH led the NIH effort to promote research on ME/CFS by convening monthly meetings of the Trans-NIH ME/CFS Research Working Group (*http://orwh.od.nih.gov/research/me-cfs/index.asp*) and by coordinating communications about ME/CFS research and activities within NIH, among other HHS agencies, and with the broader extramural research and advocacy communities. (FY 2011 and FY 2012 members of the Working Group are listed in Appendix C). The Working Group does not have grant-making authority and does not make research project awards. Instead, it advances ME/CFS research by providing NIH ICs with an evidence-based rationale for supporting ME/CFS research and for attracting investigators to study this complex illness. The chair of the Working Group represents NIH as a nonvoting, ex officio member of the HHS Chronic Fatigue Syndrome Advisory Committee (CFSAC) and provides the CFSAC with updates on NIH research related to ME/CFS, current and ongoing funding opportunities relevant to ME/CFS, and future plans for stimulating research on this condition. CFSAC provides advice and recommendations to the Secretary of HHS through the Assistant Secretary for Health on issues related to ME/CFS (*http://www.hhs.gov/advcomcfs*).

ME/CFS Funding Opportunities: ORWH Support

NIH also encourages applications for ME/CFS research funding through the use of program announcements. Two broadly focused ME/CFS program announcements were renewed in December 2011 and will continue for 3 years, with three receipt dates per year. These initiatives were cofunded by ORWH and are shown in Table 1.

In 2011, ORWH provided $353,463 in support for two research projects on ME/CFS. The first of these is an examination of the association between Epstein-Barr virus and CFS via the presence of certain HERV-K18 alleles that differ in their superantigen activity (5R01AR053821-05: HERV-K18 as a Risk Factor for CFIDS). The second project aims to identify subgroups of ME/CFS subjects with neurological abnormalities by using subgroupings based on the presence or absence of comorbid Axis I psychopathology (1R21NS075653-01: Neuropathologic Abnormalities Define a Subgroup of Patients with CFS). In FY 2012, ORWH provided $66,509 in support for this project.

Research on Violence Against Women

Research on violence against women was given increased attention across the Federal Government in FY 2011 and FY 2012. In FY 2011, NIH reported funding $32.84 million in research on violence, including domestic violence, abused women, and spousal

abuse; and in FY 2012, this amount was $29.17 million. In FY 2012, ORWH provided $181,000 in funding for a grant titled "Consortium to Evaluate a Novel Violence Prevention Program on College Campuses" (R21 HD069887-01A1).

In 2012, NIH joined a trans-Federal working group that developed "United States Strategy to Prevent and Respond to Gender-Based Violence Globally." ORWH staff were participants in the working group. That report was released in August 2012, and it resides on the Department of State Web site, *http://www.state.gov/documents/organization/196468.pdf*.

Highlights of Long-Term ORWH-Cofunded Research Initiatives

ORWH has provided support for a number of major research efforts in priority areas of women's health. Brief descriptions of ORWH FY 2011–FY 2012 support for five of these programs are provided below.

Human Papillomaviruses Vaccine Development and Evaluation

Cervical cancer is diagnosed in more than 500,000 women each year, causing approximately 250,000 deaths around the world and making it one of the most common cancers worldwide. Evidence indicates that virtually all cases of cervical cancer are attributable to cervical infection by a subset of oncogenic HPVs and that HPV can also cause cancer at other anogenital and oral sites. For multiple years, starting in the late 1990s, ORWH has supported the development and evaluation of the prophylactic virus-like particle HPV vaccine discovered by investigators at NCI. During the FY 2011–FY 2012 period, ORWH supported work in Costa Rica on the clinical efficacy of this vaccine. Results have shown that the vaccine (1) is highly effective at preventing new infections with HPV types 16 and 18; (2) confers partial protection against HPV types that are phylogenetically related to HPV 16 or 18; (3) and does not help treat existing infections. Levels of antibodies achieved in the long term following two doses of the HPV vaccine are only slightly lower than those observed after three doses, likely explaining why fewer than three doses provided a high degree of protection. Results further indicate that the vaccine protects against HPV infection of the anus and the oral cavity.

Diabetes Prevention Program/ Diabetes Prevention Program Outcomes Study

ORWH has provided cofunding for the Diabetes Prevention Program (DPP) of NIDDK since its inception. The original DPP demonstrated the efficacy of lifestyle modification and use of the drug metformin in decreasing the incidence of diabetes in an ethnically diverse population at high risk for diabetes. A longer-term follow-up study of DPP—the DPP Outcomes Study (DPPOS)—was designed to evaluate the long-term effects of active DPP interventions. This study is looking at the development of diabetes over the course of 5 to 11 additional years as well as composite diabetes-related microangiopathic and cardiovascular disease outcomes. The DPPOS includes a multiethnic sample of adults, 68 percent of them women, of whom 20 percent had gestational diabetes (GDM) on entry into the study. Phase 1 of DPPOS found that lifestyle and metformin were equally efficacious in preventing diabetes in women with GDM; among women without GDM the study found that the lifestyle intervention was significantly more effective than metformin in preventing diabetes. Phase 2 of DPPOS began in 2009; ORWH has provided funding to measure sex-hormone-binding globulin, testosterone, estradiol, and dehydroepiandrosterone (DHEA) as a measure of risk at DPP baseline. In 2011, ORWH provided support to examine a number of hypotheses related to the effect of sex steroids and changes in sex hormones with menopause on diabetes and cardiovascular events. Efforts are also under way to examine gender differences within the entire DPPOS cohort.

Osteoarthritis Initiative

Musculoskeletal conditions, such as osteoarthritis, are a source of significant disability for women of all ages, but they are especially a problem for women who are postmenopausal. ORWH was one of the original funders of the Osteoarthritis Initiative (OAI), as were the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIA, and others in a public-private

partnership supporting OAI. OAI is a multicenter, longitudinal, prospective, observational cohort study of knee osteoarthritis. This initiative has successfully recruited 5,000 male and female study subjects and serves as a national repository for biological materials that illustrate the natural history of osteoarthritis; in addition, OAI is actively involved in the evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. Major outputs for FY 2011 to FY 2012 included a report on the functional outcomes in women with knee osteoarthritis that compared Blacks and Whites. Among the 3,695 individuals at high risk for knee osteoarthritis, which was measured by a high body mass index and a large waist circumference, Black women were at greater risk than White women by every outcome measure. The report also revealed that 40 percent to 60 percent of OAI participants who had knee osteoarthritis were inactive. Additionally, both very high and very low levels of physical activity were associated with cartilage degradation.

Microbicide Innovation Program

Topical microbicides are agents that when applied vaginally, rectally, or on the penis can result in inhibition of the transmission of HIV and/or other sexually transmitted infections that may be cofactors in HIV transmission. ORWH provided cofunding in FY 2011 and FY 2012 for the Microbicide Innovation Program, which focuses on facilitation of technology or methodology design and development. The success of these tools will hinge on behavioral, cultural, and contextual factors (e.g., product characteristics, perceived risk of infection, and partner cooperation).

Health Disparities: Native American Research Centers for Health

For a number of years, ORWH has collaborated on the Native American Research Centers for Health (NARCH) program, which has been sponsored by the Indian Health Service (HIS) and coordinated by the National Institute of General Medical Sciences (NIGMS) for NIH. The NARCH initiative supports partnerships between the American Indian/Alaska Native (AI/AN) tribes or tribally based organizations and institutions that conduct intensive academic-level biomedical, behavioral, or health services research. The NARCH program provides opportunities for conducting research, research training, and faculty development to meet the needs of the AI/AN communities. As a developmental process, tribes and tribal organizations are able to build a research infrastructure, including a core component for capacity building, and thereby increase the possibility of reducing the many health disparities so prevalent in AI/AN communities. Grants supported through this program are awarded to the tribal partner, which then subcontracts with the research-intensive institution(s). Because the IHS is not a research-supporting agency, NIH provides funds to support NARCH research projects, while the IHS manages the activities of each NARCH awardee.

During FY 2011 to FY 2012, ORWH supported two NARCH awards. For the first NARCH project, the Oklahoma Native American Research Centers for Health, ORWH is supporting (1) research focused on the impact of infections on maternal and child health in Native Americans; (2) research to develop better diagnostic and prognostic tests for rheumatic disease in Oklahoma tribal members and to examine the role of environmental triggers for autoimmunity; and (3) research to prevent excessive gestational weight gain in otherwise healthy but overweight Native American women. In the second award, ORWH is providing funding to NARCH for research to improve the preconception health of adolescents belonging to the Oglala Sioux Lakota tribe in South Dakota.

Summary: ORWH Research Programs Support the Implementation of the NIH Strategic Plan for Women's Health Research

For the period FY 2011 to FY 2012, numerous activities were undertaken in support of implementing the Strategic Plan. Selected highlights included discussions across NIH with research program staff as they developed new funding opportunities, developed research conferences and workshops, and

reviewed research grant portfolios. In making funding decisions for use of ORWH funds, ORWH staff identified new research opportunities that were especially relevant to the goals and objectives outlined within the Strategic Plan. Additionally, ORWH developed analytic tools that would characterize the implementation of the Strategic Plan and help identify gaps in research.

Table 1. RFAs and PAs Related to ORWH, FY 2011 and FY 2012

RFAs and PAs Developed and Implemented by ORWH

Title	Announcement Number	NIH Lead
Advancing Novel Science in Women's Health Research (ANSWHR) (R21)	PA-10-226	ORWH
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment (R01)	PA-12-032	ORWH
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment (R21)	PA-12-033	ORWH

RFAs and PAs Cosponsored by ORWH

Title	Announcement Number	NIH Lead
Basic Research on Self-Regulation (R21)	RFA-AG-11-010	NIA [OppNet]
Fatigability, Activity Limitations, and Bioenergetics in Aging (R01)	PA-12-227	NIA
Fatigability, Activity Limitations, and Bioenergetics in Aging (R21),	PA-12-225	NIA
Fatigability, Activity Limitations, and Bioenergetics in Aging (R21)	PA-12-226	NIA
Effects of the Social Environment on Health: Measurement, Methods, and Mechanisms (R01)	RFA-DA-11-003	NIDA [OppNet]
Fogarty International Research Collaboration Behavioral and Social Sciences (FIRCA-BSS) Research Award (R03)	PAR-08-223	FIC
Limited Competition for the Global Research Initiative Program, Behavioral/Social Sciences (R01)	PAR-10-280	FIC
Neurobiology of Migraine (R21)	PA-10-259	NINDS
NIH Basic Behavioral and Social Science Opportunity Network (OppNet) Short-Term	RFA-NR-11-002	NINR [OppNet]
Research on Teen Dating Violence (R01)	PA-09-169	NICHD
Research on Teen Dating Violence (R01)	PA-09-170	NICHD
Scientific Meetings for Interdisciplinary Research Teams in Basic Behavioral and Social Science Research (R13)	RFA-CA-10-017	NCI [OppNet]
Transdisciplinary Research on Fatigue and Fatigability in Aging (R01)	PA-08-161	NIA
Transdisciplinary Research on Fatigue and Fatigability in Aging (R21)	PA-08-162	NIA
Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (R01)	PAR-10-190	NICHD
Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (R03)	PAR-10-191	NICHD
Vulvodynia—Systematic Epidemiologic, Etiologic, or Therapeutic Studies (R21)	PAR-10-192	NICHD
Pregnancy in Women with Disabilities	PAR011-259	NICHD
Research on Children in Military Families	PA-11-202	NICHD
Design and Development of Novel Technologies for Healthy Independent Living	PAR-11-021	NIBIB
Technologies for Healthy Independent Living	PAR-11-020	NIBIB

Table 2. ORWH-Cofunded Research Initiatives, FY 2011

Title	Institute or Center	Award Amount
Advanced Glycation End Products and Colorectal Cancer Risk in Women	NCI	$98,397
Cancer Center Support Grant: Cancer Institute of New Jersey	NCI	$15,000
Cancer Center Support Grant: Hollings Cancer Center	NCI	$15,000
Cancer Center Support Grant: Ohio State University Comprehensive Cancer Center	NCI	$5,000
Cancer Center Support Grant: University of Pittsburgh Cancer Institute	NCI	$15,000
Cancer Center Support Grant: Yale Cancer Center	NCI	$15,000
Cancer Health Disparities Research Among Appalachian Women	NCI	$5,000
Characterization of Novel Viruses from Human Genitals	NCI	$25,000
Comparison of the Impact of Vaccination with Gardasil and Cervarix	NCI	$50,000
Confirmation Studies of Blood-Based Biomarkers of Risk for Breast Cancer	NCI	$229,680*
Decisional Aid Intervention for Women Considering Breast Reconstruction	NCI	$200,000
Disruption of Ceramide Synthesis by CerS2 Depletion as a Tool to Increase Breast Cancer Sensitivity to Taxane Therapy	NCI	$15,000
Efficacy of HPV-16/18 Vaccine Against Oral HPV Infections	NCI	$50,000
Estrogen and Skin Cancer	NCI	$160,869*
Gallbladder Cancer Pilot Study	NCI	$150,000
Immune Markers of Protection by HPV Vaccination	NCI	$100,000
The Influence of Gender on the Relationship Between Mental Health and Smoking	NCI	$15,000
National Health and Nutrition Examination Survey (NHANES): Survey of Physical Activity Measures	NCI	$170,000
Natural History and Clinical Implications of Anal HPV Infections	NCI	$200,000
Nuclear Pore Complex Architecture and Drug Resistance in Ovarian Carcinomas	NCI	$82,208
Pilot Study of Somatic Mutations and Gene Fusions in Ovarian Cancer	NCI	$15,000
Regulatory T Cell Function in Ovarian Cancer	NCI	$15,000
Role of the Fractalkine Signaling in Epithelial Ovarian Carcinoma (EOC)	NCI	$202,968*
Single Nucleotide Polymorphisms (SNPs) in the Anti-inflammatory Cortisol Pathway and the Risk of Ovarian Cancer	NCI	$15,000
Stress, Immunity, and Cervical Cancer: Biobehavioral Outcomes of a Randomized Trial	NCI	$15,000
Survivorship Care Planning and Communication for Rural Breast Cancer Survivors	NCI	$160,950
Symposium: Opportunities and Changes in Cancer Research Among Women in Developing Countries	NCI	$5,000
Testing the Feasibility of a Nurse Patient Navigation Intervention in Lung Cancer	NCI	$20,000
Understanding the Cervical Cancer Health Gap for Women in Jail	NCI	$80,361
Urinary Estrogens and Estrogen Metabolites in Relation to Objective Measures of Physical Activity Among Controls in the NCI Polish Breast Cancer Study	NCI	$15,000
Videoconference CBT for Rural Breast Cancer Survivors with Cognitive Complaints	NCI	$170,338
Vitamin D Status, Gene Polymorphism, and Breast Cancer Progression/Prognosis	NCI	$77,710
Workshop: Postpartum Breast Remodeling, Lactation, and Breast Cancer Risk: Toward Improved Assessment and Prevention	NCI	$5,000

Table 2 (continued). ORWH-Cofunded Research Initiatives, FY 2011

Title	Institute or Center	Award Amount
Cardiovascular Disease Biomarkers and Mediation of Hormone Therapy Effects	NHLBI	$352,000*
Clinical Research United in Successful Enrollment—Workshop on Clinical Trials	NHLBI	$9,964
Endogenous Cardiac Repair in Humans	NHLBI	$40,000
Metabolism During Mechanical Circulatory Support in the Developing Heart	NHLBI	$20,000
Phytoestrogens, Insulin Resistance, and Endothelial Function	NHLBI	$238,669*
Sex Differences in Molecular Heterogeneity of Cardiac Repolarization	NHLBI	$231,240*
Sexual Dimorphism of Skeletal Muscle	NHLBI	$186,684*
Uterine-Specific Genetic Modification and Lymphangioleiomyomatosis	NHLBI	$50,000
A Biopsychosocial Investigation of Women's Health at Midlife	NIA	$200,000
Epigenetics of the Aging Astrocyte: Implications for Stroke	NIA	$100,000
Exploring Factors Influencing Gender Disparities in Access to Transplantation	NIA	$205,000
Gonadotropins in a Female Model of Age-Induced Hypertension	NIA	$230,250
Menopausal Symptoms Initiative—Finding Lasting Answers for Sweats and Hot Flashes	NIA	$200,000
Metabolic Syndrome as Women Undergo Menopausal Transition: A Multi-ethnic Study	NIA	$195,983
National Social Life, Health, and Aging Project	NIA	$200,000
Ovarian Hormone-Independent Sex Chromosome Effects in Menopause	NIA	$153,500
STRAW+10: Addressing the Unfinished Agenda of Staging Reproductive Aging	NIA	$3,500
Study of Women's Health Across the Nation—Coordinating Center	NIA	$125,000
SWAN Repository III	NIA	$200,000
SWAN: Study of Women's Health Across the Nation	NIA	$75,000
Ultra-Low-Dose Estrogen Gel for Vasomotor Symptoms in Women Failing Placebo or a Behavioral Intervention: A Randomized Trial (MSI-FLASH)	NIA	$200,000
Mechanisms for Estrogen-Dependent Myocardial Depressant Effect of Ethanol	NIAAA	$200,000
Airway Inflammation and Airway Remodeling	NIAID	$12,500
Airway Inflammation and HLA-G in Asthma	NIAID	$12,500
Autoimmunity Center of Excellence (ACE) at Stanford	NIAID	$30,000
Cervical/Vaginal Mucus and Microbicides	NIAID	$18,750
Congenital Transmission of Lineages I and II of *Trypanosoma cruzi*	NIAID	$10,000
Designing Optimal Microbicide Delivery Integrating Rheology and Acceptability	NIAID	$18,750
Development of a Novel Nanoparticle Pyrimidinedione Vaginal Polymeric Film as an Anti-HIV Microbicide	NIAID	$21,429
Development of an HIV-1 Entry Inhibitor Pre-drug as a Microbicide	NIAID	$18,750
Development of Antimicrobial Peptides as Topical Microbicides	NIAID	$21,428
Engineering Antiviral Innate Immunity for Safe and Effective Microbicides	NIAID	$21,429
Epithelial Barrier Programs in Asthma and Allergic Disease	NIAID	$12,500
Epithelial Genes in Allergic Inflammation	NIAID	$12,500
Exploring the Role of Vif Antagonists in Preventing Sexual HIV Transmission	NIAID	$21,429
Host and Viral Determinants of Infant and Childhood Allergy and Asthma	NIAID	$12,500
Mechanisms of Beta Cell Responses in Autoimmune Disease—ACE	NIAID	$30,000

Title	Institute or Center	Award Amount
Mucosal Tissue Explants as Surrogates for In Vivo Efficacy of Microbicides	NIAID	$18,750
Mucus-Penetrating Particles for Rectal Microbicides	NIAID	$18,750
Nanoparticle Microbicides for Delivery of Combination Antiretroviral Drugs	NIAID	$18,750
Oklahoma Autoimmunity Center of Excellence	NIAID	$30,000
Pathophysiologic and Therapeutic Mechanisms of Aspirin Exacerbated Respiratory Disorders	NIAID	$12,500
Phosphorothioate Oligonucleotides as Microbicides Against HIV Transmission	NIAID	$21,428
Plant-Produced Actinohivin as a Candidate HIV Microbicide	NIAID	$21,429
Role of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin in Asthma	NIAID	$12,500
The Semen Enhancer of HIV Infection as a Novel Microbicide Target	NIAID	$18,750
Sex Differences in Protective Immunity Against Influenza A Viruses	NIAID	$243,540
Sexual Dimorphism and Dysregulated Immune Responses in SLE: The Role of Leptin	NIAID	$231,000*
A Systems Biology Approach for Pediatric and Adult Autoimmune Diseases—ACE	NIAID	$30,000
T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy	NIAID	$12,500
Targeted siRNA Delivery as an Anti-HIV Microbicide	NIAID	$21,428
Thermostable Vaginal Probiotic Microbicide	NIAID	$18,750
Vitamin D and the Prevalence, Incidence, and Persistence of Bacterial Vaginosis	NIAID	$291,875*
Delayed Pubertal Development on the Mechanism of Bone Loss at Maturity	NIAMS	$73,440*
Epidemiology of Patellofemoral Pain Syndrome: Identifying Gender-Specific Risk Factors	NIAMS	$69,952*
FAK/Pyk2 Signaling Pathway and Bone Formation	NIAMS	$200,000
Fatigue and Lifestyle Physical Activity in SLE	NIAMS	$100,000
Health of Children Born by Mothers with Rheumatoid Arthritis	NIAMS	$193,877
HERV-K18 as a Risk Factor for CFIDS	NIAMS	$164,058
A Link Between Parity, Trunk Muscle Function, and Degenerative Spondylolisthesis	NIAMS	$159,833*
A New Hip Fracture Risk Prediction Tool Based on Common Predictors and Hip Geometry	NIAMS	$162,622
North American Rheumatoid Arthritis Consortium: The Genetics of Rheumatoid Arthritis	NIAMS	$175,363
Osteoarthritis Initiative	NIAMS	$650,000
Predictors of Pregnancy Outcome in SLE and APS	NIAMS	$192,240
Achieving a Critical Mass of Women Biomedical Faculty: Impact of Three U.S. Programs	NICHD	$175,144
Bench to Bedside: Adrenal Hyperplasia Among Adolescent Patients Polycystic Ovarian Syndrome	NICHD	$135,000
Brown/WIH Pelvic Floor Disorders Network Site	NICHD	$25,000
Cleveland Clinic Clinical Site	NICHD	$25,000
Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team	NICHD	$66,666
A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response	NICHD	$200,000
Empowering Daughters and Mother-in-laws to Mitigate Gender-Based Violence and Promote Women's Health in India	NICHD	$50,438

Table 2 (continued). ORWH-Cofunded Research Initiatives, FY 2011

Title	Institute or Center	Award Amount
Gender Equity-Focused, Male-Centered Family Planning for Rural India	NICHD	$60,559
Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women	NICHD	$83,333
Genetic Studies of Uterine Leiomyomata	NICHD	$83,334
Identification of Genes Predisposing to Pelvic Floor Disorders	NICHD	$66,667
India Human Development Survey	NICHD	$42,600
Interdisciplinary Research Training: NCD Epidemiology and Prevention in India	NICHD	$50,240
A Longitudinal Study of Loss of Imprinting in First Trimester CVS Samples Compared to Placental Samples at Birth	NICHD	$273,068
Molecular Basis of Treating Endometriosis by Prostaglandin E2 Receptor Inhibitors	NICHD	$200,000
Molecular Mechanism of LPA3-Mediated Uterine Receptivity	NICHD	$200,000
Novel Approaches for Disrupting Gene Expression in Mammalian Oocytes	NICHD	$200,000
ORWH/NICHD Leiomyoma Tissue Bank	NICHD	$50,000
Pelvic Floor Disorders Network Clinical Sites	NICHD	$25,000
Pelvic Floor Disorders Network: Duke University Medical Center	NICHD	$25,000
Pelvic Floor Disorders Network: University of California, San Diego	NICHD	$25,000
Perioperative Pelvic Floor Rehab: A Randomized Trial	NICHD	$25,000
Phospholipid-Reactive T Cells in Pregnancy Loss	NICHD	$77,000
Pittsburgh Pelvic Floor Research Program	NICHD	$25,000
Prostaglandin E2 Signaling in Growth and Pains of Endometriosis	NICHD	$219,750*
RCT of Hypnotherapy vs. Tpolterodine for OAB: Voiding and Brain Activation Changes	NICHD	$25,000
Tailored Outcomes for Female Urinary Incontinence	NICHD	$217,790
Uterine Leiomyoma Research Center Program	NICHD	$250,000
Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and Its Association with Incidence, Progression, and Recurrence of Pelvic Floor Disorders	NICHD	$66,667
Workshop on the Health Impacts of Indoor Air Pollution in Developing Countries	NICHD	$7,854
Xenograft Study on Growth-Control of Human Uterine Leiomyomata	NICHD	$83,333
Genes, Gendered Contexts, and Substance Use Outcomes	NIDA	$184,065
NIH Pain Consortium Centers of Excellence in Pain Education (CoEPEs)	NIDA	$50,000
Comorbid Chronic Pain Conditions—Mechanisms, Diagnosis, and Treatments	NIDCR	$28,740
International Research Registry Network for Sjögren's Syndrome	NIDCR	$150,000
Bench to Bedside: Role of Androgen and Estrogen Receptor Signaling in Pulmonary Arterial Hypertension	NIDDK	$110,000
Diabetes Prevention Program Outcomes Study	NIDDK	$900,000
Intestinal Satiation in Roux-en-Y Gastric Bypass Rats: Brain Mechanisms and Sex Differences	NIDDK	$200,000
Lifestyle Interventions in Overweight and Obese Pregnant Women	NIDDK	$100,000
The Look AHEAD Continuation: Action for Health in Diabetes	NIDDK	$100,000
Microbiomes of Interstitial Cystitis	NIDDK	$50,000
Ovarian Hormone Suppression and Regulation of Adipogenesis in Women	NIDDK	$229,500

Title	Institute or Center	Award Amount
Sensory Sensitivity and Urinary Symptoms in the Female Population	NIDDK	$50,000
Urinary Incontinence Treatment Network: DCC	NIDDK	$100,000
Weight Management in Obese Pregnant Underserved African American Women	NIDDK	$100,000
Pharmacogenetics of Phase II Drug Metabolizing Enzymes	NIGMS	$240,292
Oklahoma Native American Research Centers for Health (NARCH VI)	NIGMS/IHS	$100,000
Research to Improve Preconception Health of Adolescent Women (NARCH VI)	NIGMS/IHS	$128,436
Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia	NIMH	$99,833
Effects of Estrogen on Brain Morphology and Neuronal Integrity in Early Menopause	NINDS	$191,541*
Modifiable Risk Factors in Stroke Incidence and Mortality Among Women	NINDS	$243,441*
Neuropathologic Abnormalities Define a Subgroup of Patients with CFS	NINDS	$189,405
p38 MAPK as a Female-Specific Drugable Target in CNS Autoimmune Disease	NINDS	$228,750*
Sex Differences in the CNS During Disease	NINDS	$188,650*
Advancing Transdisciplinary Translation for Prevention of High-Risk Behaviors	NINR	$50,000
The Science of Compassion: Future Directions in End-of-Life and Palliative Care	NINR	$2,500
AIDS International Training and Research Program: University of North Carolina at Chapel Hill	FIC	$20,000
AIDS International Training and Research Program: University of Pittsburgh	FIC	$20,000
China-Rochester Suicide Research Training Program (CRSRT)	FIC	$10,000
Emory AIDS International Training and Research Program	FIC	$20,000
Enhancing Training, Research Capacity, and Expertise in HIV Care (ENTRÉE)	FIC	$60,000
Haiti AIDS Research Training: Models to Implementation	FIC	$20,000
Medical Education for Services to All Ugandans (MESAU)	FIC	$60,000
Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum* and *P. vivax* in Yunnan and Hainan, China	FIC	$50,000
Programmatic: Expanding Innovative Multidisciplinary Medical Education in Zambia	FIC	$60,000
Programmatic: Novel Education Clinical Trainees and Researchers (NECTAR) Program	FIC	$60,000
QUIPU: The Andean Global Health Informatics Research and Training Center	FIC	$10,000
Training Program on Operational and Health Services Research for Malaria in Mali	FIC	$16,743
The Universidade Eduardo Mondlane/University of California, San Diego Medical Education Partnership	FIC	$60,000
Vanderbilt University-CIDRZ AIDS International Training And Research Program	FIC	$20,000
Weight, Diet, Genes, and CVD Risk Factors (Hypertension and Diabetes)	FIC	$50,000
Acupuncture for Aromatase Inhibitor-Related Arthralgias in Breast Cancer Patients	NCCAM	$200,000
Identification of Novel Phytoprogestins from Hops and Red Clover	NCCAM	$194,287
Emotions Are Emergent Events Constrained by Affective and Conceptual Processes	OD/DPCPSI	$192,431

*Part of the ANSWHR program partnership.

Table 3. ORWH-Cofunded Research Initiatives, FY 2012

Title	Institute or Center	Award Amount
Assisted Reproductive Technology and Risk of Childhood Cancer	NCI	$18,750
Bedside to Bench—Molecular Epidemiology of Postpartum Involution of the Breast: Demonstration of Tools for Understanding Influences of Pregnancy on Breast Cancer Risk	NCI	$90,000
California Health Interview Survey	NCI	$200,000
DCEG/EBP Intramural—Follow-up of DES Cohorts	NCI	$18,750
Definition of Microenvironment in Breast Cancer	NCI	$18,750
Feasibility of Community-Based Tampon Self-Sampling to Prevent Cervical Cancer	NCI	$200,000
Feasibility of Virtual Agent Cervical Cancer Education for Hispanic Farmworkers	NCI	$100,000
HPV Vaccine Development and Evaluation	NCI	$400,000
International Pooling Project of Mammographic Density	NCI	$49,267
Low-Dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction	NCI	$18,750
Molecular Mechanisms of BRCA1-Dependent DNA Damage Response and Tumorigenesis	NCI	$18,750
National Longitudinal Mortality Study	NCI	$200,000
P3K, Retroviral Oncogene, and Homolog of PI 3-Kinase	NCI	$18,750
PET-MRI for Assessing Treatment Response in Breast Cancer Clinical Trials	NCI	$18,750
Pharmacotherapy Evaluation Tools for Improving Breast Cancer Outcomes in Rural Appalachia	NCI	$200,000
Research and Studies on the Effects of Inflammation in Gall Bladder Cancer	NCI	$200,000
Roles of EGFR and miR-143/miR-145 in Western Diet-Promoted Colonic Tumorigenesis	NCI	$150,000
Understanding and Preventing Breast Cancer Disparities in Latinas	NCI	$18,750
Using Technology to Promote Activity in Women at Elevated Breast Cancer Risk	NCI	$67,371
Broad Spectrum Molecular Therapy for Blinding Retina Disorders	NEI	$150,000
Surveillance and Treatment of Community Newcomers and Travelers for Trachoma Control	NEI	$40,000
Avoiding Toxicity Associated with MTP Ablation	NHLBI	$20,000
Endogenous Cardiac Repair in Humans	NHLBI	$72,000
A Formative Examination of the Health and Safety of Female Firefighters	NHLBI	$199,800
Molecular Mechanism of Platelet Dense Granule Biogenesis	NHLBI	$20,000
Premenstrual Syndrome and Risk of Subsequent Hypertension	NHLBI	$195,117
Saturated Fat and Protein Effects on Atherogenic Dyslipidemia	NHLBI	$200,000
Uterine-Specific Genetic Modification and Lymphangioleiomyomatosis	NHLBI	$50,000
Effects of Aging on Visual Memory: Neuroimaging Studies	NIA	$200,000
Hypertension, Angiotensin Receptor Blockers, and Cognition: Effects and Mechanism	NIA	$200,000
Menopausal Symptoms Initiative—Finding Lasting Answers for Sweats and Hot Flashes	NIA	$200,000
National Social Life, Health, and Aging Project	NIA	$200,000
The Role of Vascular Aging in Cognitive and Physical Function	NIA	$300,000
Study of Women's Health Across the Nation—Coordinating Center	NIA	$125,000
SWAN: Study of Women's Health Across the Nation	NIA	$75,000

Title	Institute or Center	Award Amount
Ethanol-Induced Conditioned Partner Preference in Mice	NIAAA	$205,000
Pharmacokinetics and Pharmacological Effects of Alcohol After Bariatric Surgery	NIAAA	$258,709
Role of MSK1, Era, and Brf1 in Alcohol-Associated Breast Cancer	NIAAA	$205,000
Airway Inflammation and Airway Remodeling	NIAID	$12,500
Airway Inflammation and HLA-G in Asthma	NIAID	$12,500
Autoimmunity Center of Excellence (ACE) at Stanford	NIAID	$30,000
Cervical/Vaginal Mucus and Microbicides	NIAID	$18,750
Designing Optimal Microbicide Delivery Integrating Rheology and Acceptability	NIAID	$18,750
Development of an HIV-1 Entry Inhibitor Pre-drug as a Microbicide	NIAID	$18,750
Epithelial Barrier Programs in Asthma and Allergic Disease	NIAID	$12,500
Epithelial Genes in Allergic Inflammation	NIAID	$12,500
Host and Viral Determinants of Infant and Childhood Allergy and Asthma	NIAID	$12,500
Mechanisms of B Cell Responses in Autoimmune Disease	NIAID	$30,000
Mucosal Tissue Explants as Surrogates for In Vivo Efficacy of Microbicides	NIAID	$18,750
Mucus-Penetrating Particles for Rectal Microbicides	NIAID	$18,750
Nanoparticle Microbicides for Delivery of Combination Antiretroviral Drugs	NIAID	$18,750
Oklahoma Autoimmunity Center of Excellence	NIAID	$30,000
Pathophysiologic and Therapeutic Mechanisms of Aspirin Exacerbated Respiratory Disorders	NIAID	$12,500
Role of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin	NIAID	$12,500
The Semen Enhancer of HIV Infection as a Novel Microbicide Target	NIAID	$18,750
A Systems Biology Approach for Pediatric and Adult Autoimmune Diseases	NIAID	$30,000
T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy	NIAID	$12,500
Thermostable Vaginal Probiotic Microbicide	NIAID	$18,375
NIH Osteoporosis and Related Bone Diseases—National Resource Center	NIAMS	$50,000
Osteoarthritis Initiative	NIAMS	$650,000
Predictors of Pregnancy Outcome in SLE and APS	NIAMS	$200,000
Role of B Cells and DCs in Lupus Pathogenesis	NIAMS	$200,000
Sex-Specific Movement Differences in Young Adults with and Without Hip Pain	NIAMS	$184,162
Steroid-Based Contrast Agents for Magnetic Resonance Imaging of Endocrine Disease	NIBIB	$250,000
Achieving a Critical Mass of Women Biomedical Faculty: Impact of Three U.S. Programs	NICHD	$175,144
Brown/WIH Pelvic Floor Disorders Network Site	NICHD	$25,000
Cleveland Clinic Clinical Site	NICHD	$25,000
A Collaborative Workshop Across the Scientific Disciplines	NICHD	$10,000
Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team	NICHD	$66,666
Consortium to Evaluate a Novel Violence Prevention Program on College Campuses	NICHD	$180,193
A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response	NICHD	$200,000
Effect of Feeding Buddies on Adherence to WHO PMTCT Guidelines in South Africa	NICHD	$300,000
Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women	NICHD	$83,333
Identification of Genes Predisposing to Pelvic Floor Disorders	NICHD	$66,667

Table 3 (continued). ORWH-Cofunded Research Initiatives, FY 2012

Title	Institute or Center	Award Amount
Mothers and Others: Family-Based Obesity Prevention for Infants and Toddlers	NICHD	$100,000
ORWH/NICHD Leiomyoma Tissue Bank	NICHD	$50,000
Pelvic Floor Disorders Network	NICHD	$25,000
Pelvic Floor Disorders Network Clinical Sites	NICHD	$25,000
Pelvic Floor Disorders Network: Duke University Medical Center	NICHD	$25,000
Perioperative Pelvic Floor Rehab: A Randomized Trial	NICHD	$25,000
A Pharmacokinetic Evaluation of Levonorgestrel Implant and Antiretroviral Therapy	NICHD	$150,734
Pittsburgh Pelvic Floor Research Program	NICHD	$25,000
RCT of Hypnotherapy vs. Tpolterodine for Overactive Bladder: Voiding and Brain Activation Changes	NICHD	$25,000
Unintended Birth, Fetal, and Infant Loss and Maternal Depressive Symptoms	NICHD	$81,000
Uterine Leiomyoma Research Center Program	NICHD	$250,000
Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and Its Association with Incidence, Progression, and Recurrence of Pelvic Floor Disorders	NICHD	$66,667
Xenograft Study on Growth-Control of Human Uterine Leiomyomata	NICHD	$83,333
NIH Pain Consortium Centers of Excellence in Pain Education (CoEPEs)	NIDA	$200,000
Novel Assessment of Maternal Distress Tolerance Underlying Substance Use Relapse	NIDA	$228,000
Bedside to Bench—Role of Androgen and Estrogen Receptor Signaling in Pulmonary Arterial Hypertension	NIDDK	$80,000
Diabetes Prevention Program Outcomes Study	NIDDK	$1,050,000
Glycated CD59 as a Novel Biomarker of Gestational Diabetes Mellitus	NIDDK	$200,000
Lifestyle Interventions in Overweight and Obese Pregnant Women	NIDDK	$100,000
The Look AHEAD Continuation: Action for Health in Diabetes	NIDDK	$100,000
Molecular Basis of *E. coli* Adhesins in Bladder Disorders	NIDDK	$200,000
Ovarian Hormone Suppression and Regulation of Adipogenesis in Women	NIDDK	$191,250
Urinary Incontinence Treatment Network: DCC	NIDDK	$100,000
Weight Management in Obese Pregnant Underserved African-American Women	NIDDK	$100,000
Dioxin Exposure and the Invasive Pathogenesis of Endometriosis	NIEHS	$250,000
Ex Vivo Female Reproductive Tract Integration in a 3D Microphysiologic System	NIEHS	$300,000
Pharmacogenetics of Phase II Drug Metabolizing Enzymes	NIGMS	$237,958
Oklahoma Native American Research Centers for Health (NARCH VI)	NIGMS/IHS	$100,000
Research to Improve Preconception Health of Adolescent Women (NARCH VI)	NIGMS/IHS	$128,436
Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia	NIMH	$189,455
Course and Predictors of Depressive Relapse During IVF	NIMH	$248,607
The Influence of Estrogen on the Fear Extinction Network in Humans	NIMH	$100,000
Trajectories of Reward Sensitivity and Depression Across Adolescence	NIMH	$200,000
Treatment of PTSD in Residents of Battered Women's Shelters	NIMH	$300,000
Scientific Conference R13	NIMHD	$1,000
Brainstem Pain-Modulating Systems in Migraine-Related Photophobia	NINDS	$300,000
Neuropathologic Abnormalities Define a Subgroup of Patients with CFS	NINDS	$66,509
AIDS International Training and Research Program	FIC	$25,000

Title	Institute or Center	Award Amount
Emory AIDS International Training and Research Program	FIC	$25,000
Fogarty Global Health Fellows Coordinating Center	FIC	$190,000
Global Health Fellows and Scholars Research Training	FIC	$40,000
Haiti AIDS Research Training: Models to Implementation	FIC	$25,000
Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum* and *P. vivax* in Yunnan and Hainan, China	FIC	$50,000
Northern/Pacific Universities Global Health Research Training Consortium	FIC	$40,000
Tobacco Control Network Among Women in Parana, Brazil	FIC	$100,000
University of California Global Health Institute Program for Fellows and Scholars	FIC	$190,000
Vanderbilt University-CIDRZ AIDS International Training and Research Program	FIC	$25,000
Vanderbilt-Emory-Cornell-Duke Consortium for Global Health Fellows (VECDor)	FIC	$40,000
Brain-Centered Therapy vs. Medication for Urgency Urinary Incontinence—A Randomized Clinical Trial	NCCAM	$100,000

II. ORWH Interdisciplinary Research and Career Development Programs

ORWH initiated its research and career development programs in women's health based on a paradigm that views interdisciplinary approaches as essential to moving forward the science associated with women's health and to increasing understanding the contributions of sex and gender to human health and disease. ORWH has recognized that the study of women's health across the lifespan required approaches that bridge and incorporate basic, clinical, and translational science and that integrate new models of collaboration, institutional support, and new ways of evaluating those who conduct such research. ORWH continues to support innovative ways to encourage collaborative, interdisciplinary research that is team based to improve women's health through two signature initiatives, the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program and the Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health. The activities of these signature initiatives for FY 2011–FY 2012 are described in this section.

Building Interdisciplinary Research Careers in Women's Health

ORWH designed, developed, and implemented the BIRCWH K12 Program in 1999 to increase the number of women's health researchers working in a mentored interdisciplinary environment. BIRCWH supports junior faculty members who have recently completed clinical training or postdoctoral fellowships and who are beginning basic, translational, clinical, and/or health services research related to women's health research by pairing junior researchers with senior investigators. BIRCWH is built around three pillars: strong mentoring, interdisciplinary research, and career development. Programs accomplish these goals by ensuring that mentors represent diverse disciplines needed to carry out interdisciplinary projects that will bridge training with research independence for BIRCWH scholars.

To date, ORWH has made 77 awards to 39 academic institutions that have sponsored over 493 junior faculty scholars in more than 25 states in the United States. The program continues to expand the network of scientists and clinicians who have the interdisciplinary research skills needed to further the study of women's health and sex differences. Currently, there are 29 active BIRCWH programs across the country. The majority of scholars have gone on to receive funding from NIH, research foundations, or the industry.

ORWH is responsible for the programmatic aspects of the BIRCWH program, but the grants management aspects reside within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The first BIRCWH grants were awarded in FY 2000. Since that time ORWH has issued five additional requests for applications (RFAs). Over the past decade, ORWH has been joined in its funding support by the Agency for Healthcare Research and Quality (AHRQ) and many NIH ICs, including the National Cancer Institute (NCI), the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NICHD, the National Institute on Drug Abuse (NIDA), the National Institute on Environmental Health Sciences (NIEHS), the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), and the NIH Office of Dietary Supplements (ODS). ORWH provided over $11 million per year in funding to the program in FY 2011 and FY 2012.

BIRCWH Accomplishments as of FY 2011–FY 2012

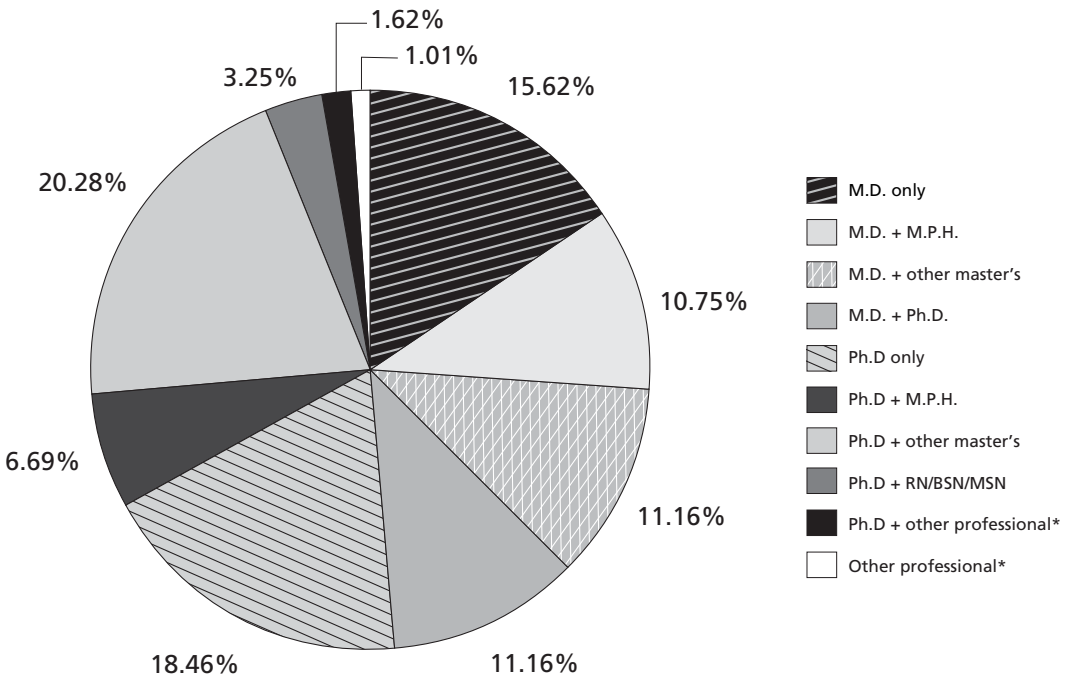
A primary goal of the BIRCWH program is to support scholars by providing them with protected time to do their research and to achieve research independence. As of November 1, 2012, a total of 493 individuals had participated in the program as scholars. While the BIRCWH program is open to both women and men, 81 percent of the BIRCWH scholars were women as of the beginning of November 2012. Of these, 123 (25 percent)

were currently active BIRCWH scholars. Of the remaining group, 335 scholars (68 percent) had completed their BIRCWH program, while 35 (7.0 percent) had withdrawn before completing it. The data that follow provide additional information on the scholars, focusing on the individuals who successfully completed the program, and submitted and obtained NIH research project grants. The information is based on data maintained by ORWH and the NICHD Office of Science Policy, Analysis and Communication:

Descriptive Data on BIRCWH Scholars

- Most BIRCWH scholars spend about 2 years in the program.
- 38 percent of BIRCWH scholars have M.D. degrees, 50 percent have a Ph.D., 11 percent have both an M.D. and a Ph.D., and 1 percent have some other professional degree (see figure below).
- 335 scholars (those who completed training) were tracked for subsequent grant activity.
- BIRCWH scholars, as a group, submitted more than 1,500 competitive NIH research applications. (See list below for grant types.)
- 79 percent of BIRCWH scholars submitted at least one NIH grant application 12 or more months after their BIRCWH start date.
- Of those that applied, 64 percent of scholars received at least one grant. This amounts to 51 percent of all BIRCWH scholars.
- 68 percent of BIRCWH scholars applied for a research grant.
- Of those that applied, 52 percent of scholars received at least one research grant. This amounts to 35 percent of all scholars.

Figure 1. BIRCWH Scholar Degrees



*Other professional degrees include Pharm.D., Dr.P.H., D.D.S., and D.V.M.

- Most BIRCWH scholars received their first grant within 2 to 5 years of their BIRCWH start date, with an average of 3 years. Those that received R01 grants received them an average of 4 years after the BIRCWH start date.
- Subsequent applications from BIRCWH scholars were directed at nearly all NIH ICs, with NCI, NHLBI (National Heart, Lung, and Blood Institute), and NICHD receiving the highest shares.
- In general, men and women applied for and received subsequent grants at the same rates and within the same timeframes, with the following exceptions:

  For individual K awards only, a greater percentage of women than men applied, but success rates did not different significantly by gender.

  For R01s only, women had higher application-based success rates than did men.

NIH Funding Success Rates for BIRCWH Scholars by Type of Grant[1]:

- Of those that applied, 63 percent of BIRCWH scholars who submitted individual K applications got funded.
- 52 percent of BIRCWH scholars who submitted research applications[2] were funded.
- 51 percent of BIRCWH scholars who submitted R-series applications were funded.
- 41 percent of BIRCWH scholars who submitted R01 applications were funded.
- Awards were primarily from NCI, NHLBI, NIA, NICHD, NIDA, NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases), and NIMH.

In addition, scholars have received Federal funding from other HHS agencies such as AHRQ as well as grants from numerous academic, foundation, and industry sources. In addition to success in securing funding, scholars are progressing up the academic pipeline. Based on the latest data from an ORWH evaluation, as of March 2011, BIRCWH scholars had published over 4,800 publications since the inception of the program. These publications have spanned the entire spectrum of women's health. A list of selected 2011–2012 publications by BIRCWH scholars can be found in Appendix D.

Highlights of BIRCWH Principal Investigators and Accomplishments of the Programs

The BIRCWH principal investigators (PIs), who are leaders in the field of women's health, are contributing to the impact that the BIRCWH programs have at their institutions by promoting strong and positive mentoring as essential to the success of junior faculty in the biomedical and behavioral sciences. For example, in FY 2011, Dr. Stacie Geller, PI of the University of Illinois at Chicago (UIC) BIRCWH program, was a winner of a Presidential Award for Excellence in Science, Mathematics & Engineering Mentoring for the UIC WISE (Women in Science and Engineering) mentoring program. In addition, the BIRCWH PIs have formed a writing group to publish on best practices and lessons learned from interdisciplinary mentoring and career development under the BIRCWH grant. The first manuscript from the BIRCWH program summarized best practices in interdisciplinary career development and the various strategies used by programs to support and encourage scholars' productivity in submitting and applying for grants and publishing articles in women's health (Domino, Bodurtha, & Nagel, 2011). Examples of strategies included Vanderbilt University's "manuscript sprint," in which teams of four or five scholars from different disciplines participate in a structured exercise over a set time period to prepare individual manuscripts that are finalized and edited. Other strategies included writing workshops, mock study sections, and forming K clubs and groups with other K awardees at institutions. The second manuscript from the BIRCWH writing group was published in November 2012 and highlighted best practices in interdisciplinary mentoring from all 29 active BIRCWH programs. The authors found,

[1] Only completed scholars were included in this analysis, and the data does not include those who went on to other K12 programs.

[2] Research applications include the R, P, and U series.

based on an electronic survey and in-person presentations, that the majority of programs conducted formal evaluations of mentorship, and 79 percent of programs offered training in mentorship for either scholars, mentors, or both, which is very encouraging (Guise, Nagel, & Regensteiner, 2012).

BIRCWH V Program Sites and Principal Investigators 2010 Awards

In FY 2009, ORWH reissued the BIRCWH RFA (RFA-OD-09-006); this fifth round of awards was made in July 2010. Over $6 million was awarded to 13 new or continuing BIRCWH programs through funding from ORWH, 7 ICs, and ODS. Nine of these programs were competitively renewed, and 4 were new centers, providing for a total of 29 active awards during this time period. These programs are now in their fourth year and will enter their final year in FY 2014. The BIRCWH V programs sites and principal investigators funded in FY 2010 are listed in the table below and detailed program descriptions follow.

BIRCWH V Program Abstracts (FY 2010)

Institution:
Brigham and Women's Hospital

Principal Investigator:
Jill Goldstein, Ph.D.

Women and men are at different risks for the onset, expression, and treatment response in a number of disorders that occur at different stages of development and throughout aging. The mechanisms that explain these sex differences or disorders specific to women are still unclear. The mission of the Brigham and Women's Hospital (BWH)/Harvard University BIRCWH is to develop the next generation of scientist-clinicians as leaders in the field of women's health who will contribute to understanding sex-specific vulnerabilities to clinical disorders and those disorders specific to women. This integrated interdisciplinary training program is based on a translational approach to understanding differential

Table 1. BIRCWH V Program Sites and Principal Investigators (FY 2010–FY 2014)

BIRCWH V Institution	Principal Investigator
Brigham and Women's Hospital	Jill Goldstein, Ph.D.
Mayo Clinic	Rebecca Bahn, M.D.
Michigan State University	Mary Nettleman, M.D., M.P.H.
University of California, Davis	Claire Pomeroy, M.D., M.B.A.
University of California, San Francisco	Mary Anne Koda-Kimble, Pharm.D.
University of Cincinnati	Joel Tsevat, M.D., M.P.H
University of Kansas Medical Center, Kansas City	Patricia Thomas, M.D.
University of Michigan, Ann Arbor	Timothy Johnson, M.D.
University of North Carolina at Chapel Hill	Eugene Orringer, M.D.
University of Rochester Medical Center	Shanna Swan, Ph.D.
University of Texas Medical Branch at Galveston	Abbey Berenson, M.D.
Washington University in St. Louis	Clay Semenkovich, M.D.
Yale University	Carolyn Mazure, Ph.D.

incidences of specific disorders important for women's health. The program is modeled in the context of a lifespan perspective to identify etiologic mechanisms during fetal development, puberty, adulthood, and aging, with some focus on female-specific periods such as childbearing years and menopause. Further, an underlying assumption of our BIRCWH program is that an understanding of the role of hormones and genes will provide the basis for understanding sex-specific vulnerabilities to clinical disorders. The Connors Center for Women's Health & Gender Biology at BWH is and will continue to be the home site for this endeavor, in the broader context of a Harvard-wide training program. Each scholar is assigned a team of mentors in order to operationalize the concept of training scholars to think in a translational manner. The BWH/Harvard BIRCWH program focuses on the following disorders, given either the known higher incidence in women than in men and/or differential expression in women, or the strengths of the Harvard community in women's health: cardiovascular disorders; reproductive endocrine and neuroendocrine disorders; neuropsychiatric disorders; autoimmune disorders; and female cancers (e.g., breast, ovarian, and uterine). Their research programs will provide scholars with the basis for the development of sex-specific treatment approaches and public awareness as to the importance of these sex-specific health issues for families and society.

Institution:
Mayo Clinic

Principal Investigator:
Rebecca Bahn, M.D.

Embedded in the design of the Mayo Clinic Interdisciplinary Women's Health Research (IWHR) Program are each of the overarching themes of the BIRCWH program, including interdisciplinary research in women's health; genetic, hormonal, and environmental determinants of sex/gender differences; and health conditions disproportionately affecting women across their lifespan. A special strength of the Mayo Clinic is the collaborative and interdisciplinary nature of our clinical, educational, and research activities that form the core of our patient-centered institution. Thus, the theme of our IWHR program is interdisciplinary research. This theme is exemplified by the diversity of research topics and mentors, many of whom have established collaborations with other IWHR faculty and across disciplines and departments. The scope of our program includes research training in basic and clinical sciences centered on the prevention and treatment of conditions or diseases (1) unique to women; (2) disproportionately impacting women; or (3) expressed differently in women compared to men. Within this scope lie our specific areas of research focus: autoimmunity, cardiovascular diseases, endocrine/metabolic, gastrointestinal, neuro/musculoskeletal, reproductive/gynecologic disorders, and pain management/quality of life/outcomes. Members of the IWHR program faculty were selected for their existing collaborative research programs both within and outside of Mayo, the excellence and significance of their programs to advancing women's health, and their interest and success record as a mentor/educator in interdisciplinary research.

Institution:
Michigan State University

Principal Investigator:
Mary Nettleman, M.D., M.P.H.

The ultimate goal of the BIRCWH program at Michigan State University (MSU) is to increase the number and diversity of researchers in women's health by providing an inspiring and supportive environment for accomplishment and advancement. The University and the College of Human Medicine (lead college) have pledged matching funds to allow recruitment of additional scholars and to encourage participation of physician-scientists. The MSU BIRCWH program is founded on key strengths of the institution, including the Center for Breast Health and the Environment and the Center for Women's Health and Reproduction, both of which will provide mentorship and a supportive environment for scholars. BIRCWH mentors are internationally recognized senior researchers who are experienced and skilled mentors. The mentors have been chosen

to reflect the overarching theme of health across the lifespan and the dimensions that influence health: biology, environment, and behavior. The MSU Office of Inclusion has agreed to partner directly with the administrative team to ensure that the program is attractive to women and minority researchers. Each scholar will work with a primary research mentor and a secondary mentor. Each of the mentors has a defined role to ensure an organized, interdisciplinary research experience. The mentored research training and the curriculum are designed to give scholars the skills to compete for external grant funding. The MSU BIRCWH program will support scholars at a time in their careers when they are at highest risk to leave research.

Institution:
University of California, Davis

Principal Investigator:
Claire Pomeroy, M.D., M.B.A.

Over the past 4 years, the University of California, Davis (UC Davis) BIRCWH program has trained a cadre of diverse interdisciplinary researchers in women's health and raised the stature of women's health research at our university. We now propose to build on this strong foundation to create a next-generation BIRCWH program that will further increase the innovation and impact of this initiative. The goal of the UC Davis BIRCWH program is to create an academically stimulating and nurturing environment for women's health researchers that facilitates career development and encourages paradigm-shifting interdisciplinary collaboration and research approaches. We will build on the best practices of our well-received curriculum, which combines (1) mentored research and career development support, (2) core didactic courses, (3) supplemental didactic training tailored to the individual scholar's needs, and (4) special interdisciplinary BIRCWH experiences. The innovative aspects of our BIRCWH program include journal clubs and work-in-progress meetings that are integrated with other training programs, monthly breakfast meetings with the VC/Dean for BIRCWH mentors and scholars to review progress, and a biannual symposium of Northern California BIRCWH programs. New advances in this renewal include our proposed BIRCWH Mentoring Academy to optimize the mentoring experience for both mentors and scholars, and expansion of our faculty mentors to additional campus disciplines. Scholars will be supported to develop a unique research experience using our new matrix approach to women's health research, with four research focus areas (neurosciences/behavioral; musculoskeletal/aging; nutrition and metabolic/ inflammatory syndromes; and cancer), intersecting with cross-cutting themes (continuum across the lifespan, sex/gender determinants, health disparities/differences and diversity, and interdisciplinary research), and embracing foundational approaches of prevention and treatment as well as the biological and behavioral bases of sex and gender differences. Our scholars and mentors will define transformative interdisciplinary approaches to women's health research, allowing new insights into the lifelong continuum of sex and gender determinants of illness and wellness and reduction of health disparities.

Institution:
University of California, San Francisco

Principal Investigator:
Mary Anne Koda-Kimble, Pharm.D.

The University of California, San Francisco (UCSF) BIRCWH program is multidisciplinary, including scholars and faculty mentors from each of the UCSF schools and Kaiser DOR. It emphasizes novel interdisciplinary approaches to a wide range of women's health issues. The program will continue its strong initiatives in women's cancer, bone disease, and menopause. New foci draw upon the unique strengths of UCSF and Kaiser DOR and include occupational and environmental health; addiction, violence, and traumatic stress; aging and dementia; autoimmunity; metabolism and obesity; maternal health and child outcomes; and muscular and skeletal health. A multidisciplinary advisory committee oversees the program in partnership with leadership, including selection of new BIRCWH scholars. The program emphasizes multidisciplinary

mentoring teams that cross disciplines and research methodologies. The diversity of scholars, in terms of fields of interest, background, training, ethnicity, and gender is a priority. A special emphasis for this renewal is placed on the cultural and ethnic diversity of scholars and affiliated faculty. BIRCWH scholars participate in program-specific seminars, assessments of progress, and mentoring activities. In addition, the program integrates UCSF Clinical and Translational Science Institute career development and training programs. This renewal features a new emphasis on leadership development that will assess the academic progress of BIRCWH alumni and facilitate leadership training for those who qualify. The UCSF-Kaiser DOR BIRCWH program provides career development mentoring and training of scholars as independent women's health scientists, broadens the range of women's health research, and supports the development of academic leaders in women's health.

Institution:
University of Cincinnati

Principal Investigator:
Joel Tsevat, M.D., M.P.H.

The mission of this program is to identify and train junior faculty members within the University of Cincinnati (UC) College of Medicine and the Cincinnati Children's Hospital Medical Center (CCHMC). The two institutions are located across the street from each other and share faculty, with all CCHMC faculty having appointments at UC. The two institutions also share a common NIH Institutional Clinical and Translational Science Award (CTSA), funded in April 2009. The academic home for the CTSA is the Center for Clinical and Translational Science and Training (CCTST). Our first BIRCWH award was based in the department of obstetrics and gynecology, but we trained scholars from many departments, including internal medicine, psychiatry, surgery, cell biology, and pediatrics. Thus, for the renewal, we will house the BIRCWH K12 program in the CCTST, through which BIRCWH K12 scholars will have access to administrative support and a vast array of research resources, including study design, database management, data analysis, pilot funding, research education, and regulatory support. The CCTST also runs the CTSA KL2 Research Scholars program and has a very successful K23 preparation process. We have assembled a cadre of mentors who have a track record of mentoring in women's health, and their own protected time for mentorship. We also plan to institute a mentor-in-training program for mid-career faculty who are beginning to mentor others.

Nationally, there is a major unmet need for training clinical and basic science trainees and faculty to conduct research in women's health. Through mentored research and coursework, the Cincinnati BIRCWH K12 program will continue to train leaders in women's health research.

Institution:
University of Kansas Medical Center, Kansas City

Principal Investigator:
Patricia Thomas, M.D.

Among the faculty at the University of Kansas are a group of very talented scientists pursuing women's health research in the schools of Allied Health, Medicine, Nursing, Pharmacy and Engineering. The existence of this talented research base in women's health ignited the interest of our leadership and resulted in the University of Kansas Medical Center (KUMC) BIRCWH Faculty Development Program (2005–2010) to formally establish and strengthen the women's health research enterprise at the University of Kansas. All four schools and others on the main campus are partners in this proposed renewal. Interdisciplinary research among schools is strongly emphasized. The KUMC Schools of Allied Health and Nursing are strong partners with Medicine and Pharmacy, ranking 12th and 31st in the nation, respectively, for NIH funding. Mentors are in five thematic areas related to women's health: (1) women's reproductive health; (2) maternal health; (3) pathogenesis of diseases prevalent in women; (4) drug design, drug delivery, and pharmacogenomics; and (5) prevention, intervention, and

health disparities. Our long-term objective is to foster career development of junior faculty pursuing basic, translational, behavioral, clinical, and health services research relevant to women's health at the University of Kansas. In addition, interactions of mentors from multiple disciplines occurring during training of IWHR scholars has fostered new research collaborations related to women's health among established faculty and heightened awareness of the need for women's health research at our institution.

Institution:
University of Michigan, Ann Arbor

Principal Investigator:
Timothy Johnson, M.D.

The goal of the Michigan BIRCWH is to develop a cadre of new junior faculty scholars through a mentored scholarly research experience leading to independent scientific careers addressing interdisciplinary women's health concerns. The University of Michigan has a broad interest and significant expertise in women's health evidenced in the Institute for Research on Women and Gender (IRWG). We propose to train a total of four scholars with a minimum of two clinician scientists and one or two nonclinical postdoctoral scientists per year for a minimum of 2 years each. Recruitment and selection will focus on identifying scholars with superior academic potential and scientific skills with special attention to achieving a diversity of scholars and scholarship. Each scholar will have an assigned research mentor: an established, independent investigator with a proven track record who has been selected for his/her commitment and support of junior colleagues in their development to independence. We will target scholars' four areas of special interest: (1) pelvic floor/urogynecology research; (2) health services research; (3) reproductive science and women's medicine; and (4) biobehavioral and aging research. An individualized career development plan will be developed with each scholar and their primary research mentor along with a departmental/disciplinary mentor and a third senior interdisciplinary mentor. All scholars participate in the monthly "First Tuesday Women's Health" interdisciplinary research seminar series at the IRWG. Access to faculty career development programs, advanced courses in biomedical research, biostatistics, epidemiology, and research methodology assistance will be available as appropriate for individual scholar needs.

Institution:
University of North Carolina at Chapel Hill

Principal Investigator:
Eugene Orringer, M.D.

This program seeks to identify, train, and mentor exceptional junior faculty members with the potential to conduct innovative women's health research. The goals of our BIRCWH program are to (1) facilitate the mentored career development of junior investigators pursing research of women's health or sex/gender factors; (2) promote interdisciplinary team science that will enhance all types of women's health research; and (3) facilitate the translation of these research findings to improve community health. All scholars participate in selected didactic programs, including the BIRCWH/KL2 Seminar; the BIRCWH Women's Health Seminar; and training in the responsible conduct of research. Other components of the curriculum are tailored to the background and training of the individual scholar, each of whom also takes part in our Women's Health Research Day and the national BIRCWH meeting. Finally, each scholar has an intensive research experience with mentors drawn from multiple disciplines. Our program focuses on eight research themes: (1) cancers affecting women; (2) nutrition, obesity, and eating disorders; (3) bone and joint health; (4) cardiovascular disease/vascular biology; (5) HIV/sexually transmitted diseases; (6) alcohol and substance abuse; (7) mental health; and (8) pain. These themes were selected because they are all highly relevant to women's health, well suited to interdisciplinary collaboration, and major strengths and areas of research emphasis at the University of North Carolina at Chapel Hill (UNC–CH). In addition, each theme has

numerous, nationally recognized mentors who are willing and available to work with selected BIRCWH scholars. The goal of the UNC–CH BIRCWH program is to create a training program that will prepare promising junior investigators to conduct innovative research in women's health. Through their mentored, interdisciplinary training, these scholars will be ideally positioned to make important new observations and then translate them into advancements that will improve the health of women throughout the community.

Institution:
University of Rochester Medical Center

Principal Investigator:
Shanna Swan, Ph.D.

Concerns about the potential impacts of environmental chemicals on human and environmental health have increased greatly in the past 10 years. Through their effects on hormonal pathways, environmental chemicals can differentially affect females, particularly at critical and sensitive periods across the lifespan. These critical periods include stages of particular vulnerability (such as fetal development and among the elderly), major life transitions (such as during midlife and into late life), and stages of rapid cell proliferation and growth (such as during fetal development, puberty, and lactation). The Women's Health and Environment across the Entire Lifespan (WHEEL) program at the University of Rochester Medical Center (URMC) has as its focus interdisciplinary research specific to the intersection of women's health, environment, and health issues specific to life stages. It will build on graduate training programs already in place at URMC and complement these with educational training and research experiences designed to meet the needs of scholars within the program. This program will train interdisciplinary women's health research scholars from a spectrum of disciplines and ultimately promote research and translation of findings that will benefit the health of women, particularity in the area of women's environmental health across the lifespan. Our long-term objectives are to (1) "graduate" scholars who go on to successful careers in interdisciplinary research in women's environmental health; (2) establish a successful and sustainable training program in women's health research; (3) create an environment at URMC conducive to interdisciplinary research in women's health; (4) develop researchers who provide positive feedback to the research environment and the fields of women's health research; and (5) build in continuing mechanisms to effectively translate results of women's health research to health professionals and the broader community. Results of this research will provide a strong foundation for risk assessment and regulation, when appropriate, thus decreasing risks to public health.

Institution:
University of Texas Medical Branch at Galveston

Principal Investigator:
Abbey Berenson, M.D.

The University of Texas Medical Branch (UTMB) program includes 17 experienced senior investigators as mentors from the Schools of Medicine, Nursing, Health Professions, and Biomedical Sciences. Research focus areas reflect the strong interdisciplinary infrastructure at UTMB and include health disparities, adolescent health, infectious disease, reproduction, and aging, especially as related to the health needs of underserved women. The Center for Interdisciplinary Research in Women's Health provides forums for interdisciplinary endeavors and administers the program. Multiple formal and informal venues provide ample opportunities for developing skills and collaborative interdisciplinary networks. Scholars may also obtain an M.S. or Ph.D. in clinical science. The UTMB BIRCWH program recruits, trains, and retains early career investigators from diverse racial/ethnic backgrounds in a variety of disciplines related to women's health. The program provides interdisciplinary mentored research experiences to promote the BIRCWH scholars' involvement in investigations aimed at improving health care and health of women across the lifespan.

Institution:
Washington University in St. Louis

Principal Investigator:
Clay Semenkovich, M.D.

The mechanisms underlying the unique course of several diseases affecting women remain unclear in part because of long-standing impediments to research efforts involving different disciplines. The long-term objective of the BIRCWH program at Washington University is to produce independent investigators conducting interdisciplinary research in women's health. The program has a single specific aim: to identify outstanding young scientists committed to women's health who have completed fellowship training, match them with mentors working in an environment that promotes interdisciplinary research, and provide them with career development experiences leading to their independence. The renewal proposes to extend the foundation of success by refining the didactic portion of the experience to make it even more relevant for scholars by coordinating the coursework with that offered by the CTSA at Washington University, reshaping our mentor pool in order to enhance the interdisciplinary character of the program, integrating the program with the newly created Center for Women's Infection Disease Research at Washington University, and adding a peer-to-peer mentoring component. Our program has the potential to help fulfill the mission of NIH and ORWH by continuing to train outstanding scholars and serving as a focal point for paradigm-shifting research in women's health.

By bridging fellowship training and independent faculty status, the BIRCWH program has the potential to significantly impact women's health by increasing the number of outstanding scientists utilizing novel and cooperative approaches to address problems that include depression, osteoporosis, lupus, type 2 diabetes, urinary tract infections, heart attacks, certain cancers, and infertility.

Institution: Yale University

Principal Investigator:
Carolyn Mazure, Ph.D.

Addictive behaviors are linked to nearly half of all causes of mortality, and disorders involving these behaviors represent the top three causes of preventable disease in the United States. Addictive behaviors in women (particularly involving tobacco, alcohol, overeating, and illicit drugs) currently rank among our most prevalent public health concerns. Emerging data suggest that sex and gender differences in these addictive behaviors and their biological substrates have important implications for the development of effective prevention and treatment strategies. We propose an innovative research career development program that will train junior faculty scholars to respond to the need for interdisciplinary research on women's health and addictive behaviors. An outstanding team of 25 experienced, productive, and dedicated mentors has been assembled with multiple ongoing interdisciplinary projects focused on addictive behaviors using basic, translational, and clinical research approaches. Our leadership team and advisory committee will direct a program that emphasizes four core career development components that will be individualized to meet the needs of each BIRCWH scholar. These components include (1) interdisciplinary research mentoring on study planning, implementation, completion, and dissemination of results; (2) coordinated professional coaching focused on the preparation of grant applications, manuscript writing, and faculty career planning; (3) structured experiences in interdisciplinary team science, and its development and evaluation; and (4) a didactic curriculum on women's health, addictive behaviors, and academic mentoring. Our long-term goal is to generate independent investigators with the skills necessary to sustain academic productivity, grant support, collaborations across disciplines, and effective mentoring of their own future trainees. Annual medical, social, and productivity costs of addictive behaviors linked to tobacco, alcohol, overeating, and illicit drugs in the United States alone exceed

$600 billion. Sex and gender differences in the etiology, course, and prognosis of these addictive behaviors have clear implications for prevention and treatment. We propose an innovative research career development program that will train junior faculty scholars in interdisciplinary research designed to make enduring contributions to the field of women's health and addictive behaviors.

In August 2012, ORWH and cosponsoring NIH Institutes, including NCI, NIA, NIAID (National Institute of Allergy and Infectious Diseases), NIAMS, NICHD, NIDA, and NIMH, funded 14 new and competing BIRCWH programs. Thirteen of these programs were competitively renewed, and one was a new site, University of Kentucky, that previously held a BIRCWH grant. The BIRCWH VI program sites and PIs funded in FY 2012 are listed in the table below, and detailed program descriptions follow.

BIRCWH VI Program Abstracts (FY 2012)

Institution:
Duke University

Principal Investigator:
Nancy Andrews, M.D.

Duke University, a research-intensive institution, and North Carolina Central University (NCCU), a historically black institution, have united to provide career development of junior faculty in interdisciplinary women's health research through the renewal of the BIRCWH Award. The long-term goal is to develop the careers of independent women's health researchers. The Duke/NCCU BIRCWH is a strong, vibrant program that has the leadership and institutional commitment for continued success in the development of junior investigators. The collaboration between Duke and NCCU strengthens our goal of training minority scholars. Our objectives are to (1) develop highly skilled, innovative junior researchers investigating women's health and the sex/gender elements of health and disease across a woman's lifespan through the use of interdisciplinary approaches; (2) foster

Table 2. BIRCWH VI Program Sites and Principal Investigators (FY 2012–FY 2016)

BIRCWH VI Institution	Principal Investigator
Duke University	Nancy Andrews, M.D.
Medical University of South Carolina	Kathleen Brady, M.D., Ph.D.
Northwestern University	Andrea Dunaif, M.D.
Oregon Health & Science University	Daniel Dorsa, M.D., and Jeanne-Marie Guise, M.D., M.P.H.
Pennsylvania State University	Carol Weisman, Ph.D.
Tulane University	Marie A. Krousel-Wood, M.D., M.P.H.
University of Colorado at Denver Health Sciences Center	Judy Regensteiner, Ph.D.
University of Illinois at Chicago	Stacie Geller, Ph.D.
University of Kentucky	Thomas Curry, Ph.D.
University of Maryland	Patricia Langenberg, Ph.D.
University of Minnesota, Twin Cities	Nancy Raymond, M.D.
University of Pittsburgh	James Roberts, M.D.
University of Wisconsin–Madison	Gloria Sarto, M.D., Ph.D.
Vanderbilt University	Katherine Hartmann, M.D., Ph.D.

research on health disparities and diversity and create an environment for the discovery of new insights into pressing minority health problems by promoting interdisciplinary team science and by identifying and recruiting minority scholars; and (3) encourage novel interdisciplinary research on all aspects of women's health, emphasizing the merits of all scientific categories and methods. The Duke/NCCU BIRCWH program will ensure the availability of a diverse pool of highly trained women's health researchers to address the nation's biomedical, behavioral, and clinical needs.

Institution:
Medical University of South Carolina (MUSC)

Principal Investigator:
Kathleen Brady, M.D., Ph.D.

The overall objective of MUSC's BIRCWH program is to attract translational scientists in the neuroscience arena to broaden interdisciplinary research related to women's health in South Carolina and throughout the United States. Since its inception, the MUSC BIRCWH has supported nine scholars, including four Ph.D.s, four M.D.s and one M.D./Ph.D. All of the program graduates are principal investigators or co-investigators on research teams funded by extramural support. The program targets junior faculty who have an interest in developing research careers addressing women's health and sex/gender issues in the neuroscience area. Scholars will remain in the program for a minimum of 2 and a maximum of 4 years, depending on their level of training and experience at entry. We plan to have five scholars in the program at any point in time, four supported by the BIRCWH program and one under-represented minority scholar supported by an institutional commitment from the Dean of the College of Medicine. The substantial expertise in translational neuroscience at MUSC assures our ability to mentor individuals and contribute significantly to the understanding and treatment of women's health issues related to brain and behavior across the lifespan. Our 24 mentor-eligible faculty members from 4 health professional colleges (Medicine, Nursing, Health Professions, and Pharmacy) have broad skills in neurological and neuropsychiatric disorders, especially pertaining to neurodegenerative disorders, stroke, age-related dementia and cognitive decline, substance abuse, depression, and other mood and anxiety disorders.

Institution:
Northwestern University

Principal Investigator:
Andrea Dunaif, M.D.

The Northwestern University (NU) BIRCWH Career Development in Women's Health (CDWH) program was established in 2007 to train the next generation of scientists for independent, interdisciplinary careers in the science of sex differences and in other fields relevant to women's health. This objective will continue to be accomplished by bringing together a cadre of mentors with expertise in reproductive sciences and in diseases that differentially affect women to provide the scholars with interdisciplinary research experiences relevant to elucidating sex and gender factors affecting health. In so doing, the NU BIRCWH CDWH program will also enhance the career development of junior faculty, with particular attention to addressing work-life balance issues that can be especially challenging for women faculty. The institutional excellence in reproductive sciences and in diseases differentially affecting women, strong collaborative culture of NU, and ongoing commitment of institutional resources to career development have greatly facilitated the program. The program has been exceptionally successful in the first award period matriculating eight scholars and graduating five, three of whom now have independent grant support. One scholar who has completed the program was an under-represented minority. The mentors have been selected for their expertise in the overarching themes relevant to women's health identified in the RFA: lifespan, sex/gender determinants, health disparities/differences and diversity, and interdisciplinary research. They are based in seven departments in Feinberg School of Medicine (medicine, neurology, obstetrics & gynecology, preventive medicine, and psychiatry & behavioral sciences) and Weinberg

College of Arts and Sciences (molecular biosciences, neurobiology and physiology). There are six general areas of NU BIRCWH CDWH mentor expertise: (1) cardiovascular health and disease, (2) epidemiology and behavioral science, (3) immune function—autoimmunity and infectious diseases, (4) metabolic function, (5) neuroscience, and (6) reproductive biology.

Institution:
Oregon Health & Science University (OHSU)

Principal Investigators:
Daniel Dorsa, M.D., and
Jeanne-Marie Guise, M.D., M.P.H.

The overarching goal is to create a stimulating and nurturing environment for junior faculty to develop into leading interdisciplinary research scientists in women's health; we plan to maintain four scholars per year. Over the last two grant cycles, the Oregon BIRCWH has trained a diverse cadre of researchers who advance basic, biomedical, behavioral, and translational research in women's health across the lifespan. OHSU provides a resource-rich environment whose culture promotes interdisciplinary team science. The Oregon BIRCWH has been successful, with scholars receiving approximately $40 million dollars in research funding, publishing over 200 publications, and assuming national leadership positions. The BIRCWH is the only K12 career development program at OHSU specifically dedicated to career development in women's health research. In this renewal we expand the centers, institutes, and mentors affiliated with the BIRCWH to address all six high priority NIH ORWH research goals and propose the following innovative expansions to (1) develop and promote best practices in mentoring interdisciplinary scientists by (a) providing formal mentorship training, (b) conducting a national BIRCWH survey to identify successful practices in mentoring interdisciplinary scientists, (c) developing and testing tools to support the mentor-mentee relationship locally, and (d) disseminate best practices (lessons and tools) for mentoring nationally; and (2) catalyze the development of women's health research leaders at the institutional, state, and national level by (a) developing core competencies in women's health research that incorporate the NIH ORWH research priorities to better define the research needs of the field and target educational research training programs, (b) providing formal leadership training to promote effectiveness of the next generation of women's health research leaders, (c) disseminating competencies and expanding interdisciplinary research in women's health through a Statewide Annual Women's Health Research Conference, and (d) formalizing a program to promote inter-institutional BIRCWH collaborations to advance women's health research and further programmatic excellence at a national level.

Institution:
Pennsylvania State University

Principal Investigator:
Carol Weisman, Ph.D.

The goal of the Penn State BIRCWH program is to contribute to the advancement of scholarship in the field of women's health across the lifespan, including understanding sex/gender differences relevant to health, by providing mentored research career development for scholars from multiple disciplines who are committed to collaboration across disciplinary boundaries and to translational science. The specific objectives are (1) to recruit eight talented junior faculty investigators during the 5-year renewal period, half of whom will be clinicians and half of whom will be basic scientists; (2) to provide intensive interdisciplinary mentored research career development for a minimum of 2 years, with a career development plan including mentorship by an interdisciplinary team of senior researchers, individualized training plans, and a monthly BIRCWH Seminar series; and (3) to evaluate the progress of each BIRCWH scholar and the success of the program using explicit milestones for the scholars as well as national data. During its first 5 years, the Penn State BIRCWH program established a successful cross-campus interdisciplinary mentoring model involving scholars and mentors from three colleges (Medicine, Health and Human

Development, and Liberal Arts) located on two campuses (medical campus and main campus). Mentors are senior investigators in the core research areas of precursors/consequences of obesity, reproductive health, cancer prevention and patterns of care, and sex and gender issues in health and disease. The notable achievements of these scholars, to date, include 34 peer-reviewed publications based on their BIRCWH research (an average of 2.4 publications per scholar per year); 8 internal grants funded; 6 NIH grants submitted as principal investigator; 3 grants submitted to other external agencies; 3 external grants funded as principal investigator (including 2 NIH grants); and several honors and awards (including a New Investigator Award from the North American Menopause Society and appointment as a consultant to the USDA). The Penn State BIRCWH program has had substantial institutional impact, including providing the cross-campus mentoring model for the newly funded Penn State CTSA and raising awareness of important career development issues for junior women faculty members.

Institution:
Tulane University

Principal Investigator:
Marie A. Krousel-Wood, M.D., M.P.H.

The Tulane BIRCWH program proposes to build on our prior success and expand and reinforce the BIRCWH program base. The long-term goal is to increase the number and diversity of highly trained culturally competent, independent, interdisciplinary investigators in women's health with an emphasis on sex differences research in the field of cardiovascular disease (CVD) and related diseases. The program focuses on CVD and related diseases because of the impacts of heart disease on women, the existing knowledge gaps on the sex differences in CVD across the research spectrum, and the strength of this focus at Tulane. Key components of our successful career development plan include (1) didactic courses tailored to specific scholar needs; (2) individualized career development training; (3) BIRCWH seminar series; (4) work-in-progress sessions; (5) required grant writing and project management workshops; (6) mentored interdisciplinary research; and (7) responsible conduct in research training. The innovative approach includes tailoring the program to scholars' needs via two career development tracks (Track 1 for scholars with limited research experience; Track 2 for scholars with prior research experience), and using a network mentoring model for each scholar, including expertise in both basic science and clinical research. Scholars are immediately exposed to research and are guided to establish a scholarly track record early, and gain presentation and organization skills by active participation in the Women's Health Research Day. New components of the enhanced BIRCWH program include additional faculty participation in new disciplines, increased interdisciplinary interactions between basic scientists and clinical researchers through network mentoring, strengthened collaboration with Xavier, a historically Black, less-research-intensive institution, and enhanced access to institutional resources. The scholars will learn cutting-edge research methods and skills from bench (cellular, molecular, and genetics), to bedside (clinical research and clinical trials) to population (epidemiology, prevention, and health services research) and conduct their own research projects in established laboratories/research groups in a mentored, interdisciplinary environment that addresses the most recent ORWH priorities. Scholars' interdisciplinary research activities will focus on sex differences in CVD and related diseases and their risk factors and address overarching themes (lifespan, sex/gender determinants, health disparities, and interdisciplinary research).

Institution:
University of Colorado at Denver
Health Sciences Center

Principal Investigator:
Judy Regensteiner, Ph.D.

University of Colorado Anschutz Medical Campus (UCAMC) BIRCWH program renewal is to provide outstanding junior

faculty with state-of-the-art interdisciplinary and individualized career development training that will maximize their ability to establish independent biomedical research careers in areas relevant to improving women's health. Long term, we seek to benefit the field of women's health research and ultimately, women's health, by adding a well-trained, diverse group of researchers to the workforce who are equipped to answer key scientific questions about women's health and sex differences. To accomplish these goals we have created an environment that nurtures interdisciplinary collaborations in focused and interactive research areas that are essential to improving the health of women. The Colorado BIRCWH will continue to be housed in the Center for Women's Health Research (CWHR), which provides key programs both on campus and in the community that support our BIRCWH scholars. In addition, since the 2007 award of the Colorado BIRCWH grant, UCAMC has successfully competed for a Clinical and Translational Science Award from NIH (CCTSI—Colorado Clinical Translational Science Institute). The programs offered by the CCTSI, with which the Colorado BIRCWH has a mutually beneficial affiliation, provide a rich environment for our BIRCWH scholars in concert with the BIRCWH-specific programs and those of the CWHR. The UCAMC has a very high level of support for BIRCWH, exemplified by strong financial support from the dean of the School of Medicine for BIRCWH. We will select promising and diverse BIRCWH scholars, as we have over the course of the current project period, who will be paired with experienced mentors (and who will have mentor teams) from our multiple campuses and schools in three interdisciplinary and interrelated focus areas across the lifespan in which UCAMC has great strength, including (1) pregnancy: placentation, lactation, and fetal/neonatal programming; (2) immunology/rheumatology/inflammation; and (3) adult health: obesity, menopause, aging, diabetes, and cardiovascular disease.

Institution:
University of Illinois at Chicago (UIC)

Principal Investigator:
Stacie Geller, Ph.D.

The overall goal of the UIC BIRCWH program, in alignment with the goals of the ORWH strategic plan, is to train a cadre of researchers to become independent investigators who will use novel, interdisciplinary approaches to advance women's health and sex/gender-based science. In 4 years, we have engaged 10 scholars in our program, all of whom remain in women's health or sex/gender-based research. Our scholars have been awarded 17 NIH grants and 26 other grants as principal investigators or co-investigators, published over 70 peerreviewed manuscripts, and given more than 70 oral and poster presentations at national or international scientific conferences. Our short-term objectives are (1) to enhance and refine three ongoing successful programmatic elements (the team mentoring approach, individualized scholar career development plans, and the combined core and tailored curriculum); (2) to develop and implement three new program elements to enhance the existing BIRCWH program and address the ORWH strategic plan goals (Mentoring the Mentor, the Knowledge Dissemination Program, and the Social Media Initiative) to enhance the existing BIRCWH program and address the ORWH strategic plan goals; (3) to recruit and train at least eight new BIRCWH scholars, particularly women and minorities, with interests in interdisciplinary women's health research; and (4) to conduct a systematic evaluation using process and outcome measures to monitor for continuous quality improvement and to demonstrate the impact of the BIRCWH program. Our long-term objectives are (1) to advance women's health and sex/gender-based science at UIC by fostering interdisciplinary collaborations and through the use of innovative research methodologies; (2) to train and mentor a diverse group of new investigators to achieve research independence and successful careers in women's health or sex/gender-based research; and (3) to raise

awareness across disciplines of the importance of examining sex- and gender-based differences throughout the lifespan.

Institution:
University of Kentucky

Principal Investigator:
Thomas Curry, Ph.D.

The University of Kentucky (UK) is uniquely positioned to continue using exceptional and outstanding research infrastructure to train the next generation of women's health scholars. We choose to focus our scholarship efforts on those health challenges unique to Appalachian Kentucky. Because the Appalachian region is disproportionately affected by drug abuse, violence, and poor health, we will actively engage women living in Appalachian Kentucky in our research agenda with research flowing bidirectionally between communities and researchers. The focused areas targeted towards improving women's health in this application include (1) substance abuse, (2) violence against women, and (3) hormonal regulation across a woman's lifespan. UK is uniquely position to address violence against women because UK has the only U.S. Center focusing on research to prevent violence against women. Through this BIRCWH program, strengthening the capacity for women's health research will be accomplished by the following specific aims: (1) to provide the environment, mentorship, and facilities to enhance the ability of BIRCWH scholars to compete for NIH research grants in diverse areas of women's health research; (2) to deepen our understanding of the unique role of gender in the manifestation of health and disease; (3) to stimulate new collaborations in focused, interdisciplinary, and interactive research areas that are essential for improving women's health; and (4) to use a thematic multidisciplinary focus as a platform for enhancing translational research between basic, clinical, and public health scientists. A strength of our BIRCWH program is its multidisciplinary, cross-departmental, and interactive nature positioned in an area with unique health needs.

Institution:
University of Maryland, Baltimore

Principal Investigator:
Patricia Langenberg, Ph.D.

The primary goal of the University of Maryland 's BIRCWH program is to continue our already highly successful program designed to foster interdisciplinary research in women's health among junior faculty scholars through a tailored mentoring experience with a team of senior faculty researchers to bridge the gap between prior specialized training and the incorporation of methods and concepts from several disciplines, leading to independent interdisciplinary research careers. To achieve this goal, we have expanded the existing research theme areas of our current program (i.e., women's health and the brain, the aging woman, and conditions specific to women) to include two others: personalized and genomic medicine, and global health. These themes represent existing research strengths at UMB and are fertile ground for interdisciplinary basic science, translational, behavioral, clinical, epidemiological, and/or health services research. Our BIRCWH scholars are able to draw from a multidisciplinary pool of senior faculty mentors as well as former scholars to form mentor teams that will provide depth and breadth to their training experiences. A unique feature of our program is that our scholars have opportunities to collaborate with faculty from all six of our UMB professional schools: dentistry, law, medicine, nursing, pharmacy, and social work.

Institution:
University of Minnesota, Twin Cities

Principal Investigator:
Nancy Raymond, Ph.D.

The University of Minnesota BIRCWH program's overarching goal is to improve the health of diverse women across the lifespan and, by extension, to improve the health of their families and communities in Minnesota, the nation, and the world. Our long-term objectives are to (1) increase the number of interdisciplinary research leaders advancing

scientific knowledge in women's health across the lifespan and in sex/gender determinants of health; (2) transform the academic environment by increasing the visibility of interdisciplinary women's health and sex/gender determinants research; and (3) effect the timely applications of women's health research findings to practice and policy. The primary components of our career development plan are addressed by our short term goals, including to (1) offer an individualized career development program that provides outstanding didactic and experiential training; (2) strengthen our BIRCWH program through new collaborations and curricular innovations; (3) provide a robust interdisciplinary mentoring program that builds a broad and diverse pool of women's health research mentors; and (4) promote the success of our scholars through strong program oversight and evaluation. Scholar research projects that are funded will reflect (but not be limited to) our main research focus areas: (1) cancers that occur primarily in women, and sex-specific aspects of other cancers; (2) obesity/eating disorders and their associated medical conditions; (3) substance abuse and associated risk behaviors; and (4) cardiovascular disease (CVD), including sex-specific basic mechanisms and disease presentation. Rationale and design of the program: We will make progress towards achieving the BIRCWH program's goal by offering a program that increases the number of well-trained, interdisciplinary researchers who focus on women's health and the effects of biological sex and gender roles on health and disease.

Institution:
University of Pittsburgh

Principal Investigators:
James Roberts, M.D., and
Yoel Sadovsky, M.D.

Our objectives are to build on our unparalleled strength in reproductive sciences and women's health research, which emanate from Magee-Women's Research Institute (MWRI) at the geographical center of the main campus of the University of Pittsburgh. MWRI is also adjacent to Magee-Women's Hospital of the University of Pittsburgh Medical Center (UPMC), one of the nation's largest and most successful academic health care systems. With nearly 110 researchers fully engaged in basic, translational, behavioral, clinical, and health services research, pursued at the six health sciences schools of the University of Pittsburgh and MWRI's research facility, we are poised to catalyze training and research in women's health locally, regionally, and nationally. Using MWRI as the BIRCWH@Pitt programmatic hub, our women's health network includes well-established nodes and links throughout our campus. The success of the BIRCWH program, coupled with the reputation of MWRI, has facilitated the integration of women's health research throughout the entire university. Indeed, the department of internal medicine provides a residency track and fellowship training in women's health, and the department of epidemiology in the Graduate School of Public Health features an emphasis on women's health and reproductive epidemiology. This strong university foundation enables us to focus on our long-term objectives of scholars' education, hands-on training, intense career development toward full academic independence, the attraction of new trainees through intellectual stimulation, the motivation of new collaborative synergies, and the implementation of sustainable women's health research. A team of mentors with diverse yet complementary skills is assembled based on the scholar's background and needs, and works with each scholar to achieve her/his didactic, technological, personal, and funding goals.

Institution:
University of Wisconsin–Madison

Principal Investigator:
Gloria Sarto, M.D., Ph.D.

The goals of the BIRCWH scholars program at the University of Wisconsin are to (1) to prepare scholars for independent academic research careers studying health equity and health disparities among diverse populations of women, and (2) to increase the diversity of academic leaders in the field of women's health. We will accomplish these goals by selecting diverse and talented applicants and providing them with dual scientific

mentorship with established investigators in both biomedical and behavioral/social sciences. The University of Wisconsin BIRCWH provides interdisciplinary, multifaceted opportunities for research that includes not only biomedical and behavioral sciences, but also investigation into the quality of care, cost, access, and satisfaction with services; causes of and barriers to reducing health disparities; social context; and identification of assessment measures for outcomes. A major strength of the University of Wisconsin proposal is the integration of the BIRCWH scholars into a thriving interdisciplinary research network that focuses on women's health and health equity and health disparities. This will provide the scholars with role models as well as cutting edge research opportunities, thus fostering their careers as academicians, scientists, and leaders. There is a need to increase public awareness and understanding of the determinants of health, disease, disability, and the opportunities for improvement (Healthy People 2020). Additionally, there is a need to increase the diversity of academic leaders in the field of women's health research in health equity and disparities including the health status and health outcomes among diverse populations of women, which is the focus of this career development program.

Institution:
Vanderbilt University

Principal Investigator:
Katherine Hartmann, M.D., Ph.D.

The goal of the Vanderbilt BIRCWH scholars program is to increase the pool of well-prepared investigators dedicated to advancing knowledge about women's health. Our scientific focus is to integrate the study of women's health and sex/gender differences into thriving research programs across the scientific spectrum in order to actualize personalized prevention, diagnostics, and therapeutics for girls and women. We are building on a tradition of research excellence that includes the ongoing Shanghai Women's Health Study with 75,000+ participants, a prospective community-based pregnancy cohort of 7,190 women, DNA samples linked with clinical data for more than 132,000 patients, large tissue and biomarker banks, two decades of Medicaid data with record linkage, and numerous other examples of large-scale programs making fundamental discoveries inside and outside the lab. Our 16 former and current scholars conduct research in content areas as diverse as immunologic aspects of lupus, gender differences in outcomes of ICU care, genetic underpinnings of racial disparities in adverse pregnancy outcomes, population-level patterns of exposure to opiates in pregnancy, and influence of iron balance on HIV disease trajectory. Alumni leave the program with an average of 17 total publications and to date have been awarded more than $9 million in extramural research support. BIRCWH scholars are grounded in the fundamentals of women's health and sex differences research, prepared to lead independent and collaborative research programs, trained to effectively deploy innovative interdisciplinary approaches to attack and solve problems, and committed to pursuing research that brings individualized care for women closer to reality.

Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health

The Specialized Centers of Research (SCORs) on Sex and Gender Factors Affecting Women's Health represent an innovative interdisciplinary research program focusing on sex differences and major medical conditions affecting women. The SCOR program supports accomplished scientists who conduct research that integrates basic, clinical, and translational research at P50 centers. ORWH developed and implemented the SCOR program in 2002. SCORs are designed to increase the transfer of basic research findings into clinical practice. The research scope for the SCOR program is derived from several sources, including:

(1) The Institute of Medicine report "Exploring the Biological Contributions to Human Health: Does Sex Matter?" (Institute of Medicine [IOM], 1999);

(2) The ORWH "Agenda for Research on Women's Health for the 21st Century" (1999); and

(3) The NIH Strategic Plan for women's health, "Moving into the Future with New Dimensions and Strategies: A Vision for 2020 for Women's Health Research" (2010).

The first SCOR RFA was issued by ORWH and participating ICs in 2002, and it funded 11 SCORs through FY 2006 (SCOR I). A second RFA, issued in 2006, funded 11 SCORs through FY 2011 (SCOR II), of which 7 were competitive renewals. In recognition of the importance and success of the interdisciplinary research focused on sex differences funded under the SCOR program over the past 10 years, ORWH renamed the SCOR program "Specialized Centers of Research (SCOR) on Sex Differences" (it was formerly called "Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health"). This third RFA was issued in 2011, and 11 new and competing SCORs were awarded in July 2012 for 5 years (FY 2012–FY 2016). Five of the 11 sites are competitive renewals, and 6 are new sites.

Every SCOR consists of at least three individual, but interrelated, research projects, each with high scientific merit and clear research objectives and, in the aggregate, devoted to a specific major health area. The projects incorporate basic and clinical research, and collaboration among institutions is encouraged. All SCORs include certain core resources to be shared among the investigators to enhance research productivity and increase the functional capacity of the SCOR. While every center has an administrative core to coordinate the research program, providing intellectual leadership as well as basic management functions (both are important components of this team-based approach), each one also includes other core resources specific to the needs of the projects.

The SCOR program is a trans-NIH, biagency effort with funds provided by ORWH and by other NIH Institutes, including NIA, NIAMS, NICHD, NIDA, NIDDK, and NIMH, as well as by the FDA. ORWH provides the majority of the funds for the SCOR program and serves as the program's coordinator, overseeing the progress in advancing sex differences research across the centers, while the day-to-day programmatic management of the SCORs resides in the participating ICs.

In August 2012, ORWH, cosponsoring ICs, and the FDA awarded the third round of SCORs. Eleven new and competing renewal awards were made. These funded SCORs will explore sex and gender differences in musculoskeletal diseases, pain, depression, vascular dysfunction and cognitive decline, substance use, tobacco dependence, and health of the urinary tract, as well as reproductive health, such as polycystic ovary syndrome, hormonal transitions, and the pelvic floor consequences of the reproductive process. In FY 2011 and FY 2012, ORWH provided over $9 million per year in funding to the program. The SCOR program represents an excellent model for stimulating interdisciplinary research and for human translational research, with significant applications to gender-specific human health. The FY 2012 SCOR sites and their research themes are listed below, followed by their program abstracts.

SCOR Program Abstracts (FY 2012)

Institution:
Mayo Clinic

Principal Investigator:
Virginia Miller, Ph.D.

Establishing a Specialized Center of Research on Sex Differences (SCOR) at Mayo Clinic is consistent with Mayo's strategic plan for research to best serve every patient, every day, through personalized medicine. Sex differences research is integral to personalized medicine. Cardiovascular disease and cognitive decline are two related conditions disproportionately affecting men and women across their lifespan with distinct differences in manifestations, responses to treatments, morbidity, and mortality. The overarching theme of this interdisciplinary SCOR is to understand how female-specific conditions associated with major hormonal shifts, hypertensive pregnancy disorders,

Table 3. SCOR Projects and Themes (FY 2011–FY 2012)

Institution and Investigator	SCOR Theme
Mayo Clinic, Virginia Miller, Ph.D. • Project 1: Hypertension in Pregnancy and Future Cardiovascular Disease • Project 2: Effects of Menopausal Hormonal Therapy on Imaging Markers of Cognitive Health • Project 3: Markers of Cerebrovascular Dysfunction in Women at Risk	Sex-Specific Risk for Vascular Dysfunction and Cognitive Decline
Medical University of South Carolina, Kathleen Brady, M.D., Ph.D. • Project 1: Oxytocin and Cocaine Dependence • Project 2: Sex Differences in Orexin and Oxytocin Mediation of Cocaine Seeking • Project 3: Stress Circuits and Sex Differences in Drug Seeking • Project 4: Gender, Sex Hormones, and Stress	Sex and Gender Differences in Addictions and Stress Response
Northwestern University, Andrea Dunaif, M.D. • Project 1: Rare Genetic Variants in PCOS • Project 2: Epigenetic and Expression Analysis of PCOS • Project 3: Estrogen Receptors and Metabolic Features of PCOS	Genes, Androgens, and Intrauterine Environment in PCOS
University of California, Davis, Nancy Lane, M.D. • Project 1: Progesterone Receptors Influence Peak Bone Mass Through Regulation of Bone Turnover • Project 2: Sex Differences in Carpal Tunnel Using Person-Reported Outcomes and High-Resolution Ultrasound • Project 3: Sex Differences in Bone Shape and Knee Osteoarthritis: the Osteoarthritis Initiative • Project 4: Sex Differences in Response to Exercise for Hyperkyphosis	Sex Differences in Musculoskeletal Conditions Across the Lifespan
University of California, Los Angeles, Emeran A. Mayer, M.D. • Project 1: HPA Axis Dysregulation in IBS and Related Animal Models, with Emphasis on Sex Differences • Project 2: HPA Axis-Dependent Visceral Adipose Tissue and Brain Changes in IBS and Related Animal Models • Project 3: IBS Subgroups Based on Endophenotypes Clusters and Interventional Phenotyping	Center for Neurovisceral Sciences and Women's Health
University of Colorado Anschutz Medical Campus, Wendy Kohrt, Ph.D. • Project 1: Bioenergetic and Metabolic Consequences of the Loss of Ovarian Function in Women • Project 2: Effects of Preexisting Obesity on Consequences of the Loss of Ovarian Function • Project 3: Sex Hormones Differentially Regulate Production of Distinct Adipocyte Populations	Metabolic Consequences of Loss of Gonadal Function
University of Michigan, Ann Arbor, John O. DeLancey, M.D. • Project 1: Biomechanics of Birth-Related Injury • Project 2: Extension of Levator Ani Muscle Injury and Prolapse Exacerbation on Second Birth • Project 3: Apical Ligament and Levator Muscle Interactions in Pelvic Organ Prolapse	Birth, Muscle Injury, and Pelvic Floor Dysfunction
University of Minnesota, Twin Cities, Marilyn Carroll, Ph.D. • Project 1: Sex Differences and Progesterone Effects on Impulsivity and Smoking Cessation • Project 2: Sex Differences and Progesterone Effects on Impulsivity and Cocaine Cessation • Project 3: Sex Differences and Progesterone Effects on Impulsivity, and Nicotine- and Cocaine-Seeking in Rats	Sex Differences and Progesterone Effects on Impulsivity, Smoking, and Cocaine
University of Pennsylvania, C. Neill Epperson, M.D. • Project 1: Prepubertal Adversity Effects on Maternal Arousal, Preterm Birth, and Infant Stress Response • Project 2: Prepubertal Adversity Effects on Affective and Cognitive Processing During the Menopause: Is there an Estrogen-Serotonin Interaction? • Project 3: Mechanistic Examination of Prepubertal Adversity Programming of Stress Dysregulation in a Mouse Model	Prepubertal Stress, Windows of Risk, and Sex Bias for Affective Disturbance
Washington University in St. Louis, Scott Hultgren, Ph.D. • Project 1: Host-Pathogen Interactions in Acute and Chronic UTIs • Project 2: Polymicrobial Synergy in Urinary Tract Infection and Preterm Birth • Project 3: Sex Differences in Susceptibility and Host Responses to UTI	Molecular and Epidemiologic Basis of UTI in Women
Yale University, Sherry McKee, Ph.D. • Project 1: Acetylcholine-Norepinephrine Interactions and Their Implications for the Effects of Nicotine in Reinforcement and Stress Reactivity • Project 2: Sex Differences in Dopamine Release in Tobacco Smokers • Project 3: Effect of an Alpha2a Adrenergic Agonist on Stress-Induced Smoking and Smoking Reinforcement: An Examination of Mechanisms and Clinical Outcome by Gender	Gender-Sensitive Treatment for Tobacco Dependence

and menopausal estrogen deficiency or menopausal hormone therapy affect cerebrovascular function and cognition in women. Three individual but interrelated projects will investigate the overarching theme. Project 1 will test the hypothesis that a history of hypertensive pregnancy disorders is a risk factor for all-cause and cardiovascular mortality, future cardiovascular disease, and cognitive impairment by using a population-based approach. Cohorts selected from the Rochester Epidemiology Project (REP) will be evaluated prospectively for cerebrovascular responses and cognitive function. Project 2 will investigate the neuroprotective effects of estrogen treatment on imaging markers of cognitive health and cognitive performance in women who were treated with estrogens compared with placebo during early menopause. Early menopause is considered the "window of opportunity" for estrogen treatment. This project leverages the cohort of the ongoing Kronos Early Estrogen Prevention Study (KEEPS). Project 3, using cohorts defined in Projects 1 and 2, will define cerebral microvascular dilator capacity, characterize the thrombotic potential of blood-borne microvesicles and platelets, and define relationships among those characteristics with cerebral microvascular vasodilator capacity and changes in brain structure and cognition. An administrative core will support operations and quality control, and a clinical analytical core will provide standardized subject recruitment, data management, and analysis for all three projects. The SCOR is highly responsive to the RFA because it addresses specific sex differences underpinning diseases affecting persons through life transitions, it integrates clinical and basic research, and it uses unique resources at Mayo Clinic. This project involves novel technical approaches of imaging and blood-soluble markers to mechanistically approach disease processes. Furthermore, the defined infrastructure and cohorts will provide the basis for future research on sex differences. Viewing research and medical delivery through a "sex-based lens," with attention to an individual's sex chromosomal complement and hormonal status, is fundamental to personalized care. The SCOR on Sex Differences at Mayo Clinic will facilitate incorporation of sex determinants of health, disease, and treatments across the research and clinical enterprise. In addition, the SCOR investigators will disseminate sex-differences research for specific and general national and international audiences.

Institution:
Medical University of South Carolina

Principal Investigator:
Kathleen Brady, M.D., Ph.D.

The establishment of the Medical University of South Carolina (MUSC) SCOR in 2002 provided a critical impetus to engage the research community in more sex- and gender-based research. MUSC had strength in translational, interdisciplinary research on addictions, but no sex- or gender-specific focus. In addition, the SCOR was the first women's health research initiative on the MUSC campus. The visible, campus-wide collaborations of SCOR investigators, combined with the institutional support of the SCOR pilot project program, have considerably increased sex- and gender-based research at MUSC. Close collaboration with the MUSC BIRCWH program, which was awarded in 2007, further enhanced campus-wide, interdisciplinary collaborations focused on women's health. We have begun collaborations with SCOR programs at other universities in order to maximize the scientific output from the ORWH investment in the SCOR initiative by sharing resources and combining data. During the renewal period, our core scientific projects will continue to focus on sex and gender differences in the relationship between addiction and stress response by using emerging technology in closely aligned clinical and basic science projects. The overarching goals of the SCOR center will focus on supporting and improving the translational scientific collaborations of the core and pilot research projects, catalyzing further growth of interdisciplinary sex- and gender-based research on the MUSC campus and creating strategic partnerships to enhance the translation and dissemination of SCOR findings and other relevant research to improve the health of women and girls. Center funding has allowed us to (1) increase interdisciplinary sex- and gender-based research on the MUSC

campus; (2) bring together institutional and scientific leadership to form a high visibility operational unit focused on research in women's health; (3) establish infrastructure to support efficient operations, integration, and stability; (4) coalesce a group of senior investigators to integrate their scientific expertise and research skills to advance sex- and gender-based research; (5) attract and train new and junior investigators in sex- and gender-based research; (6) support the development and testing of innovative ideas and new technology; and (7) provide a supportive training environment for basic and clinical researchers interested in sex- and gender-based research. The next funding period will allow us to build on these accomplishments, expand our research program utilizing innovative techniques and novel compounds, increase cross-SCOR collaborations, enhance outreach and dissemination efforts, and attract new investigators. Our SCOR, with a truly interdisciplinary and translational focus on sex and gender issues in addictions and stress response, is prepared to work collaboratively with other SCOR colleagues towards the vision, goals, and objectives outlined in the 2010 ORWH Strategic Plan.

Institution:
Northwestern University (NU)

Principal Investigator:
Andrea Dunaif, M.D.

The NU SCOR explores the overarching hypothesis that genetic variation resulting in hyperandrogenemia produces the phenotypic features of polycystic ovary syndrome (PCOS) by androgen programming in utero as well as by ongoing androgen actions at critical developmental periods and in the adult. We have found sex-specific metabolic phenotypes in PCOS families, mapped several PCOS susceptibility genes, developed animal models of androgen programming, and discovered that androgen-mediated estrogen resistance is an important mechanism for these androgen actions. It is clear that the genes for PCOS so far identified do not explain the high heritability of this disorder. We will investigate the mechanisms for this deficit in heritability as well as the molecular mechanisms by which estrogen resistance can produce obesity and metabolic abnormalities in PCOS. Our strategy for achieving the SCOR objectives is to directly investigate the genetic, epigenetic, and hormonal determinants of PCOS in three highly interactive, synergistic, and interdisciplinary projects: Projects 1 and 2 are clinical research projects and Project 3 will utilize a novel nonhuman primate model. Although each project is discrete, the proposed SCOR as a whole will continue to comprehensively investigate novel mechanisms for the pathogenesis of PCOS. Project 1 will test the hypothesis that rare genetic variants will account for much of the deficit in heritability of PCOS. We predict that we will identify rare variants in pathways implicated in the pathogenesis of PCOS in mapping of common variants, such as TGF B signaling, Wnt signaling, insulin signaling, gonadotropin action and extracellular matrix, as well as rare variants in genes in novel pathways. Project 2 will test the hypothesis that a significant component of the heritability of PCOS is due to epigenetic changes, including variation in methylation patterns, that these changes in methylation patterns correlate with changes in expression patterns, and that these changes in methylation are due to either specific changes in the DNA or environmental factors including the in utero environment. Project 3 will develop a novel nonhuman primate (marmoset) model of diet-induced obesity to test the hypothesis that androgenic programming of metabolic features of PCOS is mediated by induction of resistance to the actions of estradiol in target hypothalamic neurons that modulate energy homeostasis. These studies are extremely innovative, highly synergistic, and likely to have a major impact on the field through elucidating the pathogenesis of PCOS and its metabolic phenotypes.

Institution:
University of California, Davis

Principal Investigator:
Nancy Lane, M.D.

Musculoskeletal diseases comprise the most frequent ailment for primary care physician visits in the United States, and the increases in incidence of musculoskeletal diseases

with aging (particularly osteoporosis and osteoarthritis) is higher in women than in men, and leads to a significant amount of disability and reduced quality of life. Epidemiologic data clearly demonstrate that the proportion of women affected by musculoskeletal diseases is higher than in men with aging, yet the biologic explanation for this sex difference remains unclear. The objective of this interdisciplinary, multi-institutional proposal, entitled "Sex Differences in Musculoskeletal Conditions Across the Lifespan," is to integrate cutting-edge basic science regarding sex differences in the physiology related to acquiring peak bone mass, epidemiologic study on the relation of sex differences in bone shape to occurrence, severity and prognosis of osteoarthritis, clinical study of sex differences in high resolution ultrasound in diagnosis and prognosis of carpal tunnel syndrome with conservative and surgical treatment, and a randomized trial of sex differences in response to a physical activity intervention for kyphosis. The overarching goal of this Specialized Center of Research is to inform and transform preventive efforts and clinical practice in diagnosis and treatment of these musculoskeletal conditions in both sexes and lead to improvements in women's health. The four projects that compose the center will conduct critical, innovative research to characterize sex differences in musculoskeletal conditions via (1) a mechanistic study of sex differences in progesterone receptors that are related to regulation or influence peak bone mass, (2) a prospective clinical cohort study using novel diagnostic technology to examine sex differences in the results of this technology to diagnose carpal tunnel syndrome and sex differences in standard treatments for this condition, (3) an epidemiologic imaging study to assess sex differences in bone shape and the influence of bone shape on the development, severity, and prognosis of osteoarthritis of the knee, and (4) a randomized clinical trial of sex differences in response to an exercise intervention for the treatment of kyphosis. The center's research results will be translated to the local and national medical communities through presentations by center researchers at a number of different forums, including UC Davis and UCSF continuing medical education programs, as well as local grand rounds and national meetings.

Institution:
University of California, Los Angeles

Principal Investigator:
Emeran A. Mayer, M.D.

Since its initial funding through a SCOR grant in 2002, the UCLA Center for Neurovisceral Sciences and Women's Health has pursued the general hypothesis that many functional disorders, including irritable bowel syndrome (IBS) and interstitial cystitis/painful bladder syndrome (IC/PBS), are related to enhanced stress responsiveness, and that the greater prevalence of these syndromes in women is related to sex-related differences in responses to perturbations of homeostasis. Building on results generated during the past two funding periods, the current proposal aims to apply novel conceptual, technical and analytical tools to address the following interdisciplinary theme; "Sex-Related Individual Differences in Central Stress Response Systems and Their Role in IBS Pathophysiology and Treatment Response." We propose to test the general hypothesis that subsets of patients can be identified which are characterized by unique clusters of central and peripheral endophenotypes, and which may show differential responsiveness to treatment. The three projects of the SCOR, supported by two scientific Cores, will address two overarching themes: (1) Hypothalamic-Pituitary-Adrenal (HPA) axis and central stress systems, and (2) Endophenotype-based subgrouping of IBS patients. We will address these two themes through three synergistic, translational research projects, with an emphasis on sex differences. Project 1 will conduct a comprehensive genetic, molecular, and functional phenotyping of the HPA axis in IBS patients and healthy controls, establish regional brain CRF/CRF1R expression, and delineate engagement of central stress circuits in an animal model of IBS. Project 2 will test the hypothesis that chronic stress in IBS is associated with HPA axis dysregulation, increased visceral adipose tissue (VAT)

accumulation, and circulating adipokines, which modulate HPA axis responsiveness, and mediate regional brain changes. Project 3 will perform comprehensive endophenotyping using biomarkers collected from all three projects within a large group of IBS patients to identify unique clusters of endophenotypes, and distinguish a subgroup with an upregulated CRF/CRF1R signaling system who can be identified by their responsiveness to a selective CRF1R antagonist.

Institution:
University of Colorado
Anschutz Medical Campus

Principal Investigator:
Wendy Kohrt, Ph.D.

The overarching objective of the University Of Colorado Anschutz Medical Campus Specialized Center Of Research on Sex Differences (UCAMC SCOR) is to develop an interdisciplinary and translational research program to advance the understanding of the bioenergetic and metabolic consequences of the loss of gonadal function. There is compelling evidence from studies of laboratory animals that gonadectomy causes a dramatic decrease of 30%–80% in spontaneous physical activity in males and females. Even more intriguing is the observation that this results in excess weight gain, a marked increase in visceral fat, and metabolic dysfunction in female animals but not males. If such findings are relevant to humans, the age-related decline in gonadal function may be an important independent determinant of disease risk. Moreover, this would be expected to have a greater adverse effect on the health of women than of men, because the loss of gonadal function occurs at an earlier age in women. There will be three SCOR research projects to advance novel research in this area: (1) Project 1 (clinical): Bioenergetic and Metabolic Consequences of the Loss of Ovarian Function in Women (PI: W. Kohrt); (2) Project 2 (preclinical): Effects of Pre-existing Obesity on Consequences of the Loss of Ovarian Function (PI: P. MacLean); and (3) Project 3 (basic): Sex Hormones Differentially Regulate Production of Distinct Adipocyte Populations (PI: D. Klemm). The Administrative Core will contribute to the success of the SCOR by (1) providing scientific leadership for a focused translational and transdisciplinary research program on the consequences of the loss of gonadal function; (2) monitoring the productivity of SCOR Research Projects; (3) expanding the scope of the SCOR through an Ancillary Projects program; (4) expanding the cadre of investigators conducting research on the gonadal regulation of energy balance and metabolism through the Ancillary Projects program; (5) integrating activities of the SCOR with closely partnered programs at UCAMC, including the Center on Aging, the BIRCWH program, the Center for Women's Health Research, the Nutrition and Obesity Research Center, the Women's Reproductive Health Research Career Development program, and the Colorado Clinical and Translational Science Institute; (6) providing biostatistical and data management support for the SCOR research projects; and (7) providing administrative support for financial oversight, regulatory oversight, and scheduling and general management of SCOR activities.

Institution:
University of Michigan, Ann Arbor

Principal Investigator:
John O. DeLancey, M.D.

Although it has been known for millennia that many young women who give birth vaginally will suffer from disabling pelvic organ prolapse later in their lifespan, the factors linking these two events remain a mystery. Of the 3 million women who deliver vaginally each year, 300,000, or 1 in 10, will later require surgery for pelvic floor dysfunction due to their unique sex-determined role in reproduction. Our discovery of birth-induced levator ani muscle injury and its strong relationship to prolapse has identified a key connection between birth and prolapse. Ignorance of how birth-induced injury occurs and how it produces subsequent prolapse has blocked efforts to improve prevention and treatment. In this application we seek to continue SCOR support for our broadly interdisciplinary sex-differences research group representing four schools and two institutes. The group has won 10 awards in

the last 4 years for our discoveries and now seeks funding to begin to translate these insights into improved prevention at birth and strategies for better treatment. Project 1, "Birth Biomechanics," will test hypotheses concerning basic mechanisms of levator ani injury during vaginal birth to identify specific situations that may increase or decrease injury risk. Project 2, "Injury Extension," will determine whether minor clinically insignificant levator injury after first birth extends to a clinically significant tear during second birth. Because a second birth doubles the risk of genital prolapse, this event offers the opportunity of preventing injury and their sequelae later in life. Project 3, "Muscle-Ligament Dynamics," will establish the interaction between birth-related levator muscle injury and the properties of the uterovaginal supporting ligaments associated with prolapse. Core A, "Administrative/Human Subjects," integrates and supports the interdisciplinary team and provides project support by recruiting subjects, compiling and analyzing data, and protecting subject safety. Core B, "Biostatistics/Measurements," provides statistical and technical support for the projects along with integrated analysis for 2- and 3-dimensional spatial data gathered across projects. It will prepare data for presentation, publication, subject safety analysis, and, eventually, public use. Core C, "Translation/Mentorship," will foster insight dissemination and drive investigator development. This SCOR will produce translational insights to reduce the sex-determined consequences women suffer from their unique role in reproduction. It will establish the scientific basis for new strategies to improve treatment, identify important prevention opportunities, and train a new generation of researchers.

Institution:
University of Minnesota, Twin Cities

Principal Investigator:
Marilyn Carroll, Ph.D.

The goal of this SCOR is to take an interdisciplinary approach to studying an emerging and potentially important interaction between sex differences, hormonal status (e.g., progesterone—PRO), impulsivity, and drug-motivated behavior that could have important consequences for reducing two devastating forms of drug abuse, cigarette smoking and cocaine abuse. The central hypothesis is that reducing impulsivity will reduce drug-seeking behavior. Progesterone reduces impulsivity, and combined with drugs that have similar effects (e.g., atomoxetine—ATO), significant reductions in nicotine and cocaine abuse may be achieved. PRO will also be tested in combination with drugs that show some effect for nicotine dependence, varenicline (VAR) in the animal project. Based on a growing literature on sex differences in drug abuse, there may be sex differences in the effect of single and combined treatments. The following are the specific aims of the SCOR: (1) Investigate sex differences in the effect of exogenous PRO compared to placebo on impulsivity and smoking cessation in clinical Project 1. (2) Study sex differences in the effect of exogenous PRO vs. placebo in combination with ATO vs. placebo on impulsivity and relapse to cocaine abuse in clinical Project 2. (3) Examine sex differences in an animal model of nicotine and cocaine relapse and impulsivity for nicotine or cocaine in rats treated with PRO alone and in combination with ATO and VAR. Another goal is to study endogenous PRO effects on nicotine or cocaine self-administration in pregnant rats during gestation (high PRO) and lactation (low PRO) compared with males and nonpregnant females. This SCOR allows for an interdisciplinary and translational approach to accomplishing these aims. It also offers economic efficiency, an opportunity to exchange ideas and approaches with others who are involved with the SCOR.

Institution:
University of Pennsylvania

Principal Investigator:
C. Neill Epperson, M.D.

It is well established that childhood adversity is one of the most potent predictors of adult affective disorders, particularly among women. Further, an important dissociation has been reported for a subgroup of women who experience early life adversity but do not present with adult disease, suggesting that

there may be resiliency factors important in disease protection or amelioration. In fact, the availability of a caring and stable parent or guardian has been shown to be one of the most important aspects that distinguish between positive and negative outcomes in abused individuals. We propose that one vital contributor to the increased risk for major depressive disorder (MDD) in women, and propensity for other affective disturbances at specific reproductive time points, is the programming effect of prepubertal adversity on dysregulation of hypothalamic pituitary adrenal (HPA) activity and ovarian steroid responsiveness across the lifespan. It is well documented that from puberty to the late perimenopause, MDD and several anxiety disorders are more common in females than males. Moreover, periods of hormonal flux across the female lifespan are associated with increased risk for affective disturbance: the premenstruum (premenstrual dysphoric disorder), the postpartum (onset/relapse bipolar disorder, MDD), and the perimenopause (depression symptoms and MDD). The goal of the scientific projects in this SCOR proposal is to determine how the experience of prepubertal adversity reprograms the brain toward stress dysregulation, and how this intersects with periods of dynamic hormonal flux across the life span, including pregnancy (Projects 1 and 3) and aging (Projects 2 and 3). In addition, mechanistic epigenetic studies will examine sex differences in response to stress during this sensitive window of brain maturation (Project 3). SCOR funding would harness the respective expertise of Drs. Epperson and Bale in behavioral and molecular models of stress and reproductive neuroendocrinology, psychophysiology, and neuroimaging, to create the Penn Center for the Study of Sex and Gender in Behavioral Health. The center would provide an intellectual platform with important resources to encourage established investigators, and their mentees, to consider sex and gender as crucial factors in their research.

Institution:
Yale University

Principal Investigator:
Sherry McKee, Ph.D.

The Yale SCOR is bringing together leading basic and clinical science experts to establish an interdisciplinary, translational, cross-species program of research aimed at identifying novel therapeutics to address the critical health disparity that female smokers face. Tobacco use is the leading cause of preventable morbidity and mortality in the United States. Women, compared to men, have poorer rates of smoking cessation and exacerbated health risks, and FDA-approved medications for smoking cessation may not be as effective for women or may have emerging limits due to side effects. However, few attempts have been made to develop gender-sensitive smoking cessation treatments. The considerable body of data suggesting that women are more likely to smoke to regulate negative affect and stress while men are more likely to smoke for the reinforcing properties of nicotine suggests an important direction in the development of a new approach to smoking cessation treatments. Using both preclinical and clinical strategies, our interdisciplinary team will probe the noradrenergic system's effects on stress-reactivity and nicotine reinforcement, hypothesizing that (a) different brain systems modulated by noradrenergic activity are activated by smoking in women and men, and (b) guanfacine (an alpha-2a noradrenergic agonist) can preferentially target these gender-sensitive systems to improve smoking cessation outcomes. Using a translational approach with an interdisciplinary team effort, we are proposing three projects that will have interrelated and shared goals, with each providing unique contributions to the development of gender-sensitive therapeutics. This new application will catalyze Yale's significant resources to support interdisciplinary and translational science in women's health to pursue extremely timely scientific findings that could represent a breakthrough in our understanding of treatments for a public health problem that affects millions daily. The specific aims and objectives of

the Yale SCOR are the following: 1: Evaluate the role of the noradrenergic system and its interactions with cholinergic and dopaminergic systems in stress-induced smoking relapse and nicotine-based reinforcement, and use these findings to inform and expedite the development of gender-sensitive therapeutics for smoking cessation. 2: Mentor junior investigators in conducting interdisciplinary translational research on tobacco use and women's health through training opportunities, including "clerkships" with SCOR PIs and pilot funding. 3: Be a national resource to invigorate and galvanize the study of sex and gender differences in relation to smoking by providing expert consultation; supporting faculty training awards; mining national data on gender, smoking, and health outcomes to inform health policy; and expanding our current program of local and national community outreach.

SCOR Accomplishments at FY 2007–FY 2011 Sites

The SCOR program continues to thrive. A publication analysis from the NICHD's Office of Science Policy, Analysis and Communication was conducted using the NIH Scientific Publication Information Retrieval and Evaluation System (SPIRES) to extract all publications from PubMed that were attributed to SCOR II grants. Additional publications were identified using the Scopus (SciVerse Scopus) database as well as the grantees' annual progress report. Abstracts, presentations, and "in press" or "submitted" items were not included. A total of 665 articles were published by the second round of SCOR PIs from 2006 to 2012, an average of over 60 publications per center, with many SCOR articles in high-impact journals. Seven of these were from programs that were continuously funded for more than 10 years. The journals with the largest number of SCOR articles were the *American Journal of Obstetrics & Gynecology,* followed by the *Journal of Urology* and *The Journal of Clinical Endocrinology & Metabolism* and then *PLOS ONE*.

Research from the second cycle of SCOR programs has provided numerous insights into the sex differences observed in pain, including visceral pain and pelvic floor dysfunction; mental health, including depression, the stress response, and sex differences in the brain's response to drug cues; and new potential therapeutic targets for recurring urinary tract infections. In addition, SCOR PIs are drawing more attention to the need to perform sex/gender analyses of scientific results, and they made major contributions to a 2011 IOM workshop on Sex Differences and Implications for Translational Neuroscience Research, a summary of which was published in March 2011 (IOM, 2011). Also in 2011, ORWH sponsored the convening by the IOM of a committee to address the need to increase publication in the scientific literature of results on sex differences. The discussions and presentations at this workshop, Sex-Specific Reporting of Scientific Research, took place on August 30, 2011, and the conferees explored the benefits of and barriers to sex-specific reporting of scientific data. SCOR PIs served as members of the IOM committee and made significant contributions to the workshop summary, which was released in January 2012 (IOM, 2012). Selected FY 2011–FY 2012 SCOR Publications, Including Sex and Gender Analyses, are listed by SCOR program in Appendix E.

Examples of the interdisciplinary sex and gender research that has been conducted by the second round of SCOR sites (FY 2007–FY 2011) include the following:

- **"A Coordinated Study of Stress, Pain, Emotion, and Sexual Factors Underlying the Pelvic Visceral Disorders of Irritable Bowel Disorder and Interstitial Cystitis" at the University of California, Los Angeles.** This interdisciplinary team is investigating persistent visceral pain disorders affecting the gastrointestinal and urogenital tract, which are common, disproportionally affect women, have a considerable effect on health-related quality of life, and result in high utilization of health care. Recent results generated by the SCOR suggest that key components of central stress circuits are differentially responsive in men and women, and in women with and without irritable bowel syndrome, leading to sex differences

in peripheral outputs as well as to sex differences in the balance of endogenous pain modulation systems. This SCOR is cofunded by NIDDK and ORWH.

- **"Fetal Antecedents to Sex Differences in Depression" at Brigham and Women's Hospital.** This interdisciplinary team of investigators is exploring the associations between maternal-fetal stress indicated by maternal inflammatory hormonal markers during mid-gestation and sex differences in adult major depressive disorders in the offspring. The team's research has found that magnetic resonance imaging of healthy human brains demonstrates that brain regions affected by sex hormones during development are highly sexually dimorphic (i.e., exhibit sex differences in brain volume relative to the size of the cerebrum). This SCOR is cofunded by NIMH and ORWH.
- **"Role of Sex and Gender Differences in Substance Abuse Relapse" at the Medical University of South Carolina.** Research has demonstrated important differences between males and females in drug-taking patterns, and yet little is understood about the specific biological or psychosocial factors that account for these gender differences. Preclinical and parallel human laboratory studies are identifying sex differences that underlie triggers for cocaine and nicotine craving and relapse and the role of ovarian hormones in modulating these effects. Researchers are also testing potential medications to prevent relapse. These studies have important implications for the development of gender-sensitive relapse prevention strategies, both behavioral and pharmacologic, and for determining how consideration of a women's menstrual cycle phase can optimize treatment outcomes. This SCOR is cofunded by NIDA and ORWH.
- **"Sex, Stress, and Substance Use Disorders" at the Yale University School of Medicine.** Trauma and stress are known risk factors for substance abuse as well as triggers for relapse. In particular, stress markers such as early trauma play a pivotal role in the continued drug use and relapse cycle in women. Understanding differential stress responses between men and women could lead to improved interventions for preventing and treating substance abuse. Preclinical studies and human laboratory studies in this SCOR are examining male-female differences in adult and adolescent stress responses, including the effects of trauma in early life and prenatal cocaine exposure on physiological and neurobiological changes and on vulnerability to substance use. Information on the role of gonadal hormones in stress responses is also informing the development and testing of the ovarian hormone progesterone on stress regulation, craving, and relapse vulnerability. Together these interdisciplinary studies aim to provide the basis for the development of gender-specific prevention and treatment interventions. This SCOR is cofunded by NIDA and ORWH.
- **"Sex and Gender Influences on Addiction and Health: A Developmental Perspective" at the University of Miami Miller School of Medicine.** Studies have shown that drug exposure at different stages of development leads to differential neurochemical and behavioral effects that can persist into adulthood. This SCOR is conducting interdisciplinary studies assessing sex/gender-specific differences in drug effects across development. Preclinical studies with rodents are examining sex differences in the behavioral and neurobiological effects of prenatal drug and adolescent exposure (including nicotine, marijuana, and cocaine) and how these effects interact with social and environmental factors to influence drug reward. Complementary clinical studies are examining male and female teenagers and young adults, with and without prenatal drug exposure, across many domains of functioning, including subsequent drug use. An understanding of the differential effects in females and males of drug exposure during adolescence and of how these changes manifest in adults may lead to gender- and age-specific treatments for drug addiction. This SCOR is cofunded by NIDA and ORWH.

Select Research Foci of the Newly Funded or Renewal FY 2012–FY 2016 SCOR Sites

- ORWH and NIAMS supported the creation of a SCOR titled "Sex Differences in Musculoskeletal Diseases at the University California-Davis," an interdisciplinary, multi-institutional center that will explore the basic science behind sex differences in musculoskeletal diseases. The investigators will focus on how gender affects bone shape and peak mass, osteoarthritis severity, imaging diagnostics, carpal tunnel syndrome, and the effectiveness of physical activity.
- Three newly awarded SCORs, funded by NIDA and ORWH, will each conduct sex differences research related to nicotine and cocaine addiction. Preclinical and brain imaging studies will seek to understand the mechanisms underlying sex differences in these diseases and to identify potential targets for the development of medications. Clinical trials of already identified targets will be tested for their efficacy in treating nicotine and cocaine addiction, including examining sex-based outcomes. Currently, no FDA-approved medications exist to treat cocaine addiction in either men or women. And while several smoking cessation medications are available to both sexes, some are less effective in women than in men, and smoking relapse rates remain high.
- NIDDK is supporting, with ORWH, two SCORs, one based at Washington University, St. Louis (titled "Molecular and Epidemiologic Basis of UTI in Women") and the other at the University of California, Los Angeles (titled "Center for Neurovisceral Sciences and Women's Health"). The former is studying the biology of, and treatment for, recurrent urinary tract infections caused by a common bacterium, *Escherichia coli*, including the biology underlying sex differences in susceptibility to infection. The latter SCOR is studying the potential role of sex differences in biological responses to stress in a person's susceptibility to two pain conditions that are more prevalent in women, irritable bowel syndrome (IBS) and interstitial cystitis/painful bladder syndrome, information that could help in developing more effective treatments for these conditions.

Highlights of BIRCWH and SCOR Activities at the Annual NIH Interdisciplinary Women's Health Research Symposium

Annual Interdisciplinary Women's Health Research Symposium

Each year, an Interdisciplinary Women's Health Research Symposium is held to showcase the latest interdisciplinary research findings in women's health and sex differences from the Building Interdisciplinary Research Careers in Women's Health (BIRCWH, K12) scholars and the principal investigators (PIs) of Specialized Centers of Research (SCOR, P50) on Sex Differences. The 9th Annual Interdisciplinary Women's Health Research Symposium and Poster Session was held on November 15, 2012, in the Natcher Auditorium, NIH. Dr. Janine Clayton, Director, ORWH, provided opening remarks, and Douglas Lowy, M.D., Deputy Director, National Cancer Institute, provided a keynote address titled "Prevention of HPV-Associated Cancers: Advances, Challenges, and Opportunities." In addition, posters highlighting the research from the BIRCWH scholars and SCOR PIs were on display throughout the symposium. BIRCWH and SCOR abstracts were published in the October 2012 issue of the *Journal of Women's Health* (Nagel & Rudick, 2012).

Annual BIRCWH Scholars, BIRCWH Directors, and SCOR Directors Meetings

The annual meetings of the BIRCWH PIs and scholars and the SCOR directors are held in conjunction with the Interdisciplinary Women's Health Research Symposium. In 2012, the BIRCWH meeting included a panel on work-life balance that was led by several BIRCWH PIs: Drs. Claire Pomeroy, Kim Boggess, Stacie Geller, and Thomas Baranski. In addition, each year workshops and

presentations from senior NIH officials on peer review, grantsmanship, and strategies for grant success are held as well as a new "Speed Mentoring" event for BIRCWH scholars with NIH program officials.

Scholars Day on the Hill

In 2006, ORWH initiated the "Scholars Day on the Hill Training Program in Health Policy" in collaboration with George Washington University to enhance the BIRCWH scholars' understanding of the legislative process. The workshop coincides with the annual symposium and provides the BIRCWH scholars with a solid understanding of the health policy legislative process, especially as it relates to health, health care, and medical research policy relevant to women's health and women's health research. The daylong program on Capitol Hill is conducted by faculty of the George Washington University Department of Health Policy, led by Sara Rosenbaum, J.D., professor and interim chair of the Department of Global Health, and Susan Wood, Ph.D., associate professor and the director of the Jacobs Institute of Women's Health.

Directory of BIRCWH Scholars

In FY 2010, ORWH developed a directory of BIRCWH scholars in response to the request from many BIRCWH scholars for networking opportunities. The directory includes the affiliation, professional titles, and research areas of current scholars and a brief statement about the impact of the BIRCWH program on their research careers. The third edition of the directory currently includes over 88 scholars.

Summary: ORWH Interdisciplinary Research and Career Development Programs Support the Implementation of the NIH Strategic Plan for Women's Health Research

ORWH has developed innovative interdisciplinary research and career development programs that support and encourage collaborative research that is team based and cuts across disciplines. These programs are serving as major vehicles for advancing research in women's health and sex differences that holds the potential to be translated into clinical practice to benefit the health of women and men. The sixth round of BIRCWH maintains and sustains the cadre of women's health researchers who are available in the pipeline to conduct women's health research. As of FY 2012, a total of 77 BIRCWH programs, which were funded at 39 institutions and 29 programs, are active across the United States, and 493 scholars have been sponsored. The majority of completed BIRCWH scholars have gone on to receive independent funding from NIH and leading research foundations and remain in academia. The majority of articles that they are publishing are relevant to women's health. The SCOR PIs, who are accomplished scientists, are publishing in high-impact journals and making novel contributions to the field of sex/gender differences research. In addition, the SCOR PIs are developing strong collaborations, both intra-institutional and inter-institutional. For example, several of the current SCOR PIs are undertaking research that looks at the stress circuitry and how it is differentially responsive in men and women, and they are now collaborating to develop common elements that could be shared. It is gratifying to see what these two programs, SCOR and BIRCWH, have achieved in the past decade in terms of supporting career development for women's health researchers and how they are helping to fill the gaps in knowledge related to the influence of sex/gender on health and disease. Both programs continue to support and are critical to advancing all six of the NIH Strategic Plan for Women's Health Research goals, particularly the ultimate goal of actualizing personalized prevention, diagnostics, and therapeutics for girls and women.

References

Domino S. E., Bodurtha, J., & Nagel, J. D. (2011). Interdisciplinary research career development: Building Interdisciplinary Research Careers in Women's Health program best practices. *Journal of Women's Health, 20*(11), 1587–1601.

Guise, J. M., Nagel, J. D., & Regensteiner, J. (2012). Best practices and pearls in interdisciplinary mentoring from the Building Interdisciplinary Research Careers in Women's Health directors. *Journal of Women's Health, 21*(11), 1114–1127.

Institute of Medicine. (2001). *Exploring the biological contributions to human health: Does sex matter?* Washington, DC: The National Academies Press.

Institute of Medicine. (2010). *Sex differences and implications for translational neuroscience research—Workshop summary.* Washington, DC: The National Academies Press.

Institute of Medicine. (2012). *Sex-specific reporting of scientific research—Workshop summary.* Washington, DC: The National Academies Press. Retrieved from *http://iom.edu/Reports/2012/Sex-Specific-Reporting-of-Scientific-Research.aspx*

Nagel, J. D. & Rudick, J. (2012). Abstracts from the NIH Office of Research on Women's Health Ninth Annual Interdisciplinary Women's Health Research Symposium November 15, 2012. *Journal of Women's Health, 21*(10), 985–1013.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (1999). *Agenda for research on women's health for the 21st century* (NIH Publication No. 99-4385). Bethesda, MD: National Institutes of Health.

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2010). *Moving into the future with new dimensions and strategies: A vision for 2020 for women's health research. Strategic plan—Executive summary* (NIH Publication No. 10-7606). Bethesda, MD: National Institutes of Health.

III. ORWH Biomedical Career Development Activities

A major component of the ORWH mandate is to develop opportunities and support for the recruitment, retention, reentry, and advancement of women in biomedical careers. In 1992, ORWH held a public hearing and a major career development workshop and then published a report on its findings, "Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century" (ORWH, 1995). Since that time, ORWH has initiated a number of programs to nurture the participation and advancement of women in biomedical careers to ensure that priorities in women's health remain at the forefront of the NIH research agenda and to address career issues, barriers to participation, and the concerns of women and minorities in science. In addition, ORWH has expanded its activities to pursue career advancement for both women and men researchers who wish to conduct research on women's health, including the investigation and elucidation of the role of sex and gender factors in health and disease. The major programs of ORWH support in FYs 2011 and 2012 for mentored research training and career development are described in this section.

- A reentry program that supplements NIH grants to help scientists who have interrupted their careers to fulfill family or other obligations so that they can resume their careers and update their research skills.
- The Women's Reproductive Health Research (WRHR) and Career Development K12 Program to support the research career development of obstetrician-gynecologists.
- The Building Interdisciplinary Research Centers in Women's Health (BIRCWH) K12 Program to support junior faculty who are beginning basic, translational, clinical, or health services research in women's health. This program is described in detail in Section II.

Also described in this section are a variety of activities that received ORWH support in FY 2011 and FY 2012. These include activities in the NIH intramural program, fellowships, and collaborations with professional societies to promote the development of women in biomedical careers. Among them are the following:

- Activities of the NIH Working Group on Women in Biomedical Careers;
- Activities of the Intramural Program on Research on Women's Health (IPRWH);
- Programs of the NIH Office of Intramural Research (OIR)/Office of Intramural Training and Education (OITE); and
- Collaborations with professional societies, including fellowships, meetings, and curriculum development activities.

Research Supplements to Promote Reentry into Biomedical and Behavioral Research Careers

The NIH Reentry Program provides funding for administrative supplements to existing NIH research grants. The program is designed to support the full-time or part-time research of individuals with high potential to reenter an active research career after a qualifying interruption for family or other responsibilities. The announcement for the program was initially issued in 2004 and was reissued in 2008 and 2012.

The Reentry Program includes three components that contribute to the process of reestablishing awardees as independent competitive research scientists: participation in an ongoing NIH-funded research project, an opportunity to update and enhance research capabilities, and a carefully planned mentoring program developed by the mentor and the awardee.

In 2007, NIH issued a notice (NOT-OD-07-068) that broadened eligibility for a Reentry Award to include postdoctoral fellows. In addition to support from ORWH, the program has received support from 25 NIH Institutes, Centers, and Offices in the Office of the NIH Director. As of FY 2012, more than 135 women and men have received

awards under this program. The section below provides a brief description of the research interests and backgrounds of the FY 2011 and FY 2012 awardees who have been supported in part by ORWH.

FY 2011 Reentry Awardee

National Heart, Lung, and Blood Institute (NHLBI):
Dolena Ledee, Ph.D. (Year 2)

Institution: Seattle Children's Research Institute

Principal Investigator (PI):
Michael Portman, M.D.

Grant: R01HL060666

ORWH Contribution: $20,000

Title: Metabolism During Mechanical Circulatory Support in the Developing Heart

Dr. Ledee expressed a strong desire to reestablish her research career after taking a 2-year hiatus for family reasons. Previously, Dr. Ledee had focused on molecular and cell biological research, and she intends to transfer these skills to the field of cardiovascular research. Dr. Ledee plans to use the funds provided to receive formal and practical experience in the area of research in cardiovascular metabolism, as well as to benefit from the mentorship of senior researchers and an extended network of collaborators.

FY 2012 Reentry Awardees

NHLBI: Faye E. Martin, Ph.D. (Year 1)

Institution: Colorado State University

PI: Santiago Di Pietro, Ph.D.

Grant: R01HL106186

ORWH Contribution: $20,000

Title: Rab32, Rab38, and Myosin 5c in Platelet-Dense Granule Biogenesis

Dr. Martin has a Ph.D. in biochemistry and research experience in molecular biology and X-ray crystallography. She took a 2-year hiatus from research because of family issues. She is reentering at the assistant professor level, with strong mentoring support from Dr. Di Pietro and colleagues. She has kept up with the relevant literature during her hiatus, and she is now ready to resume her training and continue the pursuit of an independent career in biomedical sciences.

NHLBI: Ahmed Bakillah, Ph.D. (Year 1)

Institution: SUNY Downstate Medical Center

PI: Mahmood Hussain, Ph.D.

Grant: R01HL095924

ORWH Contribution: $20,000

Title: Rab32 Avoiding Toxicity Associated with MTP Ablation

Dr. Bakillah previously spent 4 years as a postdoctoral fellow in Dr. Hussain's laboratory. Following a successful postdoctoral fellowship, he took a position in the pharmaceutical industry. After several years, family issues led him to resign his position. He now plans to restart his academic career by returning to Dr. Hussain's laboratory with support from a reentry supplement.

Women's Reproductive Health Research Career Development Program

Program Overview

The WRHR Program was initiated in 1998 in response to concerns about the need for greater numbers of physician scientists in women's reproductive health. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and ORWH have cofunded the program since that time. The goals of the program are to increase the nation's supply of junior investigators in women's reproductive health research, provide junior faculty with state-of-the-art training in women's reproductive health research in an academic setting, stimulate women's research in reproductive health over a variety of disciplines, and secure outstanding research experiences for junior faculty that will lead to careers as successful independent investigators. Program eligibility is

limited to obstetrician-gynecologists, known as WRHR Scholars, who have recently completed postgraduate clinical training and are commencing basic, translational, and/or clinical research relevant to the field of obstetrics and gynecology. The program's emphasis is on research relevant to obstetrics and gynecology and its subspecialties and related fields, including, for example, maternal-fetal medicine, gynecologic oncology, reproductive endocrinology, infertility, adolescent gynecology, and urogynecology.

Twenty programs have been funded since the program's inception, and in January 2012, 17 WRHR programs were active in departments of obstetrics and gynecology across the United States. Programs were competitively reviewed and selected for funding in FY 2009 and FY 2010; ORWH continues to provide $680,000 annually in total support to these programs.

As of 2012, 189 WRHR Scholars had been appointed to the program. The majority (64 percent) of scholars are women. Scholars are required to be physicians holding an M.D. or D.O. degree and must have completed residency training in obstetrics and gynecology. If the scholar has chosen to subspecialize, she or he must be in the final research year of postdoctoral fellowship training in obstetrics and gynecology. However, completion of subspecialty training is not required of candidates practicing general obstetrics and gynecology. As of 2012, 159 scholars held faculty appointments, with 23 also holding leadership positions.

Independent Grant Support for WRHR Scholars

WRHR Scholars have demonstrated success in obtaining independent grant support. Sixty-eight percent (122) of all WRHR Scholars who had been in the program for a minimum of 12 months as of January 2012 had submitted grant applications to NIH, and as of that date, 36 percent of all WRHR Scholars had received NIH funding. Most applications were submitted to NICHD. For those who submitted applications, the person success rate (i.e., the success rate for individual applicants) for R Series awards, excluding R13, R25, and R36, was 43 percent, while the person success rate for R01 awards was 40 percent. As of January 2012, WRHR Scholars had an application success rate of 14 percent for R Series and 15 percent for R01 awards. Application and success rates for women did not differ significantly from those for men.

The WRHR program sites active in FY 2011 and FY 2012, along with their PIs and research directors (RDs), are shown in the listings below.

FY 2009 WRHR Program Sites

WRHR at the University of Washington

Institution: University of Washington, Seattle, WA

PI: David A. Eschenbach, M.D.

RD: Susan Reed, M.D., M.P.H.

Magee-Womens Basic and Translational Reproductive Health Training Program

Institution: Magee-Womens Research Institute and Foundation, Pittsburgh, PA

PI: W. Allen Hogge, M.D.

RD: Yoel Sadovsky, M.D.

WRHR Career Development Program at Washington University in St. Louis

Institution: Washington University in St. Louis, MO

PI: George A. Macones, M.D., M.S.C.E.

RD: Kelle H. Moley, M.D.

Yale WRHR Career Development Center

Institution: Yale University, New Haven, CT

PI: Charles J. Lockwood, M.D., M.H.C.M.

RD: Richard B. Hochberg, Ph.D.

Detroit Reproductive Career Development Research Center

Institution: Wayne State University, Detroit, MI

PI: Theodore B. Jones, M.D., FACOG

RD: Michael P. Diamond, M.D.

University of California, San Francisco, WRHR Career Development Program

Institution: University of California, San Francisco, CA

PI: Linda C. Giudice, M.D., Ph.D., M.Sc.

Co-RDs: Synthia Mellon, Ph.D., and Leslee Subak, M.D.

WRHR: A Mentoring Program in Women's Reproductive Health Research at the University of Vermont

Institution: University of Vermont, Burlington, VT

PI: Mark Phillippe, M.D., M.H.C.M.

RDs: George Osol, Ph.D., and Elizabeth Bonney, M.D. (Associate RD)

Iowa WRHR Career Development Center

Institution: University of Iowa, Iowa City, IA

PI: Kimberly K. Leslie, M.D.

RD: Mario Ascoli, Ph.D.

University of Texas Medical Branch at Galveston WRHR Career Development Center of Excellence

Institution: University of Texas Medical Branch at Galveston, TX

PI: Gary D.V. Hankins, M.D.

RD: Chandra Yallampalli, D.V.M., Ph.D.

Penn Center for Career Development in Women's Health Research

Institution: University of Pennsylvania, Philadelphia, PA

PI: Deborah A. Driscoll, M.D.

RD: Christos Coutifaris, M.D., Ph.D.

FY 2010 WRHR Program Sites

Brown/Women and Infants Hospital WRHR Career Development Program

Institution: Women & Infants Hospital of Rhode Island/Brown University, Providence, RI

PI/RD: Maureen G. Phipps, M.D., M.P.H.

University of Michigan WRHR Career Development Program

Institution: University of Michigan, Ann Arbor, MI

PI: Timothy Johnson, M.D.

RD: Yolanda R. Smith, M.D., M.S.

Research Career Development in Obstetrics and Gynecology

Institution: Northwestern University Feinberg School of Medicine, Chicago, IL

PI: Sharon Dooley, M.D.

RD: Serdar E. Bulun, M.D.

Colorado WRHR Career Development Center

Institution: University of Colorado Denver, CO

PI: Nanette Santoro, M.D.

Co-RDs: James McManaman, Ph.D., and Andrew P. Bradford, Ph.D.

University of Kansas Medical Center WRHR Career Development Program

Institution: University of Kansas Medical Center, Kansas City, KS

PI: Carl P. Weiner, M.D., M.B.A.

Obstetrics/Gynecology Faculty Research Career Development Program

Institution: University of Alabama at Birmingham, AL

PI: William W. Andrews, Ph.D., M.D.

RD: Ronald D. Alvarez, M.D.

Reproductive Sciences Research Career Development Center

Institution: University of California, San Diego, CA

PI: Thomas R. Moore, M.D.

RD: Pamela L. Mellon, Ph.D.

Annual WRHR Investigators and Scholars Meeting

As part of the WRHR grant award, there is an annual meeting of WRHR Investigators and Scholars. In 2012, the meeting was hosted by the University of Pennsylvania in Philadelphia. Highlights of the meeting included a keynote address by NICHD Director Dr. Alan Guttmacher and a session on the NIH grants process that was presented by NICHD staff.

Three former WRHR Scholars who successfully transitioned to independent research careers, Drs. Clarisa Gracia, Hygriv Simhan, and Kristina Adams, presented updates on their research programs and also provided guidance for a successful transition to independent research. More than 40 current scholars were given an opportunity to either make an oral presentation or participate in one of two interactive poster sessions. Scholars presented on a broad range of basic, clinical, and translational research areas that are highly relevant to the missions of NICHD and ORWH.

NIH Working Group on Women in Biomedical Careers

To identify barriers to the scientific career development of women, in 2005 ORWH provided funding to the Committee on Science, Engineering, and Public Policy, a joint program of the National Academy of Sciences (NAS), the National Academy of Engineering, the Institute of Medicine, and the National Research Council Standing Committee on Women in Science and Engineering. Additional funding was provided later by Eli Lilly and Co., the National Science Foundation, and the Ford Foundation. With this funding, NAS created the ad hoc Committee on Maximizing the Potential of Women in Academic Science and Engineering. In 2007, the Committee issued a widely read report titled "Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering" (2007).

"Beyond Bias and Barriers" noted that women comprised an increasing proportion of science and engineering majors but that their representation in leadership positions in academic institutions, scientific and professional societies, and honorary organizations was low relative to the number of qualified women. The report concluded that increasing the representation of women in academic positions would require overarching reforms, including decisive action by university administrators, professional societies, Federal funding agencies, foundations, other government agencies, and Congress.

Establishment of the NIH Working Group on Women in Biomedical Careers

In early 2007, in response to the NAS report, NIH Director Elias Zerhouni, M.D., created the NIH Working Group on Women in Biomedical Careers, a trans-NIH effort to consider barriers for women in science and to develop innovative strategies to promote entry, recruitment, retention, and sustained advancement of women in biomedical and research careers. Since that time, the Working Group has sponsored national workshops on mentoring women, issued reports on best practices, developed a funding grant program

to study causal factors in women's career development, and engaged in a number of other activities. Major activities in FY 2011 and FY 2012 are described below.

Currently, the Working Group is cochaired by NIH and ORWH directors, and its membership consists of IC directors and deputy directors as well as professionals from across NIH at different career levels, including men and women, individuals from underrepresented groups, postdoctoral fellows, young investigators, and dual-career couples. (Members of the Working Group in FY 2011 and FY 2012 are listed in Appendix F). The activities of the Working Group, which are implemented in collaboration with numerous NIH Offices and committees, are spearheaded by seven committees, each chaired by a Working Group member appointed by the NIH director and include additional appropriate intramural and extramural staff.

The Working Group Web site, *http://womeninscience.nih.gov*, which is supported by ORWH, provides a central focus for career development resources for women, from both NIH and other organizations. In addition, the site includes links to more than 300 news articles and reports about women in science. Moreover, the Working Group maintains a listserv for NIH Updates on Women in Science (NUWS), an e-newsletter containing articles and items pertaining to women in science, profiles of outstanding early-career women scientists, and examples of best practices for the recruitment, retention, and advancement of women that are being implemented in institutions and universities across the United States.

Women of Color Research Network

In August 2011, the Women of Color in Biomedical Careers Committee of the Working Group launched the Women of Color Research Network (WoCRn). A new Web site, *http://www.wocrn.nih.gov*, was designed as an instrument of outreach to women of color to assist them in finding mentors and role models, navigating the NIH grants process, and getting advice to facilitate entering biomedical careers and advancing in them. As of early 2013, membership exceeded 800 individuals. ORWH has supported the development of the WoCRn by providing funding and personnel support.

Reports from Working Group Workshops

The Working Group has produced a number of reports that continued to be in demand in FY 2011 and FY 2012. Among these are a report of the National Leadership Workshop on Mentoring Women in Biomedical Careers (Working Group, 2008) and a report titled "Women in Biomedical Research: Best Practices for Sustaining Career Success" (Working Group, 2009). Both reports are in their second printing, with more than 6,500 copies of each having been distributed. NIH videocasts of the meetings, the proceedings, and other resources are available at *http://womeninscience.nih.gov.*

Working Group Extramural Initiatives

Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering Request for Applications (RFA-GM-09-012)

This RFA (Request for Applications) was developed by the Working Group Committee on Research and Evidence to Promote Women in Science Careers. The aims of the program are to support research on 1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering; and 2) the efficacy of programs designed to eliminate sex/gender disparities and promote the careers of women in the fields described. Among the areas of interest are individual characteristics, including family and economic circumstances; the institutional/departmental environment; organizational structure, culture, or practices of different disciplines; and features of the broader social and cultural context.

In October 2009, NIH announced its funding of 14 grants estimated to total $16.8 million over 4 years with support from 11 ICs and 4 Offices within the Office of the Director (OD). The full text of the announcement,

as well as the listing of sponsoring ICs and names of grantees and their funded projects, can be found on the Women in Biomedical Careers Web site: *http://womeninscience.nih.gov/funding/index.asp*.

In FY 2011 and FY 2012, ORWH provided support for one of the grants, 1R01HD064655, to Deborah Helitzer at the University of New Mexico, Albuquerque. The study sponsored by her grant, titled Achieving a Critical Mass of Women in Biomedical Faculty: Impact of 3 U.S. Programs, examines the impact on retention and career success of individual women faculty who participated in three longstanding national programs, each of which targeted a separate career stage, in a comparison with women and men at the same career stages who did not participate in these programs. This research also aims to elucidate the patterns and processes that contribute to the experiences of individuals and their institutions as a means to identify the barriers and facilitators—historic and new, individual and institutional—that face women faculty in attaining positions of leadership at academic health centers and in transforming institutional culture.

Under the leadership of National Institute of General Medical Sciences (NIGMS) Acting Director Judith Greenberg, Ph.D., the NIH Working Group held a workshop in November 2012 for the PIs of the grants awarded under the RFA. They convened on the NIH campus to present their preliminary findings and discuss collaborations and efficient next steps. Dr. Shirley Malcolm, Head of the Directorate for Education and Human Resources Programs of the American Association for the Advancement of Science (AAAS), was the keynote speaker, and Dr. Hannah Valantine, Senior Associate Dean and Professor of Cardiovascular Medicine at Stanford University School of Medicine, offered remarks. ORWH provided funding and personnel support for this workshop. A workshop report can be found at *http://womeninscience.nih.gov/workshops.asp*.

Amendments to Instructions for Biographical Sketches in NIH Grant Applications

In 2011, the NIH Office of Extramural Research (OER), in collaboration with the Working Group, developed a mechanism to allow applicants to explain a break in their publication record on NIH grant applications. For applications submitted on or after May 25, 2011, the biographical sketch includes the following instructions: "Personal statement. Briefly describe why your experience and qualifications make you particularly well-suited for your role (e.g., PD/PI, mentor) in the project that is the subject of the application. Within this section you may, if you choose, briefly describe factors such as family care responsibilities, illness, disability, and active duty military service that may have affected your scientific advancement or productivity." The new instructions will provide peer reviewers and others with additional information on which to base their assessments of the qualifications and productivity of the applicant. The change was implemented based on comments expressing concerns that the existing biosketch could work against applicants when there were unexplained gaps.

Presidential Awards for Excellence in Science, Mathematics, and Engineering Mentoring

The OER, in collaboration with the Working Group, placed a notice in the NIH Guide to Grants and Contracts to make NIH grantees aware of the Presidential Awards for Excellence in Science, Mathematics, and Engineering Mentoring (PAESMEM) program and to encourage them to apply. Among the 2011 NIH-funded awardees were Dr. Andrew Tsin, of the University of Texas at San Antonio, who won the PAESMEM for his outstanding achievements in mentoring, particularly for underrepresented minority students. Dr. Stacie Geller, PI of the University of Illinois at Chicago (UIC) BIRCWH Program, was a winner of a PAESMEM for her UIC Women in Science and Engineering (WISE) mentoring program.

Working Group Initiatives for NIH Employees

In FY 2011 and FY 2012, a number of initiatives were developed or are ongoing by the Working Group on Women in Biomedical Careers in conjunction with OIR and the Council of Scientific Directors that were aimed at improving and enhancing employee work environment. These initiatives are described below.

Pilot Back-Up Care Program. Thanks to the efforts of the NIH Child Care Board and the Working Group, the NIH Office of Research Services (ORS) launched a pilot back-up care program in January 2012. Administered through a contract with the caregiver Bright Horizons, this program offers short-term childcare, elder care, and self-care to NIH employees and intramural trainees. In the first 8 months of the program, 686 employees registered a total of 1,055 care recipients. Care was used 195 times, saving 164 employee workdays. Through increased advertising and expanded eligibility, NIH hopes to increase usage further in 2013. More details about the Pilot Back-Up Care Program can be found on the ORS Web site: *http://www.ors.od.nih.gov/pes/dats/childcare/pages/nihback-upcareprogram.aspx.*

Pilot "Keep the Thread" Program. The Committee on the NIH Intramural Research Program (IRP) of the Working Group has launched a new pilot program to increase flexibility for NIH intramural fellows who need alternative career development schedules. This is an accommodation and reentry program open to all NIH postdoctoral fellows who are supported by Intramural Research Training Awards or Cancer Research Training Awards (IRTA/CRTA). Emphasizing flexibility, to be mutually agreed upon by the fellow and the PI and with approval of the Scientific Director, the program offers an array of options, ranging from alternative work schedules to temporary part-time work. The goal of the program is to encourage trainees to stay connected to the NIH community during times of intensive personal and/or caregiving needs in order to facilitate eventual reentry into full-time research. The program aims to recognize common roadblocks to balancing work and personal life in order to address these issues proactively. Information about this new program has been added to the NIH Sourcebook (National Institutes of Health, 2012).

Northwest Child Care Center. Funds for the construction of the Northwest Child Care Center on the NIH campus were secured in the FY 2010 budget. The project is being overseen by the NIH Office of Research Facilities; when completed, it will add an additional 130 childcare slots on campus. A contract has been awarded to a firm to begin designing and building the new center, which is projected to open in fall 2014. This center will come to fruition through the efforts of many individuals and groups at NIH, including the ORS, the Office of Research Facilities Development and Operations, the Child Care Board, and the OD. Members of the Working Group in both OIR and ORWH continue to play an active role in moving these efforts closer to their ultimate successful conclusion.

Voluntary Leave Bank Program. The NIH Voluntary Leave Bank Program (VLBP) offers income protection to eligible members of the bank who are affected by a personal or family medical emergency. VLBP can provide employees with the peace of mind that comes from knowing that they will continue to receive paychecks during times of extended medical or family leave. VLBP differs from the existing Voluntary Leave Transfer Program (VLTP) in that, under VLTP, donations are made from individuals directly to other individuals, whereas under the VLBP, donated leave is typically pooled and distributed as needed. VLBP was piloted in the National Cancer Institute in 2010, and in 2011, the National Human Genome Research Institute and the National Institute of Allergy and Infectious Diseases joined as member institutes. Members of the Working Group and others within the OD have been working with leadership throughout the OD to obtain funds required to make all computer upgrades and to open the program to all NIH employees. ORWH provided $200,000 during FY 2009–FY 2011 to launch the preliminary activities for the initiation of VLBP. These efforts include modifying the Integrated Time and Attendance

System (ITAS) to include the option for the Voluntary Leave Bank Program and supporting an independent Federal Occupational Health Medical Review Board to ensure that requests are appropriate and medically sound. More information on the NIH VLBP can be found on the Office of Human Resources Web site (NIH Office of Human Resources, 2013).

NIH Intramural Program on Research on Women's Health

The Intramural Program on Research on Women's Health (IPRWH) was developed in 2002 in conjunction with ORWH and the NIH OIR. The IPRWH serves as the focal point within the NIH IRP for women's health and sex and gender comparison research, and it provides a means of fostering cross-disciplinary collaborations and the sharing of ideas and findings. Members of the IPRWH in FY 2011 and FY 2012 are listed in Appendix G.

Women's Health Interest Group

Women's Health Interest Group (WHSIG) provides a forum for researchers across NIH to meet, establish collaborations, and learn about sex-based differences (beyond the effects of hormones) that are relevant to molecular, cellular, genetic, and developmental processes and affect organ systems, behavior, and the organism as a whole. A WHSIG lecture series is organized by the IPRWH and sponsored by ORWH. The series includes presentations on both basic science and clinical research topics of relevance to women's health. Presenters are experts in a wide variety of scientific disciplines and come from both the NIH intramural program and the outside scientific community.

IPRWH/NIH–FRQ Research Careers Transition Award Program

In 2011, ORWH and the IPRWH helped to establish a new international collaborative training program with the Fonds de Recherche du Québec (FRQ). The NIH–FRQ Research Career Transition Award Program aims to foster collaborative biomedical research in mutual areas of excellence while training the next generation of research scientists. Applicants will be selected by the FRQ through a competitive process. Selected fellows will work in NIH IRP labs for 2 to 3 years, fully funded by FRQ. Fellows are encouraged to include an element addressing sex and/or gender factors in their research projects, as scientifically appropriate. Mentoring for these fellows will occur under the auspices of the IPRWH and ORWH.

Office of Intramural Training and Education Programs

The NIH OITE is located in the OIR. OITE helps NIH trainees develop the scientific and professional skills needed to become leaders in the biomedical research community. This office coordinates programs, provides individual assistance, and prepares resources to enhance the scientific, professional, and career development of NIH trainees. OITE leads trans-NIH initiatives aimed at providing a comprehensive training experience for each trainee, from the trainee's arrival at NIH to her/his transition back to school or into the scientific workforce. The expectation is that NIH will lead the biomedical research community in promoting best-mentoring practices and in developing outstanding and innovative training programs for all trainees, including women, underrepresented minorities, and trainees from disadvantaged backgrounds. NIH trainees come from more than 75 countries, and about 50 percent are women, providing NIH with the unique opportunity to promote the career development of women scientists and future leaders in women's health research across the globe. Although postdoctoral, research, and clinical fellows are the largest trainee population in the IRP (about 4,000), there are also approximately 450 graduate students and 700 postbaccalaureate Intramural Research Training Award recipients working on NIH campuses. In addition, OITE serves the career development needs of about 1,200 summer interns, who range from high school students to graduate and professional school students. The programs that received ORWH support in FY 2011 and FY 2012 are described below.

Skill-Building Workshops and Courses

For many years, ORWH has supported the development and implementation of a number of professional skills development activities for NIH intramural trainees through OITE. Activities include career planning, teaching skills, and science communication and writing. The educational programs are provided in a range of formats, including (1) all-day symposia; (2) 1–3-hour workshops featuring a speaker and/or a panel discussion; (3) short workshops followed by breakout and small-group meetings; (4) courses on a focused topic that meet for multiple sessions; and (5) small-group discussions, support groups, and brown bag lunches. Attendance at OITE programs remains high, with participation by fellows at all training levels and on all campuses. In 2012, videocasts and podcasts of workshops, retreats, and meetings sponsored by OITE were downloaded more than 200,000 times. With the redesign of the ORWH Web site, OITE has increased its outreach to students outside of NIH. Local colleges and universities are invited to attend select offerings. OITE workshops and programs supported in whole or in part by ORWH are reviewed below:

Scientists Teaching Science. This 2-hour workshop introduces graduate students and postdoctoral fellows to concepts related to classroom teaching, including learning styles, cultural awareness and diversity, inquiry-based teaching, the writing of course objectives, creating valid assessments, alternatives to lecturing, writing a syllabus, and the history/philosophy of teaching. Workshop attendees may participate in a 9-week course that explores each topic in greater detail. This course can be taken online or in a traditional classroom format.

Basic Science Writing. This 4-week course is for trainees interested in improving their writing skills and was designed for both native and non-native English speakers. The workshop focuses on English grammar, punctuation, and sentence and paragraph structure. This course was offered 10 times in FY 12.

Writing and Publishing a Scientific Paper. This 4-week course for postdoctoral fellows and graduate students offers trainees the opportunity to write a rough draft of a scientific paper. Students write and receive feedback on sections of their manuscripts, learn how to construct figures and tables, discuss the abstract and the submission cover letter, and develop a greater understanding of the publishing process. This course is offered 10 times per year.

Leadership and Management Programs for NIH Intramural Fellows

OITE offers broad support to help trainees develop leadership and management skills in the postdoctoral, clinical fellow, and graduate student communities. ORWH funds have been used to contract with outside experts to help develop courses specifically related to research environments. Although these outside experts initially teach the courses, the primary goal is to develop the in-house expertise to deliver programs. This is because of the large number of fellows who wish to participate and because of an increase in requests to deliver this content at other universities and at national meetings. OITE offerings are described below:

Assertiveness Training. This workshop, open to all trainees, explores strategies for communicating one's needs in a variety of situations and helps fellows learn how to be more assertive, how to speak up for themselves, and how to decide when to speak up and when not to. The workshop is taught by OITE career counselors/staff and offered multiple times each year; ORWH provided course materials in FY 2011 and FY 2012.

Workplace Dynamics Series. This series of workshops provides trainees the opportunity to gain awareness of themselves and others through the Myers-Briggs Type Indicator (MBTI) instrument and interactive exercises exploring communication, conflict, influence, and teams. Using feedback from pilots tested in FY 2010, a series of five workshops was developed:

- Workplace Dynamics I: Gaining Self-Awareness
- Workplace Dynamics II: Communication, Learning, and Influencing Others

- Workplace Dynamics III: Conflict and Feedback
- Workplace Dynamics IV: Team Skills
- Workplace Dynamics V: Diversity in a Multicultural Society

The workshops were offered several times in FY 2011 and FY 2012. The workshops are offered on all NIH campuses and at national meetings, including the National Postdoctoral Association and the Annual Biomedical Research Conference for Minority Students. Sections are taught by OITE staff and outside experts. In both FY 2011 and FY 2012, ORWH funds were used to cover the cost of MBTI assessments, course materials, contractors, and books on leadership to supplement the workshops.

Management Training Course. An intensive 2-day course provides advanced postdoctoral students and fellows with an overview of common management concepts. Topics include managing yourself, staffing your group, interpersonal communication, managing expectations, diversity, and team dynamics. In FY 2011 and FY 2012, ORWH funds were used for course materials and for the cost associated with two contractors who participated.

Career Advancement Toolkit Tracks

The Career Advancement Toolkit (CAT) consists of three workshop series for postdoctoral fellows and graduate students: (1) Career Decisions 101; (2) The Academic Job Search; and (3) The Industry Job Search. Each series included three to four workshops presented throughout the year covering topics such as job materials, networking, interviewing, and negotiating. Substantial portions of each CAT track were videocast for viewing by NIH and non-NIH trainees. These recorded workshops are archived on the OITE Web site. A 2-day course on the drug discovery process that includes significant interaction was developed by OITE with industry, FDA, and NIH scientists. The Translational Science Training Program (TSTP) course was developed to prepare graduate students and postdoctoral fellows for careers in biotechnology. ORWH support was used to develop and implement TSTP, to develop course materials for other career workshops, and to purchase career books that supplemented the workshops.

Training in Diversity

In summer 2012, OITE hosted a 12-session course in which the participants explored the meaning and consequences of various dimensions of difference. Dr. Michael Sheridan, a Catholic University of America social work professor with expertise in diversity, used several specific topics, including racism, ageism, sexual orientation, and the impact of socioeconomic status, to explore difference while encouraging participants to consider implications for both their personal and professional growth. The group, which included trainees and staff, examined the relevance and application of diversity topics to health-related research. Course participants have encouraged OITE to develop additional offerings in this area and have agreed to work with OITE throughout this development process. ORWH funds were used to support the development of the course and to pay the course instructor.

NIH Community College Outreach

NIH Community College Day. ORWH provided support for this OITE program to provide community college students and faculty an opportunity to visit the NIH campus and to learn about NIH as well as to discuss careers and training opportunities in the biomedical and health care fields. Participation has grown from 75 students in the first year to more than 600 in 2012. The program includes a plenary lecture, a seminar from an NIH intramural investigator, and talks from participants in the Community College Summer Enrichment Program, as well as career workshops and a networking lunch. The program has attracted national attention, with participants this year from Florida, Texas, and most Mid-Atlantic states.

Community College Summer Enrichment Program. In 2010, OITE coordinated the first NIH Community College Summer Enrichment Program, which has hosted 18 to 22 students each year since its inception. The students participate in an intensive orientation, weekly group activities, and the summer intern poster session. Applications

have increased fourfold since 2010, with many more coming from across the United States. The program directors have completed an evaluation of the first three cohorts and are very enthusiastic about the long-term potential of this program to have a positive impact on pipeline issues, as greater than 60 percent of program participants come from underrepresented groups.

ORWH Support for Other Summer Programs

FAES High School Summer Student Program

This program (Foundation for Advanced Education in the Sciences, or FAES) exposes Washington, D.C., metropolitan area high school students (more than 50 percent of them female) to biomedical research at a time when they are still developing their career plans and thereby enhances the possibility that they will choose science careers. The students, who come from both public and private schools in Maryland, Virginia, and Washington, D.C., learn how to design and carry out experiments, as well as how to present their research. Funds are used to support stipends for the students.

In the summer of 2011, the program had 25 new students and 13 returning students. There were 24 women and 14 men, including 17 minorities (7 were African-American). In the summer of 2012, the program had 25 new students and 8 returning students. There were 19 women and 14 men, including 22 minorities (including 4 African-Americans and 3 Hispanics).

Each summer started with an informational meeting at which the students learned the history of the program and heard about the structure of NIH, IRP, and ORWH. They also received guidance on how to prepare and give effective research presentations. Each week, for 8 weeks, the students met as a group for a lunchtime session, where a subset of students gave presentations on their research. Included in the audience were their preceptors, some of the advisors for the program (all members of the NIH scientific staff), Dr. Chuck Dearolf (Assistant Director in OIR, and Debbie Cohen (Director of Post-baccalaureate and Summer Program Services). In 2011, Dr. Judith Walters (an NIH senior investigator and advisor to Dr. Michael Gottesman, Deputy Director for Intramural Research), also attended these presentations. In addition, Dr. Joslyn Kravitz from ORWH participated at the orientation meeting in 2011, and Dr. Keren Witkin from ORWH attended student research presentations in 2012. The presence of NIH scientific staff at these meetings ensured a lively discussion of each presentation, and it put each research project into a broader biomedical context. Each year, the students presented posters at the NIH Summer Student Poster Presentation Day, as they learned not only how to carry out a research project but also how to ask important questions, how to design experiments to answer those questions, and how to communicate their results to other scientists.

Wellesley in Washington Program

Each summer during FY 2011 and FY 2012, ORWH participated in the Wellesley in Washington Program, which provides a unique experience for Wellesley College students between their junior and senior years. Summer interns at ORWH focus on women's health research and policy. ORWH hosted two summer interns in 2011 as part of the Wellesley in Washington Program. Halle Ritter researched and developed background materials for a mentor training course, and Gena Hong analyzed data on breast cancer in women of color and a variety of other topics. ORWH also hosted two summer interns from Wellesley College in 2012. Madeleine Whitaker researched sex differences in autism and the potential of using oxytocin for autism therapy, and she also developed a plain-language document on bench-to-bedside research at NIH. Cobren Greer gathered information on breast cancer in women of color and created a factsheet on pelvic floor disorders. At the end of each summer, the students prepared posters for the NIH Summer Student Poster Presentation Day.

ORWH Support for Other NIH Career Development Programs and Activities

Fogarty International Clinical Research Training for Scholars and Fellows Program

In FY 2011 and FY 2012, ORWH provided support to two postdoctoral fellows in the Fogarty International Clinical Research Training for Scholars and Fellows Program for the study of air pollution, fetal growth, and maternal health in China. The expected outcome of this training program is to create a network of leaders in global health research.

National Institute of Diabetes and Digestive and Kidney Diseases Travel Awards

In FY 2011 and FY 2012, ORWH collaborated with the National Institute of Diabetes and Digestive and Kidney Diseases and the National Medical Association (NMA) in supporting residents and fellows interested in academic medicine by directing a special 2-day academic skills workshop held in conjunction with the Annual Convention and Scientific Assembly of the NMA. Topics ranged from grantsmanship to time management skills. NIH anticipates that, by taking advantage of this opportunity, a greater number of physicians from communities that are medically underserved will be trained and subsequently return to these underserved communities.

ORWH Support for Professional Society Activities

ORWH works with professional societies and other nongovernmental entities to support meetings and programs that foster women's health and career development. Presented below are descriptions of programs and activities sponsored in FY 2011 and FY 2012.

Association of Women in Science Seminar Series—Bethesda Chapter

The Association of Women in Science (AWIS) seminar series is a free yearlong program covering a range of issues of interest to women. The seminars, which are held on the NIH campus, are well attended by both men and women. Each year the series includes a networking event called "Have a Meal with Your Mentor." In addition, the Bethesda AWIS chapter honors one scientist every year with an award for his or her role in mentoring young women scientists. Topics covered seminars held in 20110 and 2012 all with ORWH support, included mentoring, decision making for career success, and careers at FDA and NIH. In addition, the AWIS Bethesda Chapter hosts a talk by the annual Pittman Lecturer on her career path.

Women in Cell Biology Workshops

The Women in Cell Biology (WICB) Committee is a longstanding committee of the American Society for Cell Biology (ASCB), which provides career support and advice for women scientists. The committee responds to reports of discriminatory practices, offers a speaker referral service to help program organizers identify female speakers, and produces monthly columns for the ASCB newsletter. ORWH provided funding to support the ASCB Annual Meeting, which took place in Denver on December 3–7, 2011. Specifically, the funds supported the Career Discussion and Mentoring Roundtables as well as the WICB workshop "Leveraging Your Ph.D. in the Real World."

Women's Health Issues in the Dental School Curriculum Survey

In 2011, ORWH co-funded a dental curriculum study with the American Dental Education Association (ADEA) to improve the training of dental health professionals by increasing their knowledge of factors affecting the oral/systemic health of women and enhancing their appreciation of the role of sex differences in dental hygiene. The desired outcome was to update curricula and identify knowledge gaps that require ongoing research. The aim of the project was to survey the 58 U.S. dental schools with regard to their curriculum content and objectives for women's health and related issues across the lifespan. The survey, which was to expand on a previous survey, is focused on knowledge gaps with regard to the oral/systemic relationships that affect the health and well-being

of women and girls. Outcomes of the survey were anticipated to serve as the basis for curriculum modification and for future research directed toward women's health. A written report of the survey results was published in 2012, and a symposium was presented in tandem with the 2012 ADEA Annual Session and Exhibition (National Program) in Orlando, Florida, in March 2012.

Summary: Biomedical Career Development Program Activities Support the Implementation of the NIH Strategic Plan for Women's Health Research

Through its support for a wide variety of career development activities in FY 2011 and FY 2012, ORWH has made significant efforts to address the sixth goal of the NIH Strategic Plan, which is to employ innovative strategies to build a well-trained, diverse, and vigorous women's health research workforce. With a focus on mentoring and on providing a wide variety of opportunities for professional growth, ORWH supported programs that meet the needs of a diverse group of scientists at all levels, with special emphasis on students, fellows, and early-career scientists. Through these efforts, which are undertaken in collaboration with the NIH ICs, IRP, and external professional societies, ORWH aims to promote the recruitment, retention, reentry, and advancement of women in biomedical careers while also furthering the participation of both men and women in research on women's health, including interdisciplinary investigations of the role of sex and gender factors in health and disease. The activities supported in FY 2011 and FY 2012 have paved the way for future endeavors that will help expand and diversify the pipeline of future scientists and clinicians in these fields.

References

National Institutes of Health. (2012). *NIH Sourcebook.* Retrieved March 29, 2013, from March National Institutes of Health via NIH Intranet: *http://sourcebook.od.nih.gov/prof-desig/Keep_the_Thread_2012.docx*

National Institutes of Health, Office of Human Resources. (2013). *NIH Voluntary Leave Bank Program.* Retrieved April 5, 2013, from *http://hr.od.nih.gov/benefits/leave/vlbp/default.htm*

National Institutes of Health, Working Group on Women in Biomedical Careers. (2012). *Women in biomedical careers.* Retrieved March 29, 2013, from *http://womeninscience.nih.gov*

National Institutes of Health, Working Group on Women in Biomedical Careers. (2008). *National leadership workshop on mentoring women in biomedical careers: Meeting proceedings* (NIH 09-6364). Retrieved March 29, 2013, from *http://womeninscience.nih.gov/mentoring/documents/National_Leadership_Workshop_on_Mentoring_Women_in_Biomedical_Careers.pdf*

National Institutes of Health, Working Group on Women in Biomedical Careers. (2009). *Women in biomedical research: Best practices for sustaining career success: Meeting proceedings* (NIH 09-7366). Retrieved March 29, 2013, from *http://womeninscience.nih.gov/bestpractices/docs/BestPracticesReport.pdf*

National Institutes of Health, Working Group on Women in Biomedical Careers. (2010). *Women in biomedical careers: Workshops and events.* Retrieved March 29, 2013, from *http://womeninscience.nih.gov/workshops.asp*

U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (1995). *Women in biomedical careers: Dynamics of change: Strategies for the 21st century* (NIH 95-3565). Bethesda, MD: National Institutes of Health.

National Institutes of Health, Working Group on Women in Biomedical Careers. (2009). *Barriers to/Factors for Biomedical Careers for Women.* Retrieved March 29, 2013, from *http://womeninscience.nih.gov/resources/dynamicsofchange.asp*

IV. ORWH Research Dissemination and Outreach Activities

ORWH, in collaboration with NIH ICs, disseminates information about research on women's health, and on sex and gender influences in health and disease. In its dissemination efforts, ORWH also works collaboratively with other Federal agencies and with various national, State, and community organizations. ORWH and its partners ensure that all information is current and science based. Formats for the information include print publications and Web-based platforms, seminars and workshops, conferences, broadcasts, and lectures. The audiences for this information include advocacy groups, public and private institutions, health care professionals, and individuals. This outreach effort helps translate information derived from research on women's health to clinical care, community interventions, and public health policy applications that improve the health and wellness of women, men, and their families. This section provides a summary of ORWH research dissemination and outreach activities in FYs 2011 and 2012.

ORWH and the National Library of Medicine Partnership: Women's Health Resources Web Portal

ORWH continues its successful collaboration with the National Library of Medicine (NLM) on research dissemination through the Women's Health Resources (WHR) Web portal, at *http://www.womenshealthresources.nlm.nih.gov*. There were several notable developments in WHR during FY 2011 and FY 2012, including those described below.

- **Social Media Outreach.** WHR used the current NIH strategic research priorities for women's health and for sex differences to identify topics to disseminate. WHR used Twitter and Facebook to meet Goal 5 of the NIH Strategic Plan: "Develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health and wellness research." WHR used Twitter to disseminate findings from new research, funding announcements, and health campaign messages. The portal reported more than 30,000 followers for @WomensHealthNIH, including many universities, university and college health centers, individual health care providers and researchers, and the general public. The portal also used Facebook to reach college-aged women and university and college health centers.
- **Evaluation of the WHR Portal.** In 2011, a user information assessment and usability study for WHR was developed to improve access and optimize the user experience, and also to collect responses to the unique research question: What are the information needs of women's health and sex and gender differences researchers? The portal team identified six target user groups for the study: senior researchers, junior researchers, advocacy groups, media professionals, consumers, and congressional staff. Sample questions were:
  - — How do the user groups define, understand, and use women's health research and sex differences research?
  - — What information, materials, tools, and messages does the user want from WHR?

  The usability study consisted of multiple focus groups for each of the user groups, the development and testing of user-specific "research brief" templates, and a usability audit of WHR. The project team was awarded an NIH Evaluation Set-Aside award to supplement this work. The study is currently underway and will be finished in 2013.
- **WHR Dissemination Outreach Project.** In 2011, ORWH and NLM partnered to fund a pilot program for information outreach dissemination projects to promote WHR and to support the ORWH strategic goals. All projects focused on information dissemination, information access, or resource development for a university, college, or community agency. Specifically, each project had to promote WHR, create a library guide on resources for research at the college or university level on sex and gender differences, and promote to students and faculty an online continuing medical

education curriculum "The Science of Sex and Gender in Human Health," which was developed by ORWH and the FDA.

NLM used its existing network of historically Black colleges and universities (HBCUs) and National Network of Libraries of Medicine partners to recruit participants that had developed projects targeting university and college students, faculty, and administrators or projects targeting community groups and consumers. A positive outcome of the project was situating the university library as "the place to go" for students and faculty for research on sex and gender differences and inclusion. Awardees included Howard University, Morehouse School of Medicine, Morgan State University, University of Alaska Anchorage, and Virginia Commonwealth University.

Based on successful feedback from the universities, NLM–ORWH is continuing this project. Hispanic-serving institutions and programs with a large Hispanic population and relations with the Hispanic community, and programs that have relationships with tribal communities have been added during this phase. Also identified were university libraries with unique connections to the medical programs at their universities and existing relationships with community colleges. These project goals continue to be linked to the NIH Strategic Plan. Additional areas are to increase in the academic community the awareness and use of research resources on sex and gender differences and inclusion using NLM and NIH resources.

The following universities are participating in this project: California State University, Northridge; Howard University; Medical University of South Carolina; Morehouse School of Medicine; Morgan State University; University of Alabama at Birmingham; University of Arizona, Tucson; University of Florida; University of Iowa; University of Massachusetts Medical School; and University of Utah.

NIH Vulvodynia Awareness Program

ORWH supports trans-NIH initiatives to expand awareness about vulvodynia, a complex chronic pain disorder that primarily affects women aged 18 to 64. ORWH developed and launched the NIH Vulvodynia Awareness Program as the cornerstone of a new ORWH Web site initiative, the "Research and Your Health Series," in June 2012. This program promoted new and updated vulvodynia resources for clinicians and consumers *(http://orwh.od.nih.gov/resources/health/researchandyourhealth/index.asp)*. ORWH collaborated with the Health Resources and Services Administration (HRSA) to provide approximately 20 million women through HRSA primary care clinicians (11,000 grantees) with updated vulvodynia resources via a link to the ORWH Web site from HRSA's Web site: *http://bphc.hrsa.gov/technicalassistance/TAResources.aspx?Mode=SubTopicSubResource&STopic=Special%20Populations*.

NIH Pain Consortium Centers of Excellence in Pain Education

In FY 2012, ORWH was part of an NIH-wide team to establish and support a new program called the NIH Pain Consortium Centers of Excellence in Pain Education (CoEPEs). ORWH provided cofunding that helped to establish 12 CoEPEs. The National Institute on Drug Abuse (NIDA) oversees this program, which will develop and disseminate curriculum resources to improve medical, dental, nursing, and pharmacy education in the assessment, diagnosis, and treatment of pain while minimizing the abuse of opioid medications. Pain management is currently underemphasized in the education and training of health professionals. Among the women's health pain issues to be addressed are headaches related to hormonal changes, fibromyalgia, temporomandibular joint (TMJ) disorders, postoperative pain, pain related to cancer, pelvic pain, ME/CFS, and irritable bowel syndrome.

ORWH-Cofunded Research Conferences and Workshops

ORWH provides funding for conferences, workshops, seminars, and research projects through which research on women's health and sex and on gender influences on health and disease is disseminated. Through partnerships with NIH ICs and Offices, other

Federal agencies, and extramural organizations, ORWH brings together researchers investigating women's health and sex differences to exchange ideas, foster collaborations, and explore emerging concepts and technologies. Research conferences and workshops cofunded by ORWH during FY 2011 and FY 2012 are described below.

FY 2011

Issues in Clinical Research: Enrolling Pregnant Women Scientific Forum, October 18, 2010. Clinical research investigates mechanisms of human disease and tests therapeutic interventions, but pregnant women are often excluded from clinical studies. Additionally, few studies are designed to address health concerns and questions relevant to pregnant women. This practice results in a lack of evidence to inform health care and treatment decisions for these women. ORWH convened this forum in partnership with several NIH ICs and Offices and the FDA to address the ethical, institutional review board (IRB), and recruitment issues that investigators face in the conceptualization, initiation, and conduct of clinical research studies that enroll pregnant women.

During this forum, the audience was challenged to address gaps in knowledge about medical treatment and pregnancy, to increase the evidence base on the inclusion of pregnant women in clinical research, and to conduct appropriate scientifically and ethically designed clinical research. Medical ethicists, clinical investigators, academic researchers, and those with an interest in and concern about clinical research in women provided information related to risk perception, risk reasoning, and the ethics of balancing risks and benefits in the clinical arena. Additionally, examples of challenges and strategies to overcome barriers to clinical research in pregnant women with chronic or infectious diseases, or to the evaluation of preventive measures, such as vaccines, in pregnancy were presented. Published proceedings from the scientific forum are available at: *http://orwh.od.nih.gov/resources/policyreports/pdf/ORWH-EPW-Report-2010.pdf*.

Third Annual Trauma Spectrum Conference: Emerging Research on Polytrauma Recovery and Reintegration of Service Members, Veterans, and Their Families, December 7–8, 2010. The Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, NIH, and the U.S. Department of Veterans Affairs (VA) convened this 2-day conference, which was attended by more than 400 people representing researchers and clinicians from the military, NIH, and other HHS agencies, academia, and the VA. Also in attendance were advocacy representatives, policy analysts, and clinicians from the community that serves returning military service members and their families.

During the conference, the focus was on emerging polytrauma research and its impact, including research on traumatic brain injury (TBI), psychological health conditions such as posttraumatic stress disorder (PTSD), vision and eye injuries, hearing injuries, extremity injuries and amputations, pain management, substance use and abuse, and cognitive problems. The conference provided a forum at which existing evidence-based science was examined relative to these complex health issues and their impact on the return of military service members and veterans to their communities.

This conference provided a unique opportunity to showcase what science could offer to the military- and civilian-practice worlds. The number of Federal agencies that participated in this research conference was higher than in the previous year, and the conference represented a military-civilian model for the sharing of ideas and resources that can positively affect America's military service members, veterans, and their families and communities. The Federal agencies represented at the conference focused in a collaborative way on improving both research about those affected by polytrauma and the clinical care they require, with polytrauma defined as multiple, complex conditions occurring in a single individual that require a team of clinicians to properly diagnose and design treatment and rehabilitation regimes. The individual had to be part of the Iraq and Afghanistan cohort of military service members and veterans.

Clinical Research United in Successful Enrollment Workshop on Clinical Trials, December 7–8, 2010. The goal of this workshop was to provide recommendations to the National Heart, Lung, and Blood Institute (NHLBI) and ORWH in three areas that affect enrollment in clinical trials in order to optimize enrollment in such trials:

1) Public and professional awareness and acceptance of clinical trials;

2) Policies, guidelines, and reimbursement related to research on human subjects; and

3) Experience and practice in clinical trial enrollment.

NHLBI cosponsored the workshop with ORWH.

Women's Health 2011: The 19th Annual Congress, April 1–3, 2011. This annual women's health congress is presented by the Virginia Commonwealth University Institute for Women's Health and the Journal of Women's Health. In 2011, ORWH cofunded the preconference session held on March 31: "Toward a Better Understanding of the NIH Grant Process." Participants learned techniques on how to prepare a successful research proposal, in consultation with an NIH program officer; how to use appropriate mechanisms and mentors to develop a research career; and how to better understand the NIH peer review process, e.g., what happens in a study section? The names of the sessions and the presenters were as follows:

- "Grantsmanship: Strategies for Success," Willo Pequegnat, Ph.D., Associate Director, NIMH (National Institute of Mental Health) International AIDS Prevention Research Program, Division of AIDS Research
- "The Role of NIH Program Officials," Karen Sirocco, Ph.D., Program Official, Division of Clinical Neuroscience and Behavioral Research, NIDA (National Institute on Drug Abuse)
- "NIH Peer Review: Understanding the Scoring System and Review Process," Cheryl Kitt, Ph.D., Deputy Director, Center for Scientific Review, NIH
- "NIH Career Development Programs," Henry Khachaturian, Ph.D., Health Scientist Administrator, Division of Loan Repayment, NIH Office of the Director

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) State-of-the-Knowledge Workshop, April 7–8, 2011. ORWH sponsored a State-of-the-Knowledge Workshop on ME/CFS, which was widely attended by over 900 individuals via live videocast and by over 100 individuals in person. A panel of 32 experts in the field and patient advocacy group members discussed various topics including infectious diseases, systems biology, immunology, neurology, exercise physiology/energy metabolism, diagnosis and biomarkers, and treatments, to address the goals of the workshop:

1) Document what is known about the illness;

2) Identify gaps in knowledge needing more research; and

3) Identify opportunities in science and technology that might advance biomedical research on ME/CFS.

A report from the workshop is available at *http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf*.

Workshop on the Health Impact of Indoor Air Pollution in Developing Countries (Cookstove), May 9–11, 2011. NIH, the Centers for Disease Control and Prevention (CDC), and the Office of Global Health Affairs, all within HHS; the U.S. Agency for International Development; the U.S. Environmental Protection Agency; the National Science Foundation; and the U.S. Department of State collaborated on this workshop. The workshop explored the state of the science on the health impact of indoor air pollution—specifically the negative health effects of inefficient cookstoves and open-fire cooking on women and girls who are predominantly responsible for cooking in developing countries. The health burdens caused by these cooking methods include emphysema, cataracts, cancer, and heart disease. The workshop also worked to determine critical research gaps that, if addressed, will permit implementation of effective strategies

to reduce the impact of indoor air pollution and to improve human health for poor women and children exposed to open-fire or inefficient cookstoves and fuels. ORWH cosponsored this workshop.

Comorbid Chronic Pain Conditions—Mechanisms, Diagnosis, and Treatment Conference—the Sixth Scientific Meeting of the TMJ Association, June 5–7, 2011. The focus of this 2011 meeting, cofunded by ORWH and the National Institute of Dental and Craniofacial Research (NIDCR), was the pathophysiological process underlying the chronic pain conditions that exist alongside temporomandibular disorders (TMD). The goal of the conference was to advance research in TMD—disorders that affect over 10 million Americans and appear to be more common in women than men.

The Science of Compassion: Future Directions in End-of-Life and Palliative Care, August 10–12, 2011. This summit, which was held at the Hyatt Regency in Bethesda, MD, was cosponsored by ORWH and the National Institute of Nursing Research. The main objectives were to:

1) Examine the current status of palliative care and end-of-life research, practice, and policy;

2) Propose strategies to overcome barriers to conducting research and ensure scientific and methodological rigor in the research; and

3) Delineate new action items that galvanize progress in this vital area of science.

Men's Health Network Exhibits and Conferences. ORWH collaborated with the Men's Health Network (MHN) to provide information on men's health at exhibits at conferences in partnership with NIH ICs and other NIH Offices. ORWH also cosponsored workshops with MHN. In FY 2011, as part of its commitment to sex and gender research and inclusion, ORWH provided support to MHN to develop pamphlets and brochures on men's health-related issues.

FY 2012

Caribbean HIV Conference: Strengthening Evidence to Achieve Sustainable Action, November 18–21, 2011. ORWH cosponsored this conference with the NIH Office of AIDS Research to help sharpen the focus on HIV in the Caribbean, the region with the world's second-highest adult HIV prevalence. In 2008, approximately 240,000 people in the region were living with HIV; 20,000 new infections were documented; and 12,000 deaths resulted from AIDS-related illnesses. UNAIDS (the Joint United Nations Programme on HIV/AIDS), which includes Caribbean stakeholders, assembled to build on earlier successes and to demonstrate the synergistic results of regional cooperation and collaboration.

The 4th Annual Trauma Spectrum Conference—Bridging the Gap Between Research and Clinical Practice of Psychological Health and Traumatic Brain Injury: Prevention, Diagnosis, Treatment, and Recovery for the Iraq and Afghanistan Cohort, December 8–9, 2011. The Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, NIH, and VA held this 2-day conference, which was attended by more than 640 people representing researchers and clinicians from the military, NIH and other HHS agencies, academia, and VA. Also in attendance were advocacy representatives, policy analysts, and clinicians from the community that is serving returning military service members and their families. ORWH staff coordinated trans-NIH and trans-HHS contributions, and they served on the conference-planning group that developed the agenda. A videocast of the conference is available at *http://videocast.nih.gov/summary.asp?Live=10837&bhcp=1*. During the conference, plenary sessions and eight breakout sessions were held. Among the major goals and topics of the conference were the following:

- There are several evidence-based practices and training tools ready for implementation in clinical practice. One goal of the conference was to increase knowledge of these practices and tools among doctors and other health care providers.

- Plenary sessions focused on important research findings in TBI, PTSD, major depressive disorders, sleep disorders, integrative telehealth/mobile technologies, evidence-based practice and comparative effectiveness, and an update on the Army STARRS (Study to Assess Risk and Resilience in Servicemembers) program, which focuses on suicide research.
- Breakout sessions included a variety of research topic areas, including neuroimaging, TBI Common Data Elements and the NIH Toolbox, substance use disorders, women's health, co-occurring disorders, cognitive rehabilitation, PTSD and depression, TBI and depression, and implementation science.

STRAW + 10: Addressing the Unfinished Agenda of Staging Reproductive Aging, December 20–21, 2011. Building on the first conference on this topic more than 19 years ago, the purpose of the 2011 conference was to assess the guidelines and criteria for including groups of women or characteristics that were not previously included due to the state of the science at the time. STRAW + 10 provides a more comprehensive basis for assessing reproductive aging in research and clinical contexts. Application of the STRAW + 10 staging system should improve the comparability of studies of midlife women and facilitate clinical decision making. ORWH cosponsored this conference with the NIH National Institute on Aging. An executive summary of the meeting is available online at *http://staging.menopause.org/straw10.pdf*.

Women's Health 2012: The 20th Annual Congress, March 16–18, 2012. This annual women's health congress was presented by the Virginia Commonwealth University Institute for Women's Health and the Journal of Women's Health, in collaboration with ORWH, NIH, the National Cancer Institute (NCI), and the American Medical Association. ORWH cosponsored the annual preconference workshop, "Women's Health Research and Clinical Practice: An Interdisciplinary Approach," on March 15, which featured two panels.

The first panel was designed to showcase existing women's health and women's health research programs, provide best practices and lessons learned, and discuss the role of interdisciplinary approaches in fostering a comprehensive approach to women's health. Speakers for this panel included principal investigators from the Building Interdisciplinary Research Careers in Women's Health (BIRCWH, K12) Program, a mentored scientist career development award, and the Specialized Centers of Research on Sex Differences. The second panel provided strategies for preparing a successful NIH research proposal, explained the peer review process, and described efforts to diversify the women's health research workforce. Speakers from the NIH included Dr. Wally Schaffer, senior scientific advisor for extramural research; Dr. Cheryl Kitt, Deputy Director, Center for Scientific Review (CSR); and Dr. Willo Pequegnat, associate director, International AIDS Prevention Research, NIMH (National Institute of Mental Health). Dr. Janine Clayton, then the Acting Director, ORWH, moderated the second panel.

Howard University Fibroid Summit, March 29, 2012. Cosponsored by ORWH and the National Institute on Minority Health and Health Disparities, and Howard University, the summit was designed to facilitate the exchange of information and ideas among basic, clinical, and translational researchers about the multidisciplinary aspects of the molecular basis of leiomyoma and treatment modalities, with a focus on African-American women. The summit featured scientific presentations that addressed the current state of knowledge and emerging issues regarding leiomyoma in African-American women. The causes and treatment of leiomyoma in minority populations were a special emphasis for this summit.

Enhancing Diversity in Science: Working Together to Develop Common Data, Measures, and Standards Conference, May 24, 2012. This workshop was designed to establish a standard for data collection and measurement for diversity-enhancing programs across scientific disciplines and societies. This task should increase the underrepresented minorities and women in sciences, technology, engineering, and mathematics (STEM), a critical national need.

The main topics of the conference were data collection and metrics, guidelines, and the dissemination of best practices. ORWH was one of the cosponsors.

Chronic Overlapping Pain Disorders Conference, August 13–14, 2012. ORWH cosponsored (with NIDCR, NINDS, and the NIH Pain Consortium) a workshop on chronic overlapping pain conditions, which was cochaired by Dr. Elizabeth Unger, a research expert on ME/CFS from the CDC. Chronic overlapping pain conditions represent a complex set of painful disorders that occur frequently in the population, lack a firm mechanistic understanding, and are in need of hypothesis-driven research efforts. The workshop brought together researchers with expertise in various pain conditions and other relevant expertise to discuss these conditions and to develop a forward-thinking research agenda. The overlapping chronic pain conditions include conditions such as fibromyalgia, irritable bowel syndrome and other functional gastrointestinal disorders, interstitial cystitis/bladder pain syndrome, temporomandibular joint disorder, CFS, vulvodynia, tension headache, myofascial pain syndrome, Gulf War illness, and multiple chemical sensitivities. A report from the workshop, including recommendations for future research priorities, is available at *http://www.ninds.nih.gov/news_and_events/events/meeting-summary-chronic-pain.htm*.

Women's Health Symposium: Targeted Information Dissemination of Resources on Women's Health and Sex/Gender Differences in Health and Behavior, September 11–12, 2012. This conference was held at the Louis Stokes Health Sciences Library at Howard University, Washington, DC. The keynote speaker was Janine Clayton, M.D., Director, ORWH.

ORWH Women's Health Seminar Series

The ORWH Women's Health Seminar Series features nationally recognized leaders in women's health research who present the latest information on topics important to women's health. The seminar series, sponsored by ORWH, began in 1993. Its goal is to educate the NIH community and the public on issues that affect the health of women and to showcase research on sex and gender. Seminars presented in FY 2011 and FY 2012 are described below.

FY 2011

Social Media and the NIH Mission: Innovations for the Future in Women's Health Research, Outreach, and Communications, March 24, 2011. ORWH developed this seminar to explore the growing social media universe and its influences on women's health research. Speakers from a range of expertise provided specific examples of innovative social media projects in the research and public health arenas. The seminar was moderated by John T. Burklow, associate director for communications and public liaison, NIH. Topics and presentations were as described below.

- Building a business case for social media
  - — "Leveraging Social Media: People, Process, and Technology," Jonathan Cho, chief, Communications Technology Branch, Office of Communications and Education, NCI
- Use of social media in research and public health efforts
  - — "Social Media Tools, Behavioral Intervention, and Site Usage Data: NCI's Smoke-Free Women Campaign," Erik Augustson, Ph.D., M.P.H., behavioral scientist, Tobacco Control Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences, NCI
  - — "The Power of Partnerships to Improve Public Health: The Text4baby Mobile Health Service," Judy Meehan, chief executive officer, National Healthy Mothers, Healthy Babies Coalition

- Use of social media in communications and outreach efforts
  - — "From Blogs to Music Videos: Meeting the Audience Where They Live," Carol Krause, communications director, NIDA
  - — "Social Media: A Research Tool for Resource Development," Laura Bartlett, technical information specialist, Outreach and Special Populations Branch, Specialized Information Services, NLM
- Thoughts on the future for NIH's social media efforts
  - — "Moderated Session: Open Discussion with Question and Answer," John T. Burklow.

Sex Differences and Pain Research, September 27, 2011. ORWH developed this seminar to explore current research on the influences of sex and gender on pain. The Office has a longstanding commitment to pain research. Experts at the seminar represented diverse disciplines in pain research. Emmeline Edwards, Ph.D., Director, Division of Extramural Research at the National Center for Complementary and Alternative Research, NIH, served as moderator. Topics and presentations at the seminar were as listed below.

- "Sex and Gender Differences in Pain and Analgesia: Overview of Clinical and Experimental Findings," Roger B. Fillingim, Ph.D., professor, University of Florida College of Dentistry; Research Health Scientist, Rehabilitation Outcomes Research Center, North Florida/South Georgia Veterans Health System
- "Sex Differences in Persistent Pain Syndromes," Emeran A. Mayer, M.D., director, Gail and Gerald Oppenheimer Family Center for Neurobiology of Stress, Division of Digestive Diseases, David Geffen School of Medicine at the University of California, Los Angeles
- "The Science of Inclusion: Racial, Gender, and Aging Influences on Pain," Carmen R. Green, M.D., professor of anesthesiology, Health Management and Policy, and Obstetrics and Gynecology, Department of Anesthesiology, University of Michigan
- "Thoughts on the Future for Sex Differences and Pain Research: Open Discussion with Question and Answer," Emmeline Edwards, Ph.D., Moderator

FY 2012

Innovations in Reproductive Technologies, May 17, 2012. ORWH developed this addition to the Women's Health Seminar Series (presented in FY 2012) to be part of National Women's Health Week at NIH. The purpose was to explore contemporary research in reproductive technologies with research experts in that field. The presentations included the following:

- "Ethical Issues in Emerging Technologies in Reproductive Medicine," Alan Hersh DeCherney, M.D., head, Section on Implantation and Oocyte Physiology Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- "Emerging Technologies in Infertility," Clarisa R. Gracia, M.D., M.S.C.E., assistant professor of obstetrics and gynecology, Perelman School of Medicine at the University of Pennsylvania; Fertility Care, Penn Medicine
- "Health Disparities and Access to Emerging Technology in Reproductive Medicine," Alicia Brooks Armstrong, M.D., MHSCR, associate Fellowship Program director, Reproductive Endocrinology and Infertility, NICHD
- "Multipurpose Prevention Technology for HIV, STIs, and Pregnancy," Gustavo F. Doncel, M.D., Ph.D., professor of obstetrics and gynecology, Eastern Virginia Medical School; deputy director, Preclinical Research, CONRAD
- "New Technology in Contraception Research," Regine Sitruk-Ware, M.D., reproductive endocrinologist, Distinguished Scientist, Population Council Center for Biomedical Research

Women's Health Scientific Interest Group Lecture Series

The Women's Health Scientific Interest Group (WHSIG) Lecture Series is sponsored by ORWH and the Intramural Research Program on Women's Health (IRPWH) at NIH. Lectures on both basic science and clinical research topics of relevance to women's health have been presented by experts in a wide variety of scientific disciplines from within the NIH IRP as well as from the outside scientific community.

FY 2011

- **Update on Fatigue and Physical Activity: Translating the Evidence to Improve Outcomes in Cancer Survivors, November 12, 2010.** Lynn Gerber, M.D., professor of rehabilitation science and director, Center for Study of Chronic Illness and Disability, George Mason University; Kathryn Schmitz, Ph.D., M.P.H., associate professor of epidemiology, University of Pennsylvania; Sandra A. Mitchell, Ph.D., C.R.N.P., research scientist and program director, Outcomes Research Branch, Applied Research Program, NCI
- **Human Papillomavirus (HPV): A Bigger Threat Than Previously Realized, May 20, 2011.** Allan Hildesheim, Ph.D., chief, Division of Cancer Epidemiology & Genetics, NCI; Eileen Dunne, M.D., M.P.H., Division of STD Prevention, CDC; Vundavalli Murty, Ph.D., associate professor of clinical pathology, Columbia University Medical Center
- **Understanding a Silent Nightmare for a Bullying-Free Workplace, June 24, 2011.** Richard Nakamura, Ph.D., Deputy Director, NIMH; Paula L. Grubb, Ph.D., CDC; Loraleigh Keashly, Ph.D., interim chair and associate professor, Department of Communication, Wayne State University
- **Posttraumatic Stress Disorder and Other Co-occurring Psychological Disruptions Following Trauma, July 8, 2011.** Kerry Ressler, M.D., Ph.D., associate professor and principal investigator, Ressler Lab, Department of Psychiatry and Behavioral Sciences, Center for Behavioral Neuroscience, Yerkes National Primate Research Center; Michael Handrigan, M.D., director, Traumatic Brain Injury Clinical Standards of Care, Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury; Farris K. Tuma, Sc.D., chief, Traumatic Stress Research Program, NIMH
- **Sex Differences in Mild Traumatic Brain Injury Outcomes and Potential Effects of Pleiotropic Hormones, August 19, 2011.** David W. Wright, M.D., associate professor of emergency medicine and director, Emergency Neurosciences, Emory University School of Medicine; Jeffrey J. Bazarian, M.D., M.P.H., associate professor, Department of Emergency Medicine, School of Medicine and Dentistry, University of Rochester; Walter J. Koroshetz, M.D., Deputy Director, National Institute of Neurological Disorders and Stroke (NINDS)
- **Atrial Fibrillation Guidelines and the Sex Differences and Similarities in the Epidemiology and Management of Atrial Fibrillation According to the Guidelines, September 23, 2011.** Cynthia M. Tracy, M.D., director of electrophysiology and associate director of cardiology, George Washington University Medical Center

FY 2012

- **Will This Day Get Better? Searching for Complementary and Integrative Strategies of Headaches and Migraines Through Science and Practice, September 7, 2012.** Senior Moderator and Speaker: Emmeline Edwards, Ph.D., director, Division of Extramural Research, National Center for Complementary and Alternative Medicine, NIH. Speaker: Wendy Weber, N.D., Ph.D., M.P.H., program officer, Division of Extramural Research, National Eye Institute, NIH

Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH

The NIH Women Scientist Advisors Committee and ORWH jointly sponsor the Anita B. Roberts Lecture Series: Distinguished

Women Scientists at NIH to highlight outstanding research achievements of women scientists in the NIH IRP. The seminar series is dedicated to the memory of Dr. Anita B. Roberts, chief of the Laboratory of Cell Regulation and Carcinogenesis at NCI from 1995 to 2006, and honors her role as an exceptional mentor and scientist. The lectures below were presented in FY 2011 or FY 2012.

FY 2011

- **Integrating T Cell Signals, October 28, 2010.** Pamela Schwartzberg, M.D., Ph.D., head, Cell Signaling Section, Genetic Disease Research Branch, National Human Genome Research Institute (NHGRI)
- **The Shape of Things: Complex Genetics in the Domestic Dog, April 29, 2011.** Elaine Ostrander, Ph.D., chief and senior investigator, Cancer Genetics Branch, NHGRI

FY 2012

- **Chromatin Regulation of Innate Immunity, October 27, 2011.** Keiko Ozato, Ph.D., chief, Section on Molecular Genetics of Immunity, Laboratory of Molecular Growth Regulation, NICHD
- **Inside the Parkinsonian Brain: Is Too Much Rhythm a Bad Thing? April 5, 2012.** Judith Walters, Ph.D., chief, Section on Neurophysiological Pharmacology, Experimental Therapeutics Branch, NINDS
- **Neural Immune Connections: From Bench to Bedside and Beyond, September 28, 2012.** Esther M. Sternberg, M.D., research director, Arizona Center for Integrative Medicine, University of Arizona at Tucson; former chief, Section on Neuroendocrine Immunology and Behavior, NIMH

Association of Women in Science Seminar Series—Bethesda Chapter

The Association of Women in Science (AWIS) Seminar Series is a free year-long program covering a range of issues of both general interest and special interest to women. The seminars, which are held on the NIH campus, are well attended and include both men and women as speakers. The series includes a networking event called "Have a Meal with Your Mentor." In addition, the Bethesda AWIS chapter honors one scientist every year with an award for his or her role in mentoring young women scientists. FY 2011 and FY 2012 lectures are listed below.

FY 2011

- **Telomerase and the Consequences of Telomere Dysfunction, December 1, 2010.** Carol Grieder, Ph.D., professor, Molecular Biology and Genetics, Johns Hopkins University.
- **Making Key Decisions for Career Success, December 8, 2010.** Sharon Milgram, Ph.D., Director, Office of Intramural Training & Education, NIH; Carole Bewley, Ph.D., senior investigator, Section on Natural Products, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases; Alison Davis, Ph.D., science writer/consultant. Go to *http://www.youtube.com/watch?v=iOy2HMd92yM* to view this program.
- **FDA Panel Discussion, March 15, 2011.** Nicole Mahoney, Ph.D., Center for Drug Evaluation and Research, FDA; Brinda Dass, Ph.D., Center for Veterinary Medicine, FDA; Kerian K. Grande, Ph.D., Center for Drug Evaluation and Research, FDA. Held at the Visitor Center, NLM, NIH, Bethesda, MD.
- **Policy, Program, and Review, April 11, 2011.** Margaret Ames, Ph.D., acting director, Office of Science Planning and Assessment, NCI; Della Hann, Ph.D., Deputy Director, Office of Extramural Research, NIH; Yuan Luo, Ph.D., scientific review officer, CSR; Sacha Vignieri, Ph.D., associate editor, Science.

FY 2012

- **Panel Discussion: Science Policy Fellowships, October 18, 2011.** Rashada Alexander, Ph.D., health science policy analyst, Office of the Director, NIH; Lisa Nichols, Ph.D., science and technology policy fellow, American Association for the Advancement of Science (AAAS); Kate

Greenberg, Ph.D., genetics writer, NLM; Jennifer C. Shieh, Ph.D., AAAS science and technology policy fellow, Small Business Innovation Research Development Center, NCI

- **Panel Discussion: From Bachelors or Masters to a Career in the Sciences—It Can Be Done! November 15, 2011.** Patricia Stranen Connelly, B.A., research analyst/laboratory manager, Electron Microscopy Core, NHLBI; Rebekah Smith, B.S., animal care and use program administrator, NHLBI; Audrey Noguchi, B.A., NHLBI
- **Joining Us to Talk About Her Career Path, February 2, 2012.** Bonnie Berger, Ph.D., professor of applied mathematics, Massachusetts Institute of Technology, and NIH 2011 Pittman Lecturer
- **Improving College STEM Education, March 2, 2012.** Jo Handelsman, Ph.D., professor of molecular, cellular, and developmental biology, Yale University and Howard Hughes Medical Institute
- **My Life in Science: A Preliminary Study, March 27, 2012.** Marina Picciotto, Ph.D., professor of neurobiology and of pharmacology, and assistant chair for basic science research, Department of Psychiatry, Yale University
- **At the Intersection of Research, Regulation, and Royalty, May 24, 2012.** Karen Elkins, Ph.D., Senior Investigator, U.S. Food & Drug Administration.

Special Events and Meetings

Actress Geena Davis Engages NIH on Gender Balance in Media

ORWH hosted Academy-Award-winning actress Geena Davis at the Clinical Center on April 25, 2011. Davis gave a presentation to IC directors, NIH leaders, and invited guests on the goals and progress of her nonprofit Geena Davis Institute on Gender in Media, and she took a tour of the Clinical Center. Ms. Davis won the 1988 Academy Award for Best Supporting Actress for "The Accidental Tourist" and is also known for her roles in "A League of Their Own" and "Thelma and Louise."

Davis' institute analyzes television and movies aimed at children for the presence and depiction of female characters. The institute's research shows little change in the inclusion of females over the last 20 years and hypersexualization of those included. The conversation at the Clinical Center revolved around the psychological effects of females' marginalization in children's programming and strategies to train the next generation of writers and directors. Davis was part of the U.S. delegation appointed by President Obama to the Commission on the Status of Women. The Geena Davis Institute on Gender in Media is the leading resource for research on gender in the media, trends in that area, and education on this subject for the entertainment industry and the public. Parallels between the institute's interests and the mission and focus of ORWH include a commitment to education and the career development of women in science.

Sex-Specific Reporting of Scientific Research: A Workshop, Institute of Medicine, August 30, 2011. ORWH requested that the Institute of Medicine convene a workshop to assess the benefits and barriers to scientific journals of reporting clinical outcomes in men and women separately as well as reporting sex differences in basic research. The workshop offered presentations and panel discussions that represented a range of perspectives, including those of researchers and journal editors. A final report was published in January 2012. The sessions were titled:

- "Why Sex-Specific Reporting Is Important"
- "Sex-Specific Reporting Policies: Implications for Researchers, Experiences of Journal Editors Implementing Editorial Policies"
- "Sex-Specific Reporting Policies: Implications for Journals"

ORWH Exhibit Program

ORWH exhibits at local women's health and/or community-related events to support its mandate for research dissemination and outreach. ORWH also supports exhibits on women's health information nationwide in partnership with ICs by distributing appropriate information produced by ORWH and ICs when requested. Tables 1 and 2 below list exhibits during FY 2011 and FY 2012 for which ORWH provided materials and/or other support.

National Women's Health Week at NIH

Each year, ORWH coordinates the National Women's Health Week activities at NIH. Publications and resources from ORWH and other ICs are disseminated at a large ORWH exhibit located at the NIH Clinical Center. In addition, ORWH participates in outreach activities throughout the week. Women's Health Week exhibits, programs, and other activities in FY 2011 and FY 2012 are described as follows.

FY 2011

More than 17,000 publications were distributed at the ORWH exhibit to celebrate National Women's Health Week. The Office also coordinated these activities:

- **A scientific forum and panel discussion, "Lessons in Lupus."** Leading NIH and extramural lupus researchers explored lupus risk factors and current treatment options. Lupus advocates and forum partners presented perspectives on living with lupus and other insights. The National Institute of Allergy and Infectious Diseases (NIAID), the Alliance for Lupus Research, the American Autoimmune Related Diseases Association, the Lupus Foundation of America, the Lupus Research Institute/S.L.E., and the Lupus Clinical Trials Consortium participated.
- **A mind and body workshop: "Incorporating Mindfulness into Day-to-Day Life."** Cosponsored with the NIH Office of Research Services and presented by Rezvan Ameli, Ph.D., chief psychologist and director of clinical training, NIMH, this interactive and engaging

Table 1. ORWH Exhibits in FY 2011

Month	Exhibit	Location
April	Women's Health 2011: The 19th Annual Congress	Arlington, VA
April	Coppin State University Health Fair	Baltimore, MD
June	Coordinating Committee on Women's Health Annual Meeting	Arlington, VA
September	Links Twilight Walk	Washington, DC
September	NIH Health Wellness Expo	Bethesda, MD
October	Links Caregiver Forum	Washington, DC

Table 2. ORWH Exhibits in FY 2012

Month	Exhibit	Location
March	Women's Health 2012: The 20th Annual Congress	Arlington, VA
April	Links Caregiver Forum	Washington, DC
April	NIH National Minority Health Month Celebration	Bethesda, MD
May	Girls Rock II	Washington, DC
August	NIH Wellness Day	Bethesda, MD
September	Links Twilight Walk	Washington, DC
November	Links Caregiver Forum	Washington, DC

mind-and-body seminar addressed how to practice mindfulness every day and why this practice is important to health.

FY 2012

Approximately 6,400 publications were disseminated at the ORWH exhibit to celebrate National Women's Health Week. Additionally, ORWH organized several events, including the following:

- **ORWH Women's Health Seminar: "Innovative Technologies in Reproductive Medicine."** Leading experts in reproductive medicine presented research on multipurpose prevention technologies for HIV, sexually transmitted infections (STIs), and pregnancy; health disparities and access to emerging technologies in reproductive medicine; bioethics and emerging technologies in reproductive medicine; emerging technologies in infertility research; and new technologies in contraception research.
- **A mind/body workshop: Back by popular demand, "Incorporating Mindfulness into Day-to-Day Life."** This event was cosponsored by the NIH Office of Research Services and presented by Rezvan Ameli, Ph.D.

ORWH Pinn Point on Women's Health Podcasts

The Pinn Point on Women's Health Podcasts feature conversations between former ORWH Director Dr. Vivian Pinn and NIH intramural and extramural scientists about a variety of subjects.

- **Cardiovascular Disease and Older Women, August 2011.** Jacques Rossouw, M.D., chief of the Women's Health Initiative Branch of the NHLBI, discussed important findings on cardiovascular disease in older women from the 5-year followup to the landmark Women's Health Initiative study.
- **Posttraumatic Stress Disorder and Women's Health, June 2011.** Farris Tuma, Sc.D., chief, Traumatic Stress Research Program, NIMH, explored sex differences in susceptibility to PTSD.
- **Lupus and Women's Health, May 2011.** Fran Ashe-Goins, R.N., M.P.H., Deputy Director, Office of Women's Health, HHS, explained the National Lupus Awareness Campaign, which she helped conceive and launch in 2009.
- **ORWH 20th Anniversary Reflections, November 2011.** Dr. Pinn recaptured ORWH's 20th anniversary scientific symposium in short interviews with some of the luminaries of women's health research.

ORWH Publications and Resources

ORWH provides evidence-based information on women's health research to those who request it. The diverse group of requestors includes private and public organizations, the public, health care professionals, and other key stakeholders. Providing information derived from research on women's health facilitates application of research to clinical care and public health policy, and it can help improve health care for women, men, and their families while also raising health awareness. ORWH published the materials described below in FY 2011 and FY 2012.

Publications on Women's Health Topics

FY 2011

- U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2012). *Science series fact sheets: Minority women's health: Understanding minority women's health and NIH research efforts* (NIH 11-7698). Bethesda, MD: National Institutes of Health.

FY 2012

- U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2012). Science series fact sheets: Understanding vulvodynia (NIH 12-7931). Retrieved from *http://orwh.od.nih.gov/resources/health/researchandyourhealth/ORWH-Understanding-Vulvodynia.pdf*
- U.S. Department of Health and Human Services, National Institutes of Health,

Office of Research on Women's Health. (2012). Women of color health information collection: Cardiovascular disease (NIH 12-7680). Retrieved from *http://orwh.od.nih.gov/resources/policyreports/pdf/ORWH-HIC-Cardiovascular-Disease.pdf*

Publications on Mentoring and Biomedical Research Careers

- U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2012). Science series fact sheets: A mentor: Key to career success (NIH 12-7871). Retrieved from *http://orwh.od.nih.gov/career/pdf/ORWH-Mentee-Factsheet.pdf*
- U.S. Department of Health and Human Services, National Institutes of Health, Office of Research on Women's Health. (2012). Science series fact sheets: Mentoring women in science (NIH 12-7871). Retrieved from h*ttp://orwh.od.nih.gov/career/pdf/ORWH-Mentor-Factsheet.pdf*

V. Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

NIH Monitoring Compliance Efforts

Introduction

ORWH was established in response to concerns from members of Congress and the women's health community that women should be included in clinical research funded by NIH. Today, after years of attention to NIH inclusion policies and extended focus on sex differences research, ORWH has expanded the foundation for the inclusion in clinical research of women, men, children, and the elderly, as well as underserved and understudied populations, by calling attention to the scientific, clinical, and public health importance of such diversity. ORWH has provided information on the distribution of diverse populations in clinical research and on trends and shifts in inclusion data. Such information has been of major use to the research community, potential volunteers from diverse communities, and members of Congress, the media, scientific organizations, advocacy groups, health professionals, and individuals. Nonetheless, a number of challenges related to inclusion still exist, such as the ethics and enrollment of pregnant women, children, and the LGBTI (lesbian-gay-bisexual-transgender-intersex) community in clinical research. To that end, ORWH and the NIH community continue to stress the importance of the inclusion of underserved and understudied populations who are affected by or who are at risk for the diseases under study as well as the importance of evaluating potential differences in response to interventions, or in disease manifestations, with appropriate data analyses or research results and findings. Examination of results by sex, gender, race, ethnicity, and other relevant factors, such as age or geographic location, is important to ensure that all populations benefit from the results of clinical studies. Inclusion is not just a matter of having women, men, and people of diverse backgrounds included in clinical studies; it is an approach whereby the scientific value of research studies is greatly enhanced by providing knowledge about differences and/or similarities between different populations that are affected by the diseases under study.

To demonstrate the effective implementation of the NIH Revitalization Act of 1993 and the implementation of NIH policies on the tracking and inclusion of women and minorities in clinical research, ORWH has, since its establishment, led efforts in collaboration with the Office of Extramural Research (OER), the Office of Intramural Research (OIR), the National Institute on Minority Health and Health Disparities (NIMHD), and other ICs to monitor efforts for compliance. Monitoring efforts includes documentation of the distribution of women and men and of racial and ethnic groups enrolled in clinical studies funded by NIH. Every 2 years, each IC must produce a report documenting efforts to monitor inclusion and to comply with guidelines, and NIH produces a biennial report that demonstrates the agency's adherence to Public Law (PL) 103–43. A summary of aggregate IC inclusion data, including discussion and figures, is found within this section of the ORWH biennial report under Summary Report of NIH Inclusion Data (pp. 90).

Data monitoring of the magnitude and range of clinical studies funded by NIH is not a simple task, and many representatives from NIH ICs have contributed to efforts to ensure the consistency of data entry and reporting and to improve understanding of the NIH inclusion policy.

2009 Task Force on Inclusion of Women, Minorities, and Other Populations in Clinical Research

In 2009, NIH established the Task Force on Inclusion of Women, Minorities, and Other Populations in Clinical Research to conduct a review of the history and implementation of NIH inclusion policies. This task force has addressed three major issues: (1) How should NIH ensure the inclusion of women

Inclusion Philosophy Statement

NIH-supported clinical research should address/include the population(s) at risk for the disease or condition under study. The purpose of NIH inclusion policies is to ensure that the distribution of study participants by sex/gender, race, ethnicity, and age reflects the population needed to accomplish the scientific goals of the study, rather than the enumeration of research participants. All NIH-funded studies that meet the NIH definition for clinical research are subject to NIH inclusion policies, regardless of funding mechanism. "Funding mechanism" includes any activity code associated with extramural grants, cooperative agreements, intramural projects, and R&D contracts.

Principles

- **Focus** on the **science**
- **Simplify** and streamline the processes
- **Enhance consistency** across NIH
- **Increase value** of reporting on inclusion for investigators and staff
- **Enhance communication** with staff and investigators

and racial/ethnic minorities in clinical research? (2) How should NIH ensure the inclusion of children and other populations uniquely affected by disease but not covered by the legislative mandate? (3) What form of governance and oversight would be effective for ensuring the success of NIH efforts to meet the goals of the inclusion policies?

Review by the task force resulted in a report, "NIH Task Force for Inclusion of Women, Minorities, and Other Populations in Clinical Research: Report and Recommendations," which produced several recommendations. Based on these recommendations, the Subcommittee on Inclusion Governance (E-SIG) was established as a subcommittee of the NIH Extramural Activities Work Group (EAWG). E-SIG was constituted with representation from the NIH Intramural Research Program and R&D (research and development) contracts personnel to oversee and assess NIH policies for ensuring inclusion in clinical research. The subcommittee, chaired by the Director, ORWH, and the Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), comprises representatives from ICs with small, medium, or large clinical research/clinical trial portfolios as well as members that represent such different business areas as contracts, review, legal, and technology. A workgroup on inclusion operating procedures (IOPW) was also established. An inclusion philosophy statement and guiding principles were created, and the design of a new inclusion management system was begun.

Subcommittee on Inclusion Governance (E-SIG)

Under the governance model, E-SIG is charged with monitoring NIH's success in meeting inclusion policies, providing operating procedures and compliance monitoring, and identifying training needs for NIH staff to promote the inclusion policy. Within the governance model, ORWH continues to have legislatively mandated responsibility for monitoring adherence to the 1993 Revitalization Act (PL 103–43) and the NIH policy on the inclusion of women and minorities as subjects in clinical research; and the OER has taken primary responsibility for reporting and educating NIH staff and extramural scientists on the importance of collecting and reporting the inclusion of participants in NIH-funded research.

E-SIG also makes recommendations for policy changes to ensure that NIH is meeting goals for inclusion, reports to EAWG on its activities, and sends decisions to NIH leadership for final approval when appropriate. In 2012, E-SIG reexamined the importance and effectiveness of the inclusion of participants

in NIH-funded research. The result was the articulation of a basic philosophy and set of principles to guide the refinement and implementation of NIH policies.

Inclusion Operating Procedures Workgroup

An additional recommendation on governance from the task force report established the Inclusion Operating Procedures Workgroup (IOPW), which comprises IC and Office staff with responsibility for and expertise in implementing the NIH inclusion policies. This workgroup is charged with developing and recommending to E-SIG ways to enhance (1) standardization and efficiency in inclusion operating procedures across NIH, and (2) training about the effective implementation of the inclusion policies for NIH intramural and extramural staff as well as the extramural research community.

Inclusion Management System

Based on feedback from a survey completed by individuals in ICs who work directly with the enrollment data, as well as those in OER who analyze these data, NIH is developing a new inclusion management system (IMS) and updating operating procedures to facilitate consistency, streamline staff administrative responsibilities, enhance the quality of the data, and permit greater oversight of compliance with inclusion policies.

Communication of Inclusion Policies to the Scientific Community

In addition to monitoring inclusion in NIH-funded studies, NIH provides outreach to the scientific community to help increase its understanding of inclusion policies. These training and outreach efforts provide education about the NIH inclusion policy and assist investigators and NIH intramural research staff on how to appropriately address these issues throughout the research grant and contract process. Investigators are instructed to address issues related to including women and minorities in the development of their proposals for clinical research.

Reference documents such as the Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research (NIH Office of the Director, 2002a) and the Frequently Asked Questions on the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research (NIH Office of the Director, 2002b) have been published and distributed for investigators and NIH staff. These publications discuss the elements of recruitment and retention, the NIH inclusion policy, current Office of Management and Budget requirements for reporting race and ethnicity data, and information for application submission, peer review, and funding. Inclusion policies and information are posted on the ORWH Web site *http://orwh.od.nih.gov/research/inclusion/index.asp* and on the OER Web site *http://grants.nih.gov/grants/funding/women_min/women_min.htm*.

Other Activities Related to NIH Inclusion Policies and Reporting of Sex Differences

ORWH has undertaken a range of activities to support and promote the broad understanding of the scientific importance of inclusion in the context of the entire scientific community. Some specific examples include an IOM neuroscience workshop, a sex-specific reporting workshop, and a workshop on the inclusion of pregnant women in clinical research.

Sex Differences and Implications for Translational Neuroscience Research Workshop

In March 2010, the Institute of Medicine's (IOM's) "Forum on Neuroscience and Nervous System Disorders" convened the "Sex Differences and Implications for Translational Neuroscience Research" workshop (Institute of Medicine, 2011), which was cofunded by ORWH. The workshop's main objectives were to consider the appropriateness of studying differences between males and females in neuroscience research and the implications of sex differences for translational neuroscience research. Some participants indicated that study section reviewers often lacked expertise in recognizing the importance of sex differences research

and that no study sections or special emphasis panels existed that specifically reviewed applications for sex differences research. The workshop identified sex differences in neurological disorders and examples of ongoing studies of differences across the spectrum of diseases, such as in gene expression. One challenge identified was how to use current knowledge to inform the practice of stakeholders involved in the development of CNS (central nervous system) drugs, journals, industry, or patient advocacy groups. The full report of the workshop is available at *http://www.nap.edu/openbook.php?record_id=13004&page=89.*

Sex-Specific Reporting of Scientific Research Workshop

In August 2011, the IOM convened the workshop "Sex-Specific Reporting of Scientific Research" cosponsored by ORWH. The workshop's main objectives were to explore the need for sex-specific reporting of scientific results and to identify potential barriers to such reporting. The workshop planning committee also summarized some suggestions for advancing sex-specific reporting, such as identifying the sex of populations in journals, sharing sex-identified raw data, giving "extra credit" in reviews to manuscripts that included sex-specific information, and requiring sex-stratified analyses. A report from the workshop is available at *http://www.iom.edu/Reports/2012/Sex-Specific-Reporting-of-Scientific-Research.aspx.*

Findings of the workshop on sex-specific reporting were presented at a meeting of the Advisory Committee on Research on Women's Health in 2012. Through such activities, ORWH continues to affirm the importance of sex-specific reporting in publications, reports, meta-analyses, and other products that summarize or present data or research; ORWH maintains that it is only through such practices that full information becomes available to the public and scientists who can then use such data to inform future studies, thereby building the knowledge base in a manner that takes into consideration the influences of sex on health and disease.

Enrolling Pregnant Women in Clinical Research Forum

The inclusion and enrollment of pregnant women as participants in clinical research has garnered renewed interest in the scientific community. Pregnant women are often excluded from clinical studies, and few studies are designed to address health concerns and questions relevant to pregnant women. This is unacceptable for two reasons, as summarized very briefly by Baylis (2010): "Pregnant women get sick and sick women get pregnant." The exclusion of pregnant women from most clinical research has resulted in a lack of evidence to inform health care and treatment decisions by clinicians. In October 2010, ORWH convened a scientific forum to address the ethical/institutional review board (IRB) and recruitment issues that investigators face in conceptualizing, initiating, and conducting clinical research studies that enroll pregnant women so as to enhance the formulation of recruitment plans, the development of new protocols, the interactions with local IRBs, and the facilitation of clinical studies. (A summary of workshop presentations is available at *http://orwh.od.nih.gov/resources/policyreports/pdf/ORWH-EPW-Report-2010.pdf.*) More than 100 medical ethicists, clinical investigators, academic researchers, and others with an interest in clinical research in women shared information related to risk perception, risk reasoning, and the ethics of balancing risks and benefits for pregnant women in the clinical arena. Examples of challenges and strategies for overcoming barriers to clinical research in treating pregnant women with chronic or infectious diseases and in evaluating preventive measures such as vaccines in pregnancy were discussed and presented (Foulkes, Grady, Spong, Bayes, Clayton, 2011; Blehar, Spong, Grady, Goldkind, Sahin, Clayton, 2013).

Current Status and IC Practices

NIH staff members continue to monitor, document, and work with recipients of grants and research contracts to ensure compliance with the inclusion policy. Program officers and staff provide technical assistance to investigators throughout the application

process as they develop their applications and proposals. Review officers introduce and discuss with reviewers the guidelines/instructions for assessing the inclusion of women and minorities in clinical research as well as the instructions and requirements for designing NIH-defined phase III clinical trials so that valid analyses can be conducted for sex/gender and ethnic/racial differences. Scientific review groups (SRGs) are instructed to focus on scientific considerations when assessing the planned enrollment for a particular study. The SRG determines the implementation plan for an application to be unacceptable if it (1) fails to provide sufficient information about target enrollment, (2) does not adequately justify the limited inclusion or even the total exclusion of women or minorities, or (3) does not realistically address recruitment and retention. For NIH-defined phase III clinical trials, the SRG also evaluates the description of plans to conduct analyses, as appropriate, to address differences in the intervention effect by sex/gender and/or racial/ethnic group. Applications with unacceptable inclusion plans cannot be funded until NIH staff are assured that the investigator's revised inclusion plans meet the inclusion policy requirements. Research awards covered by this policy require the grantee to report annually on the enrollment of research participants by sex/gender and race/ethnicity so that compliance with the NIH inclusion policy can be monitored.

At the time of the award and the submission of progress reports, program officials monitor and verify that requirements of the inclusion policy are met. When new and competing continuation applications selected for payment are deficient in meeting policy requirements, grants management staff and program officials are required to withhold funding until the investigator has satisfactorily addressed the policy requirements.

Summary Report of NIH Inclusion Data: Comparison of FY 2011 and FY 2012 and 5- and 10-Year Trend Data

Introduction

Data on inclusion are tabulated from human subject populations in NIH-defined clinical research[1] and NIH-defined Phase III clinical trials. Identification with specific sex/gender, racial, and ethnic categories is based on self-identification by the participants; participants always have the option to not identify. NIH is mandated to monitor inclusion in all clinical research projects it conducts or supports; however, for the purpose of this summary, the primary focus of the racial and ethnic analyses is on studies involving domestic populations. (Appendix H and Appendix I provide summaries of NIH inclusion policies, reporting guidelines, and key definitions. A complete set of aggregate data tables is provided in Appendix J).

New clinical research studies begin each year, while other studies may be ending so that inclusion data will vary from year to year because of changes in the scientific topics under study and in the prevalence of the diseases or conditions within each individual study.

Analysis of aggregate NIH inclusion data for FY 2011 and FY 2012 demonstrates that substantial numbers of women and men, and individuals of different races and ethnicities, have been included as research subjects in NIH clinical research studies and NIH-defined Phase III clinical trials. In addition, 5- and 10-year data have been provided to demonstrate trends in inclusion data over time. Caution should be

[1] NIH defines human clinical research as research with human subjects that is one of the following: (1) "Patient-oriented research." This type of research is conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that use human tissues that cannot be linked to a living individual. Patient-oriented research includes (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical studies, and (d) development of new technologies. (2) "Epidemiologic and behavioral studies." (3) "Outcomes research and health services research." Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

exercised to avoid over-interpreting the figures and data tables provided.

The purpose of many of the summary figures in the body of the report is to demonstrate the relative distributions of participants as defined by sex/gender, race, and/or ethnicity. Some key trends:

- Total enrollment has ranged from approximately 14.8 million individuals in FY 2003 to a high of over 23 million in FY 2010. The most recent reported FY (FY 2012) indicates participation of approximately 17.7 million individuals.[2]
- Between FY 2003 and FY 2012, percent enrollment of females has ranged from a low of 56.1% in FY 2010 to a high of 63.9% in FY 2006. In FY 2012, females comprised 57% of enrollment. These tables also include data on the participation of females excluding female-only studies.[3]
- Total enrollment of minorities in clinical research has varied from a low of 28.6% in FY 2008 to a high of 43.1% in FY 2006. In FY 2012, 36.5% of participants were from minority categories.[4]
- Total enrollment of minorities in NIH-defined Phase III clinical trials has generally been on an increasing trend, with a low of 24.7% in FY 2003 to a high of 65.8% in FY 2012.[5] These data are significantly impacted by the inclusion of foreign participants. In domestic NIH-defined Phase III trials, the 5-year trend (FY 2008–FY 2012) indicates a range of 20.2% in FY 2008 to a high of 29% in FY 2012.[6]

[2] From Table 2A: Total Enrollment for All NIH Clinical Research from FY 2003–FY 2012 (10 Year Trend).

[3] From Table 2A: Total Enrollment for All NIH Clinical Research from FY 2003–FY 2012 (10 Year Trend).

[4] From Table 3A: Total Enrollment and Minority Enrollment for All NIH Clinical Research from FY 2003–FY 2012 (10 Year Trend). Note that these data also include foreign participants. Refer to additional tables in Section 3 of Appendix J for more summary data on percent of minorities enrolled in domestic research.

[5] From Table 4A: Total Enrollment and Minority Enrollment for All NIH-Defined Phase III Clinical Trials from FY 2003–FY 2012 (10 Year Trend)

[6] From Table 4B: Total Enrollment and Minority Enrollment for Domestic NIH-Defined Phase III Trials (Five Year Trend).

Previous inclusion reports and aggregate enrollment figures for sex/gender, race, and ethnicity for FY 1994 to the present can be found on the ORWH Web site at *http://orwh.od.nih.gov/research/inclusion/index.asp.*

Acceptability of Inclusion Plans for Extramural Research Awards

Figure 1 depicts the percentage of competing clinical research awards in which the plans for the inclusion of women and minorities were found to be acceptable or unacceptable for FY 2003 through FY 2012. The data indicate that the vast majority of applications had acceptable plans for the inclusion of women and minorities during the peer review process, ranging from 97% acceptable/3% unacceptable starting in 2003 and improving to 99% acceptable/1% unacceptable in 2011 and 2012. This trend is quite stable.

Metrics Based on Enrollment Records

Figure 2 illustrates the trend data for the number of data records (also referred to as protocols) reporting enrollment each FY since 2003. In FY 2003, there were 10,216 data records with enrollment. The highest number in the past 10 years was 12,079 in FY 2010. In FY 2011 and FY 2012, there were decreases in the number of data records, with 11,296 and 10,774, respectively. Interpretation of these data should be approached with caution because investigators and IC staff have some latitude in how inclusion data are reported and whether a given study will be divided into separate data records (often the case for multisite studies or studies spanning multiple awards) or consolidated under a single record. In addition, these data only reflect those data records for which actual enrollment has been reported to the NIH; those where recruitment has not begun are not included. The decrease over the past 2 FYs may reflect the end of the ARRA (American Recovery and Reinvestment Act of 2009) funding period as well as a level NIH budget.

Figure 3 indicates the number of data records reporting enrollment for NIH-defined Phase III clinical trials. These data have ranged from a high of 852 in FY 2003 to a low of 547 in FY 2005. The data then increased starting

Figure 1. Review of Inclusion Plans in Competing Clinical Research Awards

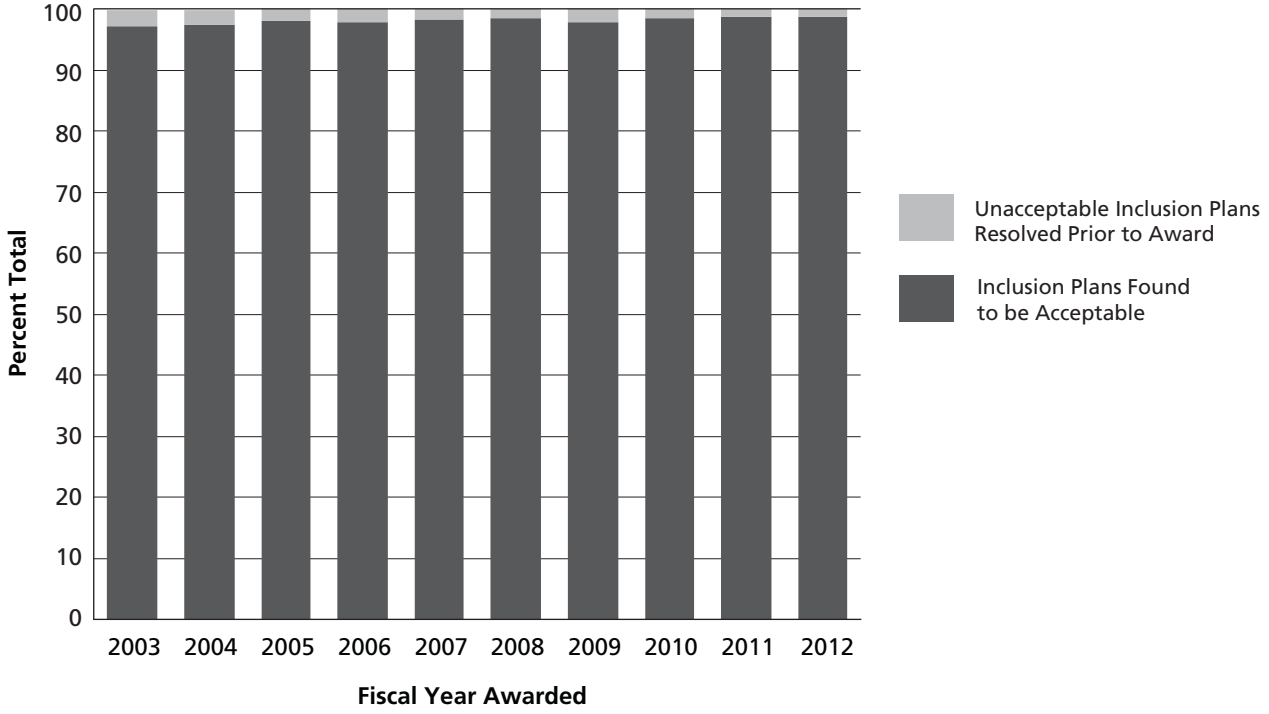


Figure 2. NIH Clinical Research: Number of Records with Enrollment

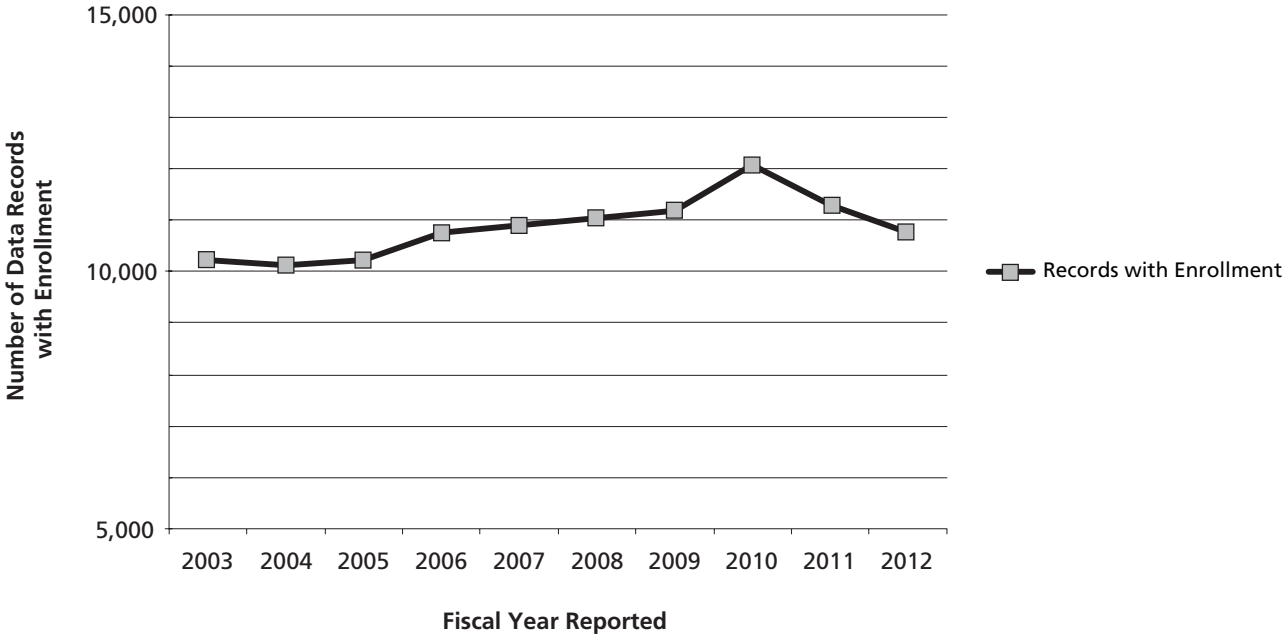
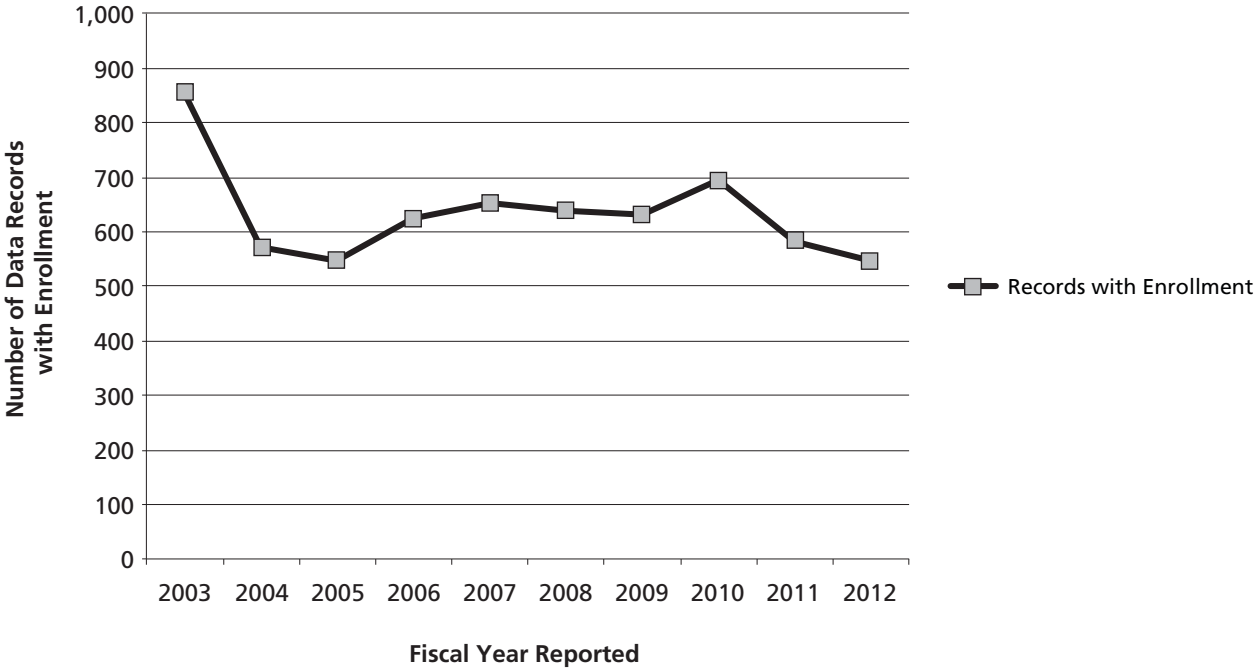


Figure 3. NIH-Defined Phase III Clinical Trials Records with Enrollment



in FY 2006 and stabilized until declines for FY 2011 (582) and FY 2012 (548). These declines may be a result of a level NIH budget and/or the end of ARRA funding. Caution should be used in over-interpreting these data shifts, given that principal investigators and the ICs have latitude in how to report inclusion data on data records.

Figure 4 illustrates the distribution of sex/gender across data records for all NIH clinical research and NIH-defined Phase III clinical trials for FY 2011 and FY 2012. While the overall number of data records has decreased from FY 2011 to FY 2012 for both NIH clinical research and NIH-defined Phase III clinical trials, the percentage distribution of male-only, female-only, and studies with males and females (excluding male-only and female-only) has remained quite stable. For NIH clinical research, there were no changes between FY 2011 and FY 2012 in percentage distribution across data record groups, with 11% for female-only data records, 6% for male-only data records, and 83% for data records excluding male-only and female-only studies. For NIH-defined Phase III clinical trials, there was a two-percentage point decrease in the proportion of female-only data records and a two percentage point increase in data records excluding male-only and female-only studies. The male-only data record distribution remained stable at 6%.

Metrics Based on Aggregate Enrollment: Sex/Gender

Figure 5 illustrates the long-term trend of recruitment by sex/gender in all NIH clinical research. In FY 2003, there were 57.6% females and 41.4% males. This 10-year trend has remained relatively stable with a return to 57% females and 41.8% males in FY 2012. The 10-year trend ranges from 56.1% females and 43.0% males (FY 2010) to 63.9% females and 34.9% males (FY 2006).[7]

Figures 6 and 7 compare the percentage enrollment by sex/gender for FY 2011 and FY 2012 for all NIH-defined clinical research. Figure 6 includes the percent enrollment totals for females, males, and unknowns; Figure 7 presents these data excluding female-only and male-only studies. In Figure 6, there appears to be a slight shift in the ratio of males to females enrolled in FY 2012 as

[7] In Figure 5, the percentage of females and males does not total to 100% in each fiscal year because there is also a small percentage of individuals reported with unknown sex/gender in each fiscal year.

Figure 4. Distribution of Sex/Gender in Data Records

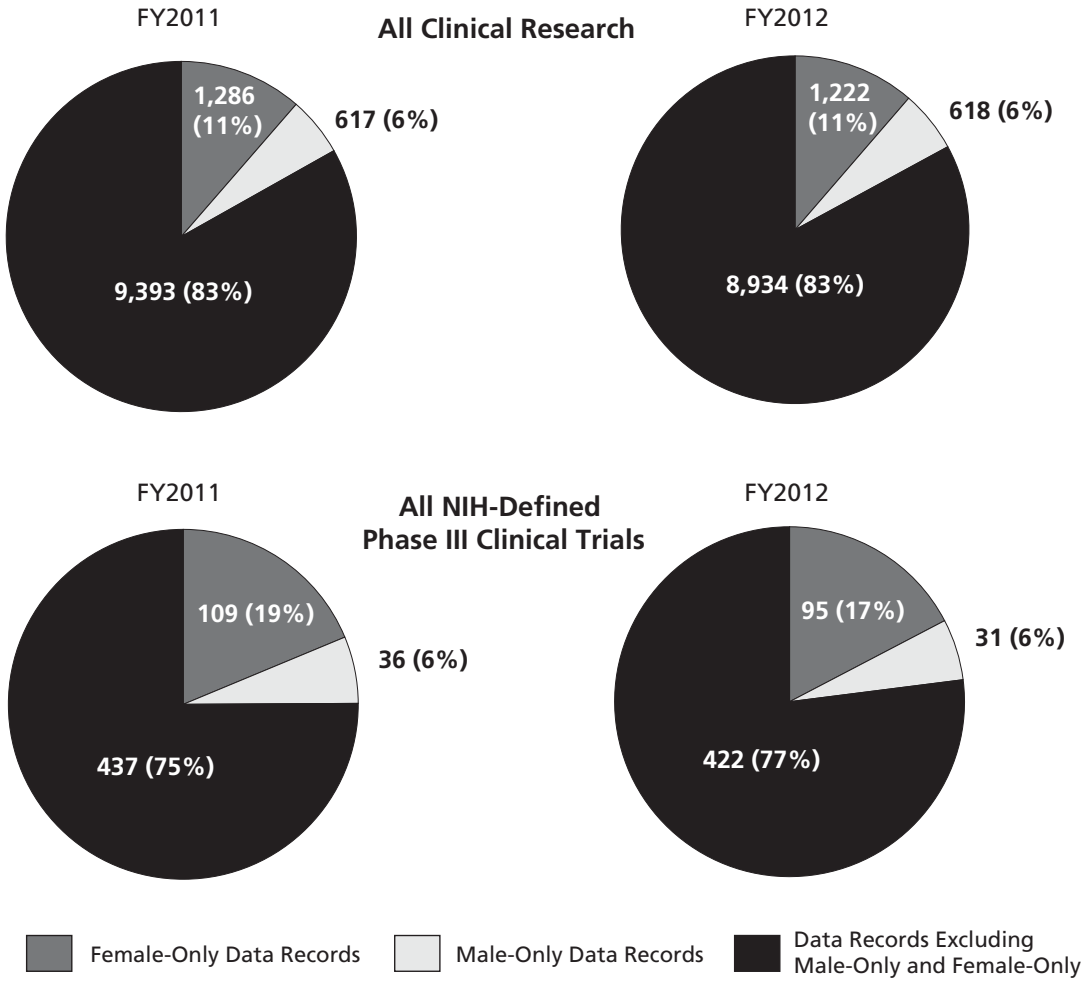


Figure 5. Long-Term Trend of Enrollment by Sex/Gender in NIH Clinical Research

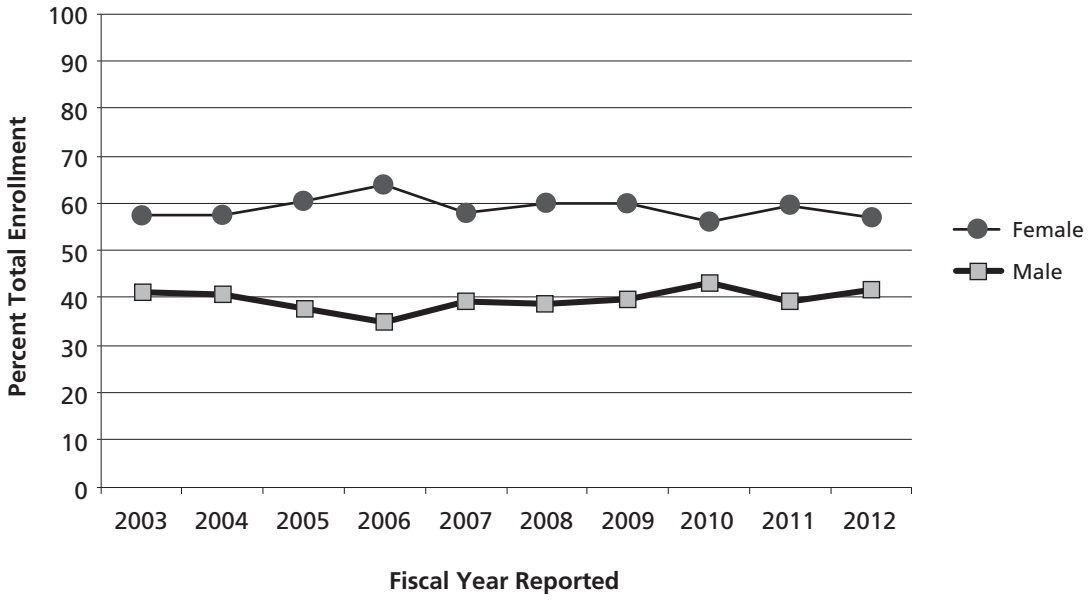


Figure 6. Percent Enrollment by Sex/Gender in All NIH Clinical Research

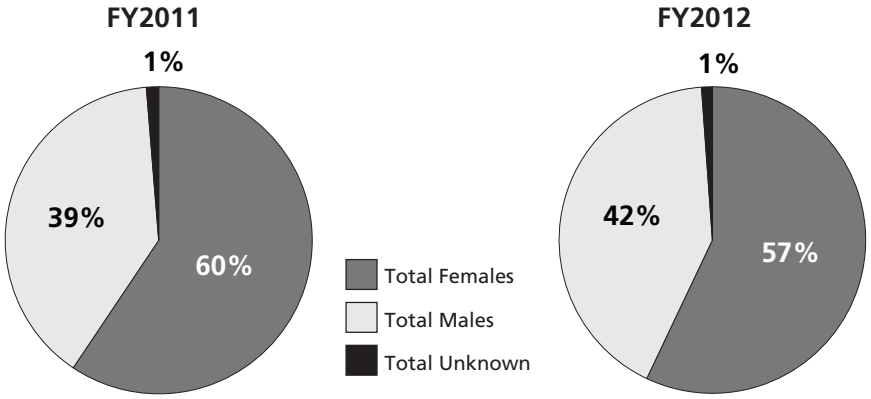


Figure 7. Percent Enrollment by Sex/Gender in All NIH Clinical Research Excluding Male- and Female-Only Studies

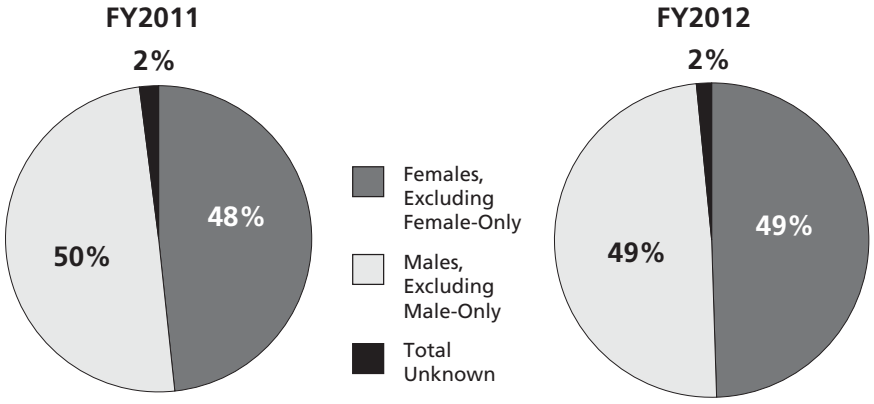


Figure 8. Long-Term Trend of Enrollment by Sex/Gender in NIH-Defined Phase III Clinical Trials

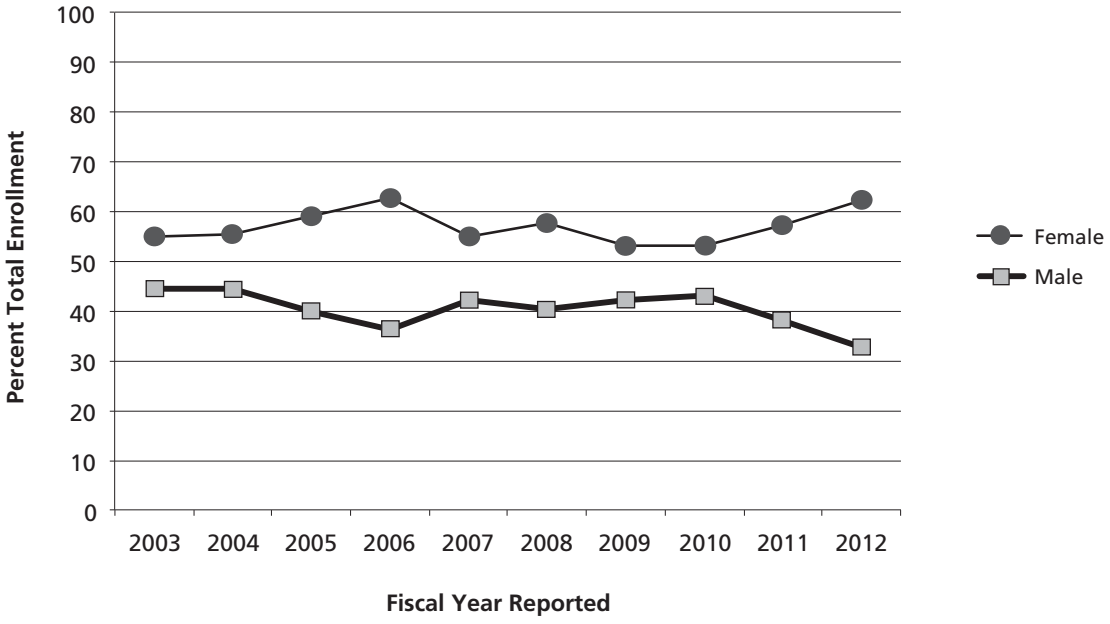


Figure 9. Percent Enrollment by Sex/Gender in NIH-Defined Phase III Clinical Trials

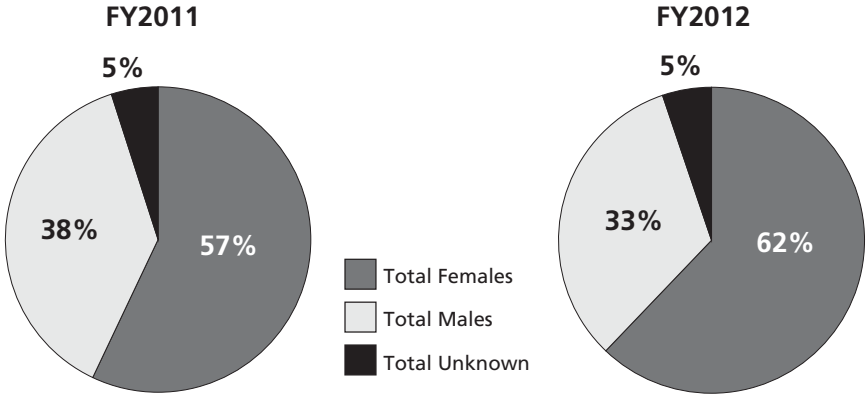
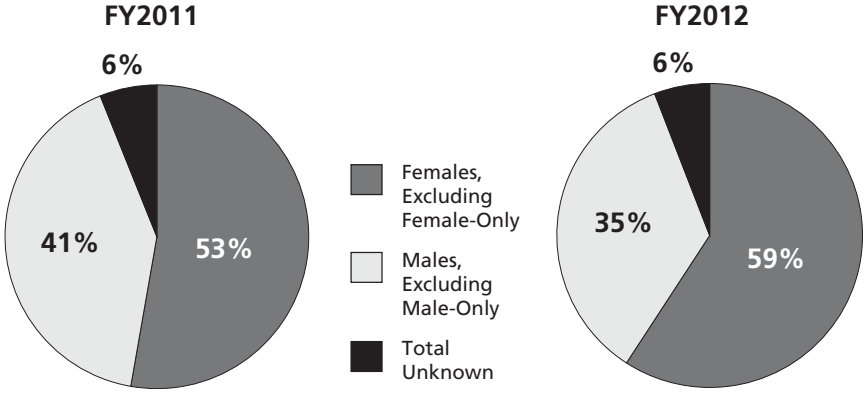


Figure 10. Percent Enrollment by Sex/Gender in NIH-Defined Phase III Clinical Trials Excluding Male- and Female-Only Studies



compared to FY 2011, with a decrease in the proportion of females in FY 2012 (from 60% to 57%) and a 3% increase in the proportion of males. This trend appears to mostly be the result of shifts in female-only or male-only studies. In Figure 7, there was only a 1% shift in the proportion of females relative to males when female-only and male-only studies were excluded from the analysis.

Figure 8 indicates the long-term trend data of enrollment by sex/gender in NIH-defined Phase III clinical trials. There is an increase in the number of females (62.1%) in FY 2012 over FY 2011 (57%). The 10-year trend ranges from 53% females and 42.3% males (FY 2009) to 62.9% females and 36% males (FY 2006).[8]

[8] In Figure 8, the percentage of females and males does not total to 100% in each fiscal year because there is also a small percentage of individuals reported with unknown sex/gender in each fiscal year.

It is not entirely clear what is contributing to the differences in the distribution of females relative to males. It is possible that there have been changes in single-sex/gender studies (beginning or ending) as well as shifts in the rate of participation of a given sex/gender in studies recruiting males and females.

In Figures 9 and 10, the distribution of enrollment by sex/gender in NIH-defined Phase III clinical trials is compared for FY 2011 and FY 2012. For all NIH-Defined Phase III clinical trials as well as those excluding male-only or female-only studies, there appears to be a modest increase in the number of females relative to males in these studies. This shift suggests that, at least for FY 2011 and FY 2012, the changes in proportion are due to changes in enrollment of trials including females and males rather than trials enrolling only females or only males.

Metrics Based on Aggregate Enrollment: Race and Ethnicity

Figure 11 illustrates the percent of minority enrollment over the past 5 years in domestic clinical research. From FY 2008 to FY 2011, there was a trend of increased enrollment, which slightly decreased for FY 2012. Specifically, minority enrollment was 24.1% in FY 2008, 27.8% in FY 2009, 28.1% in FY 2010, 32.6% in FY 2011, and 28.7% in FY 2012.

The percent total enrollment for racial categories in domestic clinical research is presented for FY 2011 and FY 2012 in Figure 12. The proportions of most racial categories decreased or remained stable in FY 2012, including American Indian/Alaska Native (–0.3%), Asian (–2.3%), Black or African-American (–0.9%), Native Hawaiian or Pacific Islander (0.0%), White (–7.8%), and More than one race (–0.2%). There is an increase from 10.0% to 21.7% (+11.7%) in proportion of individuals in the Unknown/Not Reported category. These data are likely affected by a large study in the intramural division of the National Cancer Institute where sex/gender data were available from the health records dataset used; however, race and ethnicity information were not available to the investigator.

In Figure 13, the percent total enrollment for ethnic categories in domestic clinical research is illustrated for FY 2011 and FY 2012. The proportion of Not Hispanic participants decreased from 80% to 67.1% (–12.9%) with a smaller decrease in the proportion of Hispanic or Latino participants (–0.2%). The same trend observed in Figure 12 of an increase in the percentage of Unknown/Not Reported individuals is also observed in Figure 13 (+13.1%) and is likely a result of the same intramural study where race and ethnicity of the dataset were unknown to the investigator.

Figure 14 illustrates percent minority enrollment in domestic NIH-defined Phase III clinical trials. The overall trend in Phase III trials has been for modest increases in the proportion of minority populations enrolled over the past 5 years. Specifically, enrollment

Figure 11. Minority Enrollment in NIH Domestic Clinical Research

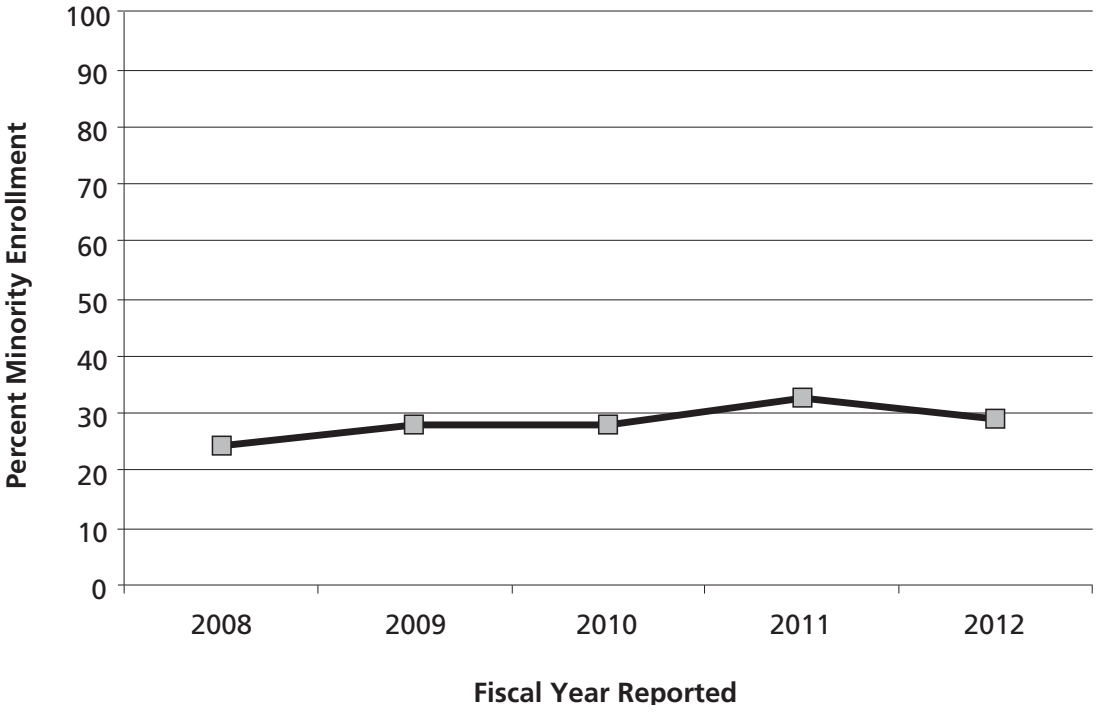


Figure 12. Total Domestic Enrollment in NIH Clinical Research: Racial Categories

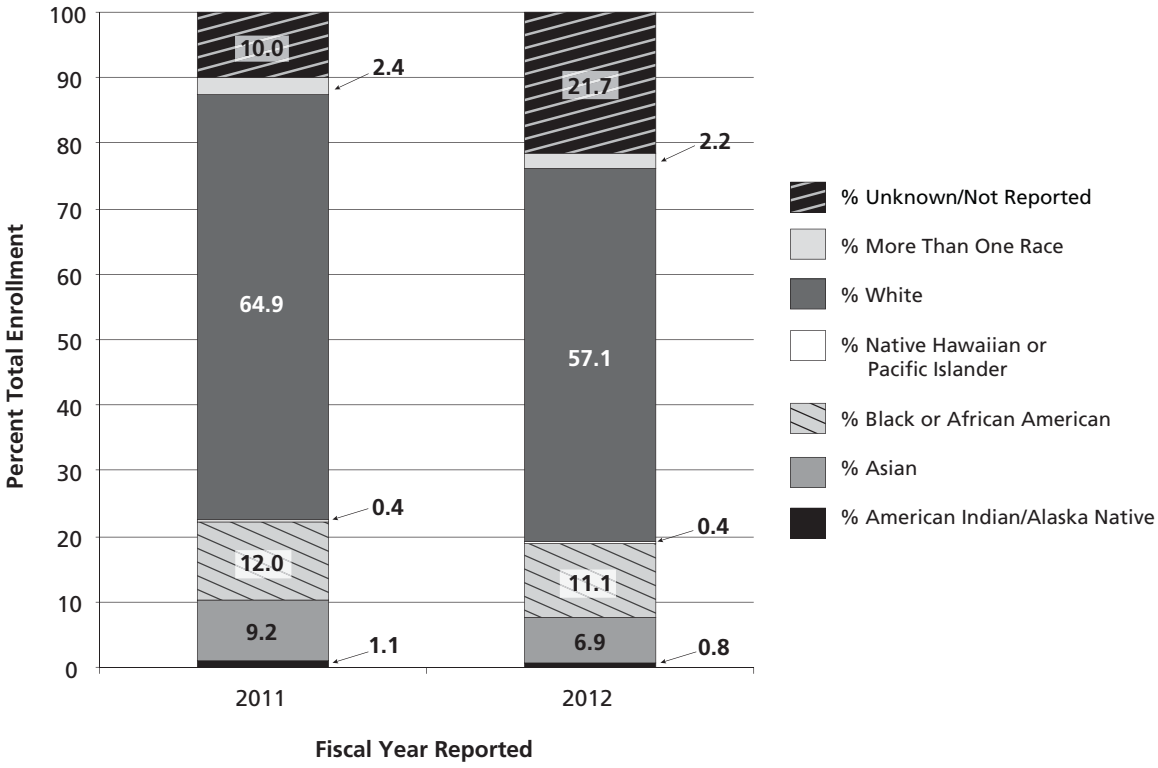


Figure 13. Total Domestic Enrollment in NIH Clinical Research: Ethnic Categories

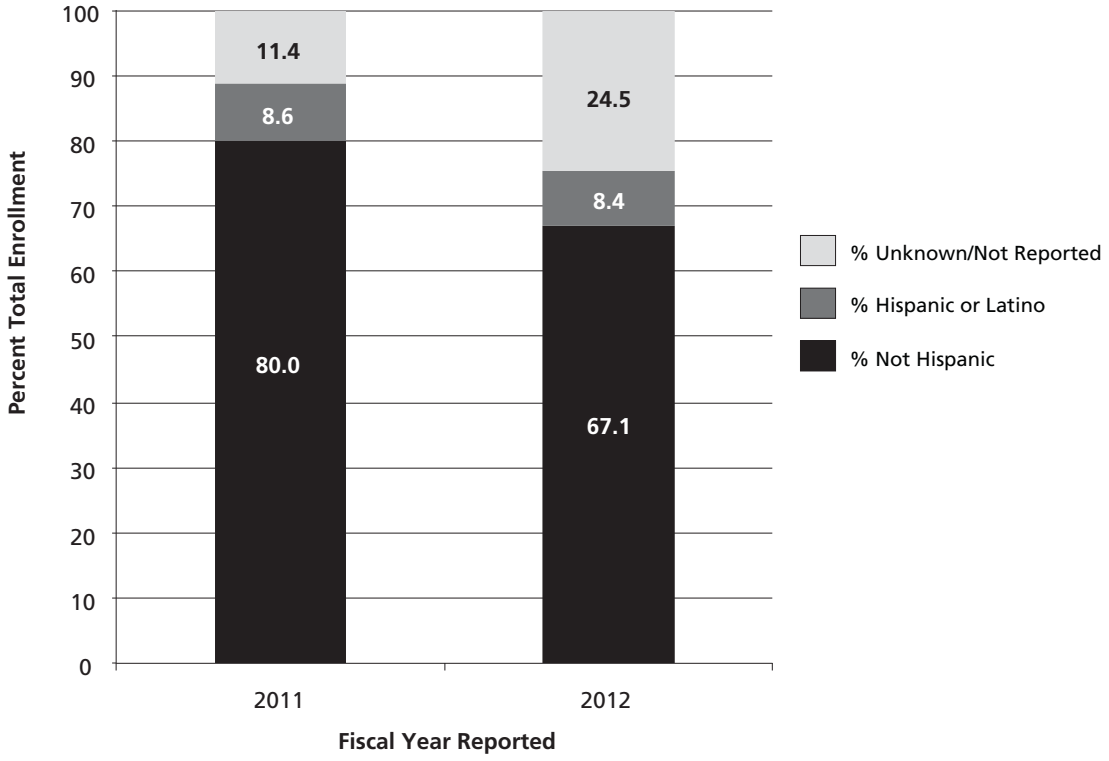


Figure 14. Minority Enrollment in NIH Domestic Phase III Clinical Trials

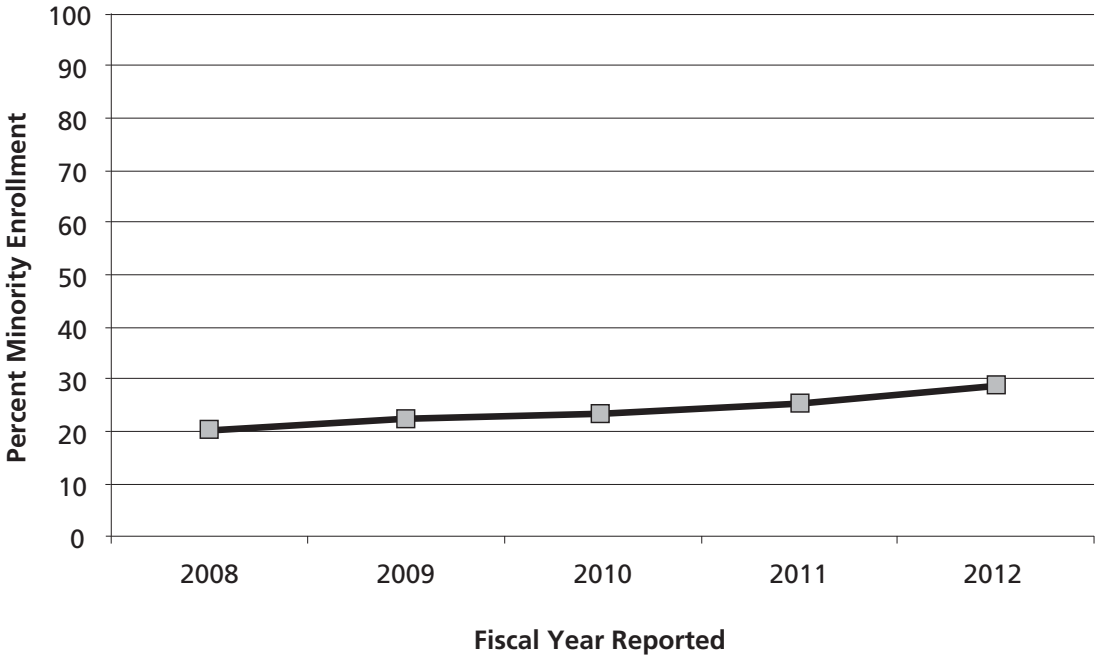
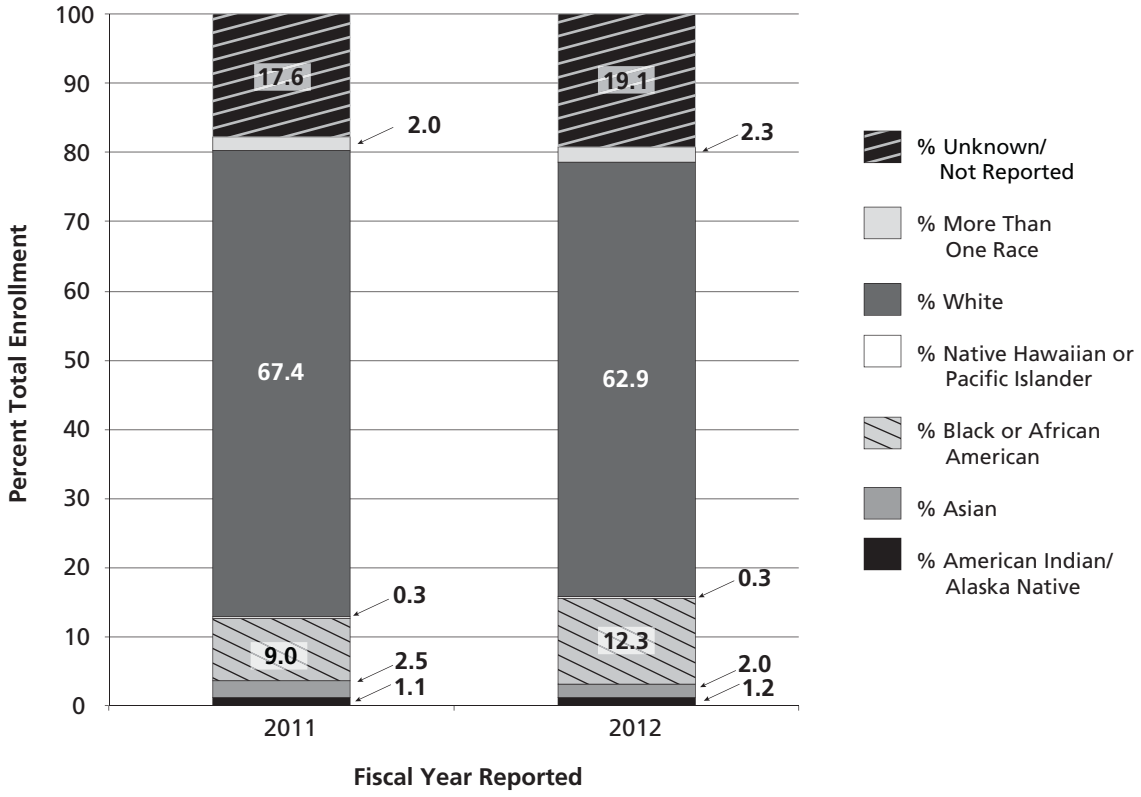


Figure 15. Total Domestic Enrollment in NIH-Defined Phase III Clinical Trials: Racial Categories



in FY 2008 was 20.2% minority and has increased to 29.0% for FY 2012.

Figure 15 provides the percent total enrollment for racial categories in domestic NIH-defined Phase III clinical trials. Increases from FY 2011 to FY 2012 are noted in the following racial categories: American Indian/Alaska Native (+0.1%), Black or African American (+3.3%), More than one race (+0.3%), and Unknown/Not Reported (+1.5%). Decreases from FY 2011 to FY 2012 are noted for the Asian (–0.5%) and White (–4.5%) categories; Native Hawaiian or Pacific Islander remained stable at 0.3% of the distribution.

In Figure 16, the percent total enrollment for ethnic categories in domestic NIH-defined Phase III clinical trials indicates increases from FY 2011 to FY 2012 in the proportion of Hispanic or Latino (+0.9%) and Unknown/Not Reported (+2.3%) participants while the proportion of individuals in the Not Hispanic or Latino category decreased (–3.2%).

Metrics Based on Aggregate Enrollment: Domestic Race and Ethnicity by Sex/Gender

Figure 17 indicates the 5-year trend for percent minority enrollment broken out by sex/gender in domestic clinical research. The trend remained relatively stable through FY 2008 (60.2% females, 39.4% males), FY 2009 (59.9% females, 39.8% males), and FY 2010 (58.9% females, 40.5% males). There is an increase in the proportion of female enrollment relative to male enrollment in FY 2011 (62.5% females, 37.0% males) and a slight decrease in the percent female enrollment relative to male enrollment in FY 2012 (55.9%

Figure 16. Total Domestic Enrollment in NIH-Defined Phase III Clinical Trials: Ethnic Categories

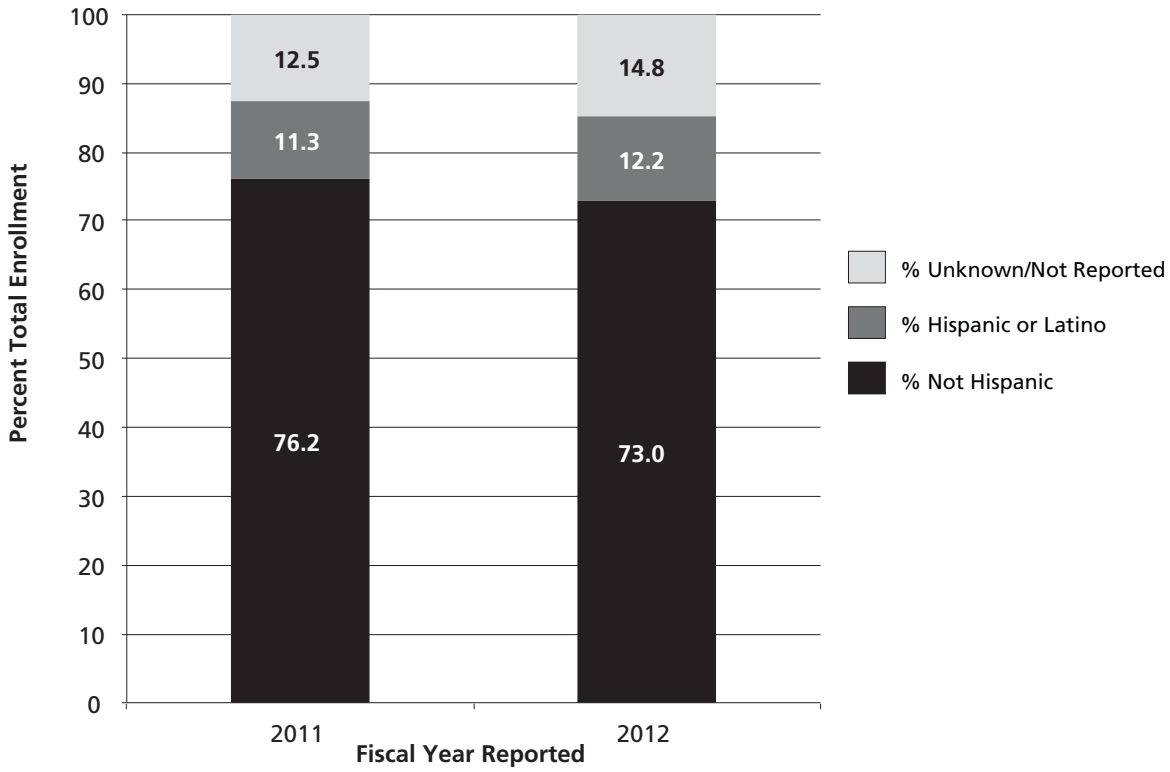
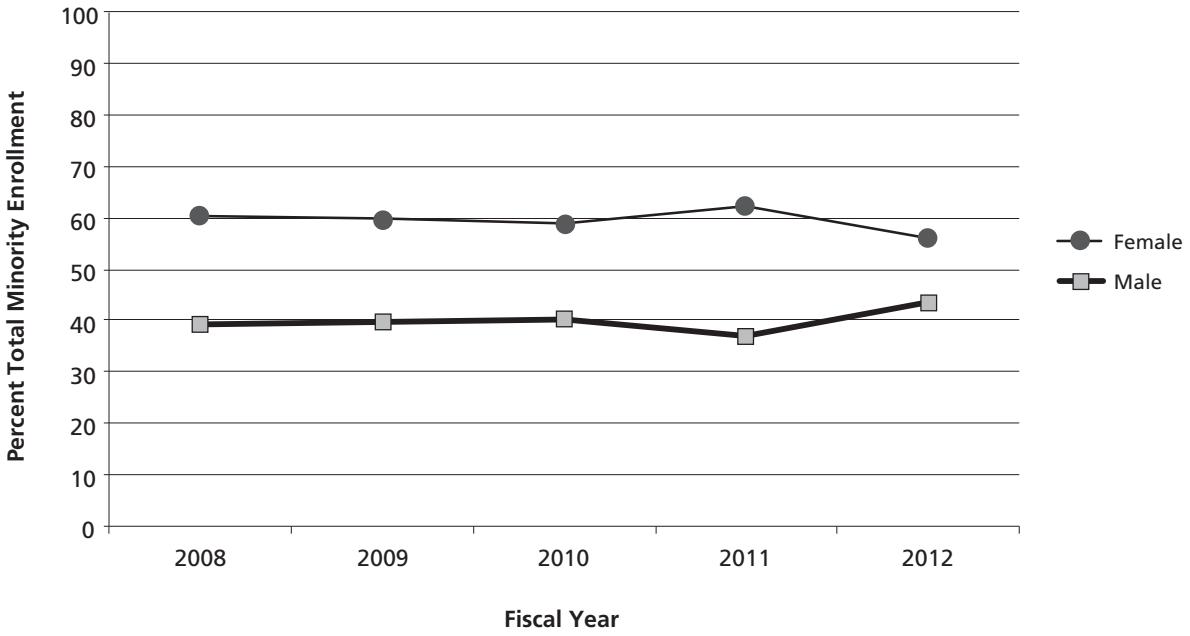


Figure 17. Minority Enrollment by Sex/Gender for Domestic NIH Clinical Research



females, 43.4% males).[9] The decrease in the percent of male participants in FY 2011 is likely influenced by conclusion of a large clinical study funded by the National Institute of Mental Health on suicide prevention in military personnel where the population consisted of more men than women. It is not clear what is contributing to the proportional shift back to closer relative distributions of males and females in FY 2012 but it could be the typical fluctuations observed due to changes in funding that occur each year. The overall trend suggests fairly stable distributions.

In Figures 18 and 19, percent total enrollment figures are provided for each racial (Figure 18) and ethnic (Figure 19) category within the sex/gender categories of female, male, and unknown/not reported for domestic clinical research. When comparing the percent distribution of females across racial categories (Figure 18) for FY 2011 and FY 2012, there was a decrease in proportion of participants identifying as American Indian/Alaska Native (–0.4%), Asian (–3.5%), Black or African-American (–0.6%), White (–11.3%), and More than one race (–0.2%). Increased proportions were observed for female participants identifying as Native Hawaiian or Pacific Islander (+0.1%) and females in the Unknown/Not Reported racial category (+16.0%).

When comparing the percent distribution of males across racial categories (Figure 18) for FY 2011 and FY 2012, there was a decrease in the proportion of males identifying as American Indian/Alaska Native (–0.1%), Asian (–0.5%), Black or African American (–1.5%), White (4.2%), and More than one race (–0.3%). There was no change in the percent enrollment of Native Hawaiian or Pacific Islander males, and there was an increase in the proportion of males with Unknown/Not Reported race (+6.7%).

When comparing individuals of unknown or not reported sex/gender, there were increased proportions of Asians (+2.8%), White (+3.6%), and More than one race (+0.2%). No changes in the percent enrollment were observed for individuals identifying as American Indian/Alaska Native and Native Hawaiian or Pacific Islander. Decreases in the percent enrollment were noted for Black or African American (–0.6%) and individuals of Unknown/Not Reported race (–5.9%).

[9] In Figure 17, the percentage of females and males does not total to 100% in each fiscal year because there is also a small percentage of individuals reported with unknown sex/gender in each fiscal year.

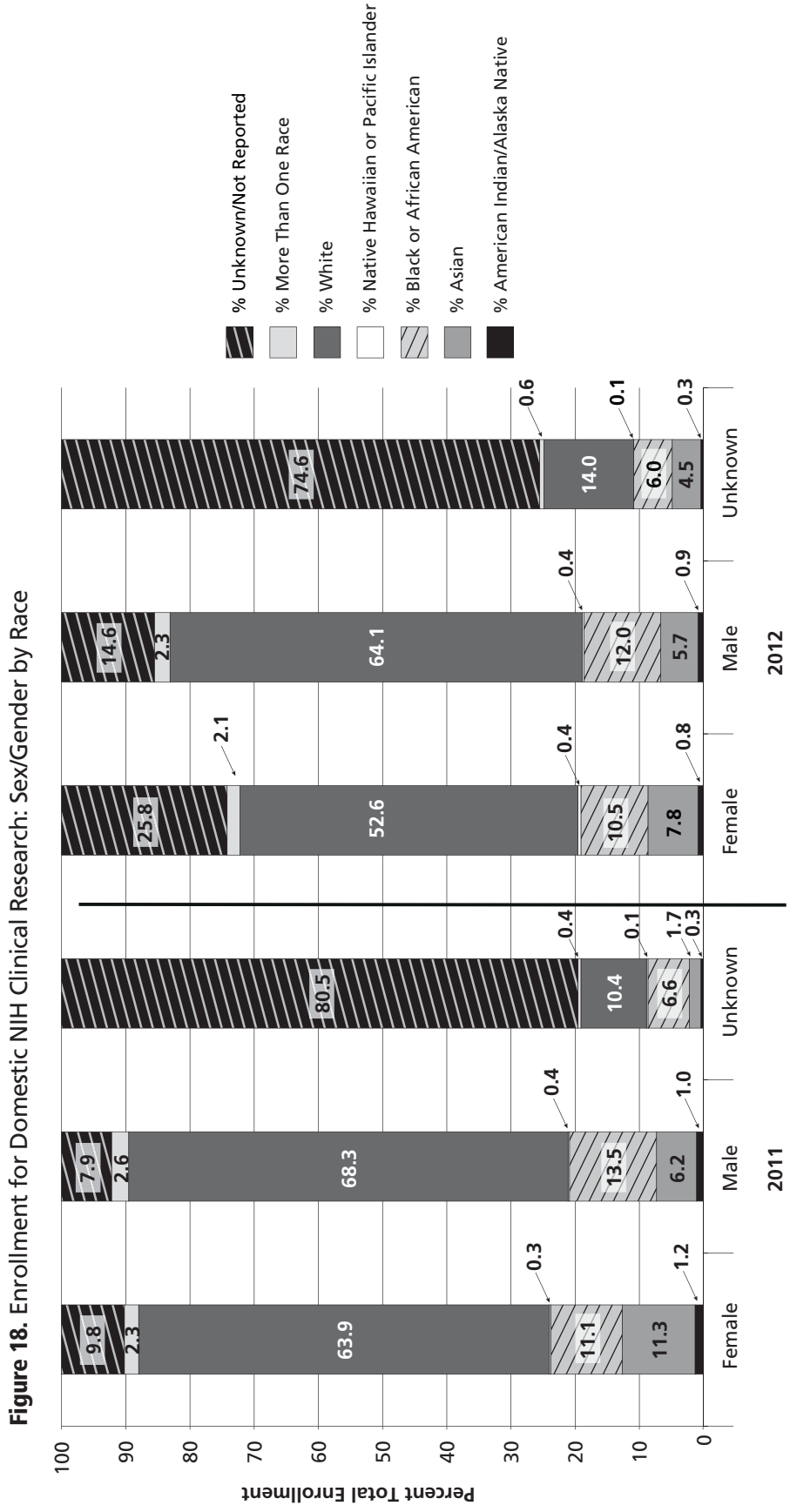


Figure 18. Enrollment for Domestic NIH Clinical Research: Sex/Gender by Race

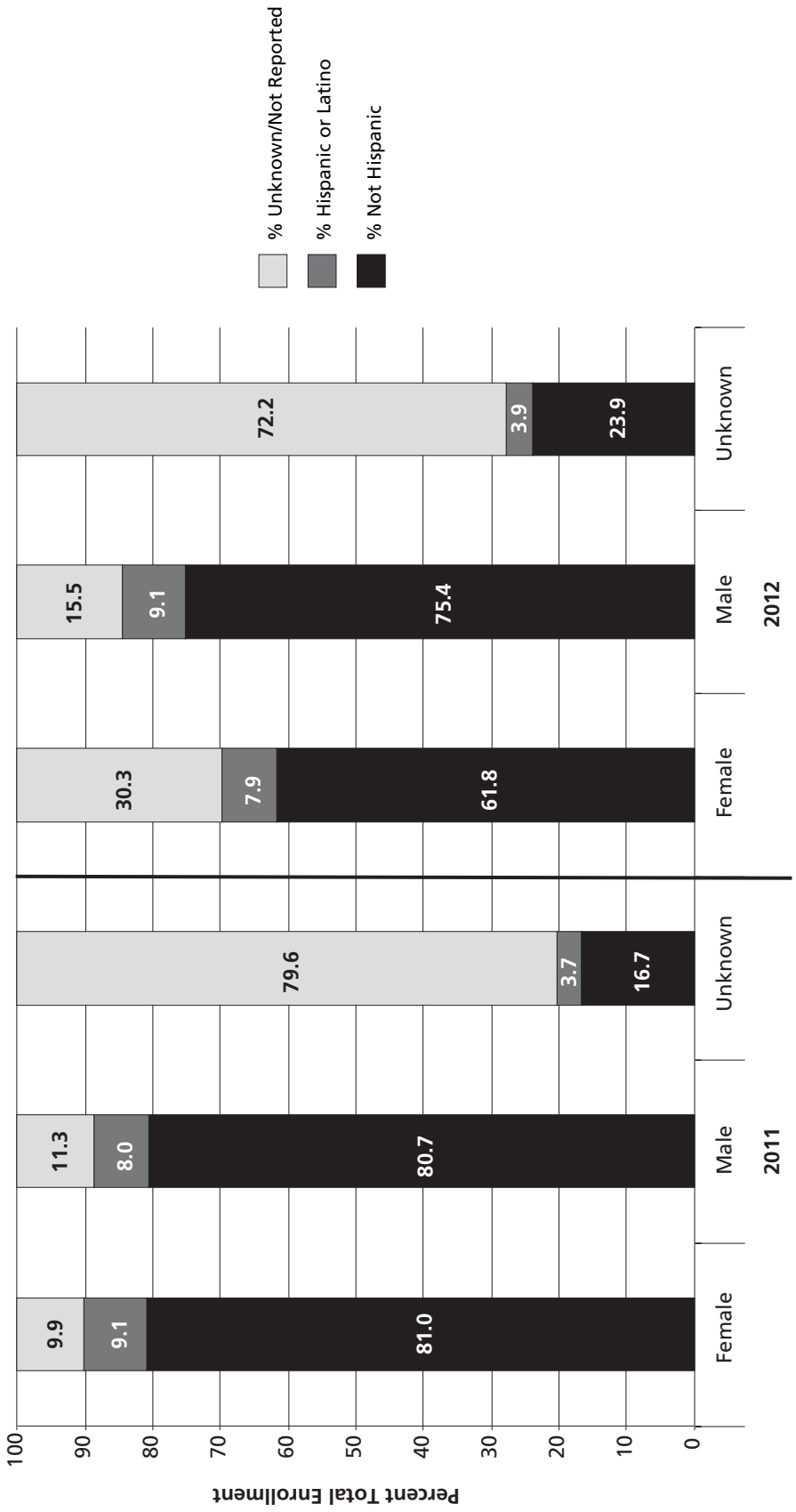


Figure 19. Enrollment for Domestic NIH Clinical Research: Sex/Gender by Ethnicity

Figure 20. Minority Enrollment by Sex/Gender for Domestic NIH-Defined Phase III Clinical Trials

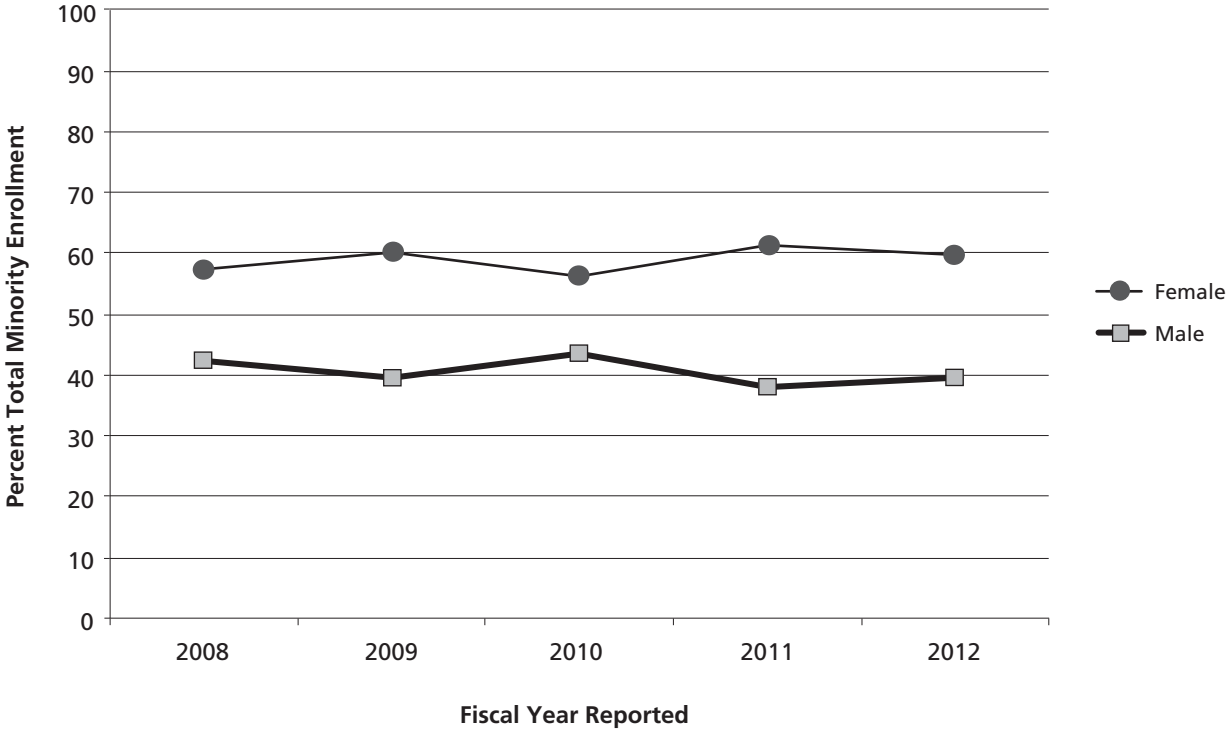


Figure 19 illustrates the percent enrollment of ethnicity by sex/gender for FY 2011 and FY 2012. When comparing the percent enrollment of females by ethnicity in domestic clinical research for FY 2011 and FY 2012, Not Hispanic or Latino and Hispanic or Latino categories decreased (19.2% and –1.2% respectively) while the proportion of females of Unknown/Not Reported ethnicity increased substantially (+20.4%). However, for males, increased percent enrollment was observed for Hispanic or Latino males (+1.1%) and males of Unknown/Not Report ethnicity (+4.2%) in FY 2012 compared to FY 2011. Males of Not Hispanic or Latino ethnicity decreased somewhat (–5.3%) from FY 2011 to FY 2012. These data may be affected by a large study in the intramural division of the National Cancer Institute where sex/gender data were available from the health records dataset used; however, race and ethnicity information were not available to the investigator.

When comparing individuals of unknown or not reported sex/gender, there were increased proportions of individuals identifying as Not Hispanic or Latino (+7.2%) and individuals identifying as Hispanic or Latino (+0.2%). A decrease in the percent enrollment was noted for individuals of Unknown/Not Reported sex/gender and ethnicity (–7.4%).

Figure 20 indicates the 5-year trend for percentage minority enrollment broken out by sex/gender in domestic NIH-defined Phase III clinical trials. The trend has remained relatively stable with a range of 56.2% females to 43.3% males (FY 2010) to 61.4% females to 38.0% males (FY 2011), with a slight decrease in female enrollment relative to male enrollment in FY 2012 (59.9% females, 39.4% males).[10]

In Figures 21 and 22, percent enrollment figures are provided for each racial (Figure 21) and ethnic (Figure 22) category within the sex/gender categories of female, male, and unknown for domestic NIH-defined Phase III clinical trials. When comparing the proportion of females for each racial category (Figure 21) between FY 2011 and FY 2012, decreases

[10] In Figure 20, the percentage of females and males does not total to 100% in each fiscal year because there is also a small percentage of individuals reported with unknown sex/gender in each fiscal year.

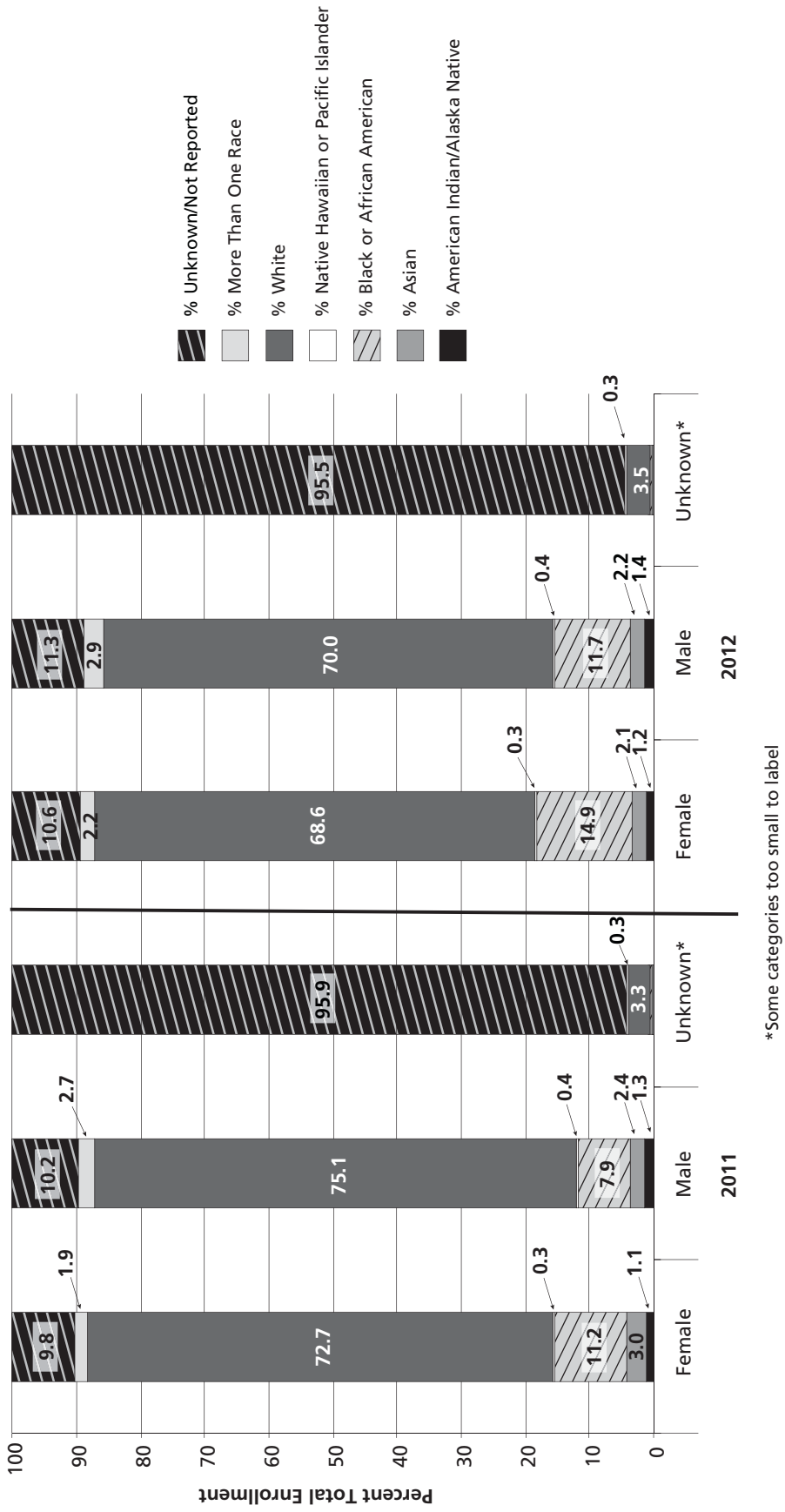


Figure 21. Enrollment for Domestic NIH-Defined Phase III Clinical Trials: Sex/Gender by Race

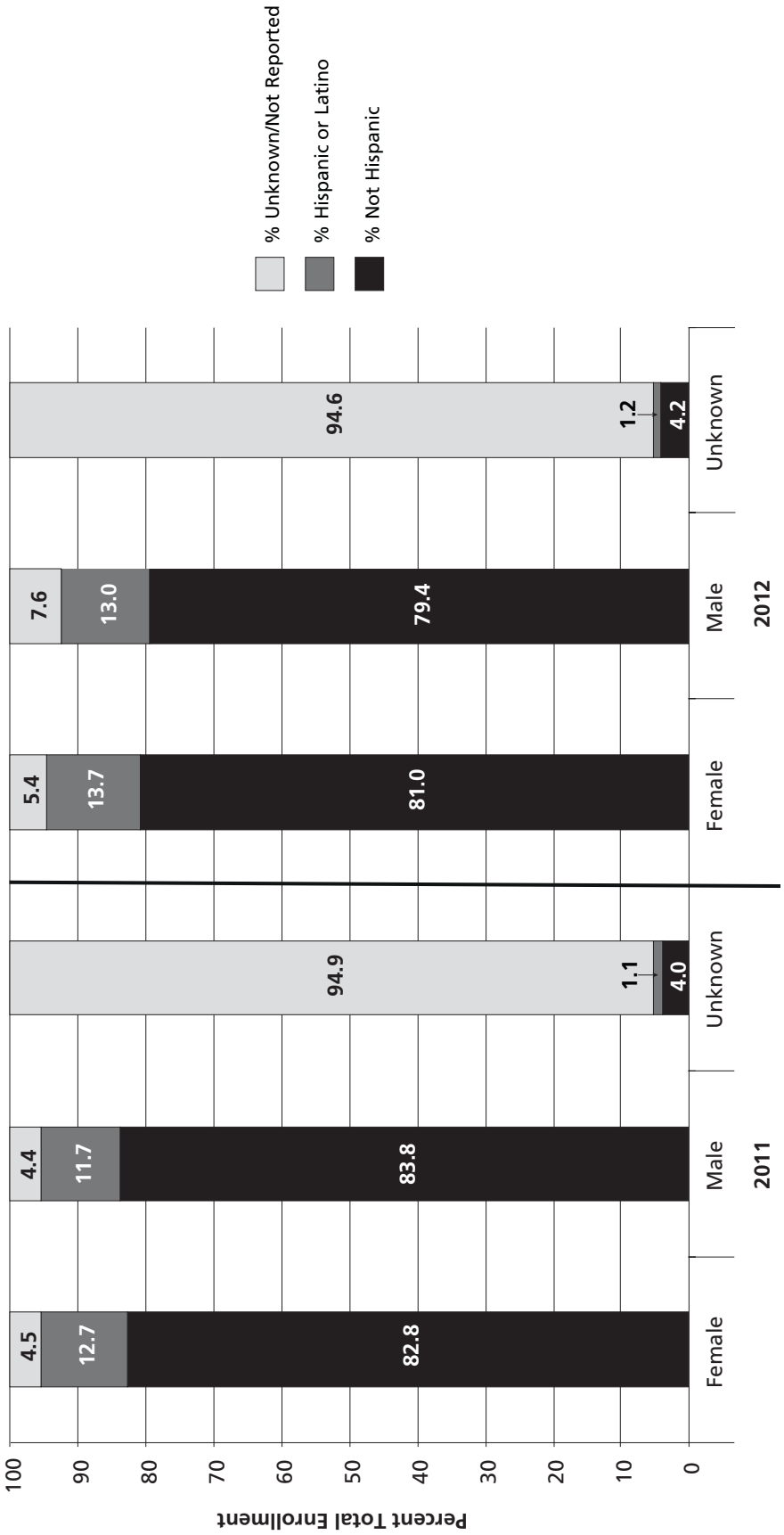


Figure 22. Enrollment for NIH-Defined Phase III Clinical Trials: Sex/Gender by Ethnicity

were observed for Asian (–0.9%) and White (–4.1%) racial categories, with increased percent enrollment for American Indian/Alaska Native (+0.1%), Black or African American (+3.7%), More than one race (+0.3%), and Unknown/Not Reported race (+0.8%). No change in percent distribution was observed for Native Hawaiian or Pacific Islander.

When comparing FY 2011 and FY 2012 percentage enrollment of males across racial categories for domestic NIH-defined Phase III clinical trials, the same pattern is observed with decreased proportions in the racial categories of Asian (–0.2%) and White (–5.1%), with increases in American Indian/Alaska Native (+0.1%), Black or African-American (+3.8%), More than one race (+0.2%), and Unknown/Not Reported race (+1.1%). No change in percent distribution was observed for Native Hawaiian or Pacific Islander.

Figure 22 depicts the FY 2011 and FY 2012 percent enrollment for ethnicity broken out by sex/gender in domestic NIH-defined Phase III clinical trials. For females, a decrease in the proportion of Not Hispanic or Latino individuals is observed from FY 2011 to FY 2012 (–1.8%) while there is an increase in Hispanic or Latino (+1.0%) and Unknown/Not Reported (+0.9%) categories. The same pattern is observed for the percent enrollment of males for Not Hispanic or Latino (–4.4%), Hispanic or Latino (+1.3%), and Unknown/Not Reported ethnicity (+3.2%). For individuals of unknown sex/gender, there is a slight increase in the percent enrollment of Not Hispanic or Latino individuals (+0.2%) and Hispanic or Latino individuals (+0.1%) as well as a small decrease in those with Unknown/Not Reported ethnicity (–0.3%).

Summary

In summary, the overall trends demonstrate relatively stable inclusion of women and minorities in clinical research and NIH-defined Phase III clinical trials over time, particularly with respect to the proportion of minority enrollment. Some variability in the distribution of males and females has been observed. Trend data will vary because the data for each year represent the net total of data resulting from: (1) studies continuing from the prior year; (2) the addition of new studies reported; and (3) the subtraction of studies that are no longer reported. When a large-scale trial starts or ends, this can be illustrated by a shift in distributions of sex/gender and/or race and ethnicity. In addition, as noted in the report, an increase in racial and ethnic unknowns in the clinical research category was observed in FY 2012 relative to FY 2011, likely due to a large study in the intramural program that used an existing dataset in which sex/gender information was available to the investigator but racial and ethnic composition was not.

References

Baylis, F. (2010) Pregnant women deserve better. *Nature, 465*, 689-690.

Blehar, M. C., Spong, C., Grady, C., Goldkind, S. F., Sahin, L., & Clayton, J. A. (2013). Enrolling pregnant women: Issues in clinical research. *Women's Health Issues, 23*(1), e39–e45.

Foulkes, M. A., Grady, C., Spong, C., Bates, A., & Clayton, J. A. (2011). Clinical research enrolling pregnant women: A workshop summary. *Journal of Women's Health, 20*(10), 1420–1432.

Institute of Medicine (US) Forum on Neuroscience and Nervous System Disorders. (2011). *Sex differences and implications for translational neuroscience research: Workshop summary.* Washington, DC: National Academies Press (US).

NIH Director's Panel on Clinical Research. (1997). *Report to the Advisory Committee to the NIH Director.* Bethesda, MD: NIH Director's Panel on Clinical Research.

NIH. (2002a). *Outreach notebook for the inclusion, recruitment and retention of women and minority subjects in clinical research: Principal investigators' notebook* (NIH Publication No. 03-7036). Bethesda, MD: NIH.

NIH. (2002b). *Outreach notebook: Frequently asked questions concerning the NIH guidelines on the inclusion of women and minorities in clinical research.* Bethesda, MD: NIH.

NIH Revitalization Act of 1993 § 42 U.S.C. § 287d (2006).

VI. NIH Budget for Women's Health Research

NIH Budgetary Expenditures for Research on Women's Health, FY 2011 and FY 2012

The amount of funding that NIH invested in research during FY 2011 and FY 2012 is presented in this budget summary and focuses on diseases or conditions of relevance to women. The data in the tables in this chapter were obtained from budget officials at the individual NIH ICs, compiled by the NIH Office of Budget, and submitted to ORWH for inclusion in this report.

"Women's health conditions," as defined in section 141 of the NIH Revitalization Act of 1993 (42 U.S.C. § 287d), include all diseases, disorders, and conditions—

(1) That are unique to, more serious, or more prevalent in women;

(2) For which the factors of medical risk or types of medical intervention are different for women, or for which it is unknown whether such factors or types are different for women; or

(3) With respect to which there has been insufficient clinical research involving women as subjects or insufficient clinical data on women.

Research on women's health conditions includes research on preventing such conditions and applies to women of all ages and racial and ethnic groups.

ORWH has collaborated with the HHS Coordinating Committee on Women's Health (CCWH), to coordinate and standardize the procedures for reporting budgetary expenditures on women's health throughout HHS. Multiple groups are involved in this effort, which is coordinated by the Office on Women's Health in the Office of the Assistant Secretary for Health; they include the HHS Office of the Assistant Secretary for Financial Resources and other women's health offices and programs across HHS agencies.

Data collection for budgetary reporting on women's health research relies on the use of spending categories for diseases or disorders relevant to women. However, over the years, changes have been made to the data collection process to include (1) new disease categories; (2) new methods to standardize the proportion of the budget accounted for by women's health research when enrollment data are not available; and (3) the inclusion of men as a comparison for those women's health categories in which both men and women may be affected. For this latter point, the data collection process has evolved to account for studies in which men and women are both included and reported. For example, in some of the reports prior to FY 2003 and FY 2004, the budgetary reporting on women's health expenditures focused on single-gender studies; studies to evaluate sex/gender differences; and studies of diseases, disorders, and conditions that are unique to women. Previous reporting also used prevalence data as part of the reporting criteria and included research on diseases, disorders, and conditions that are not unique to one sex but for which there is documented evidence of greater prevalence in one sex by a ratio of at least two to one, or for which a specific gender-related consideration exists.

For the purpose of this report, budgetary expenditures are categorized as either inseparably combined or as supporting research on women's health only or men's health only. As a step toward establishing uniform procedures for determining the appropriate categorical allocations, and based upon discussions of the CCWH and the NIH Coordinating Committee on Research on Women's Health, general guidelines for budget calculations are provided below:

(1) For activities that focus primarily on women, such as the Nurses' Health Study, the Mammography Quality Standards Act, or the Women's Health Initiative, the entire funding for these projects should be attributed to women.

(2) For research, studies, services, or projects that include both men and women, recommended methods to calculate the

proportion of funds spent on women's health are as follows:

(a) If target or accrual enrollment data are available, multiply the expenditure by the proportion of female subjects included in the program. For example, if 50 percent of the subjects enrolled in a trial, study, service/treatment program are women, then 50 percent of the funds spent for that program should be counted as for women's health. On the other hand, for diseases, disorders, or conditions without enrollment data, expenditures can be calculated based on the relative prevalence of that condition in women.

(b) Where both men and women are included, as may be the case for many basic science research projects, multiply the expenditure by 50 percent.

Although each IC applied the criteria according to its discretion and judgment, ORWH, along with its advisory and coordinating committees, continues to monitor potential inconsistencies in the evolving methodology for collecting budget data, and will provide input to the HHS CCWH's efforts to develop best methods for future budget data collection.

Table 1 lists the overall NIH research expenditures in FY 2011 and FY 2012 for specific diseases, disorders, and conditions by women only and men only and for both women and men. The health categories and subcategories in this table were developed to accommodate all agencies in HHS. Certain subcategories are not applicable to the NIH mission; for those subcategories, the table will show a "0" across all columns. In some cases, however, a "0" may be shown even when the subcategory is relevant. This occurs because the table is additive. Funding included in each budget allocation may be listed only once, even though conceptually it applies to more than one category. For example, expenditures on infertility in cancer survivors could apply to infertility or cancer. In this example, the IC would determine the most scientifically appropriate category. Furthermore, amounts listed for each specific topic area are likely to underestimate the total expenditures for a given topic area because no overlap in reporting is allowed by the prescribed method of data collection for this report.

Table 2 shows the dollar amounts and percentages of the NIH research budget in FY 2011 and FY 2012 for women only and for men only. Overall, the proportion of the research budget supporting women only was 12.8 percent and 12.5 percent for FY 2011 and FY 2012, respectively. Of interest is that the proportion of the research budget supporting men only was 5.7 percent and 5.6 percent, for FY 2011 and FY 2012, respectively, which likely reflects the implicit bias in the data categories on diseases, conditions, or disorders relevant to women or occurring only in women.

Table 1. HHS–NIH Research Budget for Women's and Men's Health by Disease, Condition, and Special Initiatives, FY 2011 and FY 2012 (Dollars in Thousands)[1,2]

I. Cancer

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Breast cancer (including mammography and other services)	680,858	39	4,041	684,938	659,761	32	6,549	666,342
Reproductive cancers: cervical	77,610	682	11,204	89,496	72,181	627	8,285	81,093
Reproductive cancers: ovarian	113,784	0	5	113,789	113,441	0	37	113,478
Reproductive cancers: vaginal, uterine, and other	24,531	0	0	24,531	23,121	0	0	23,121
Lung cancer	141,405	68	164,452	305,925	145,772	62	192,220	338,054
Colorectal cancer	133,468	100	166,866	300,434	117,613	728	169,493	287,834
Other neoplasms	30,384	74,833	3,862,910	3,968,127	28,475	70,319	3,992,691	4,091,485
Subtotal	**1,202,040**	**75,722**	**4,209,478**	**5,487,240**	**1,160,364**	**71,768**	**4,369,275**	**5,601,407**

II. Cardiovascular/Pulmonary

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Blood diseases	25,360	36,569	386,819	448,748	40,842	53,389	406,719	500,950
Heart disease	128,453	127,646	784,991	1,041,090	126,265	132,885	817,035	1,076,185
Stroke	28,435	43,979	206,715	279,129	22,913	42,442	209,365	274,720
Other cardiovascular diseases/disorders	117,847	73,125	943,634	1,134,606	132,594	82,409	868,152	1,083,155
Pulmonary diseases	89,835	95,535	369,529	554,899	67,500	70,787	388,381	526,668
Asthma	45,478	35,984	133,859	215,321	52,496	30,552	135,328	218,376
Other	5,286	0	543,709	548,995	1,332	0	304,423	305,755
Subtotal	**440,694**	**412,838**	**3,369,256**	**4,222,788**	**443,942**	**412,464**	**3,129,403**	**3,985,809**

[1] These data are exclusive of overlap and will not agree with funding reported for total NIH spending on disease areas.
[2] Figures shown in this table do not include NIH Buildings and Facilities program spending.

III. Reproductive and Maternal/Child/Adolescent Health

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Contraception	36,210	9,201	33,699	79,110	37,854	5,749	49,277	92,880
Infertility	7,699	1,594	12,077	21,370	2,873	1,452	11,336	15,661
Female reproductive physiology	97,645	0	7	97,652	82,011	0	2,076	84,087
Hysterectomy	158	0	0	158	0	0	0	0
Endometriosis/ leiomyomas (fibroids)	2,157	0	0	2,157	8,391	0	1,076	9,467
Pregnancy/pregnancy prevention/maternal health	207,623	501	32,829	240,953	216,111	463	7,351	223,925
Diseases related to DES exposure	239	0	0	239	0	0	0	0
Female genital cutting	0	0	0	0	0	0	0	0
Pelvic floor disorders	2,394	0	0	2,394	1,985	0	0	1,985
Other	1,573	10,861	566,913	579,347	3,815	10,133	590,501	604,449
Subtotal	**355,698**	**22,157**	**645,525**	**1,023,380**	**353,040**	**17,797**	**661,617**	**1,032,454**

IV. Aging

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Menopause	31,403	0	0	31,403	28,329	0	0	28,329
Menopausal hormone/ nonhormone therapy	14,620	0	0	14,620	10,518	0	0	10,518
Alzheimer's disease	82,757	68,981	240,568	392,306	92,686	79,330	263,411	435,427
Malnutrition in the elderly	0	0	14	14	0	0	0	0
Osteoarthritis	28,775	2,187	32,150	63,112	30,518	3,430	32,352	66,300
Osteoporosis (including fractures)	109,791	8,011	14,119	131,921	100,048	4,814	18,775	123,637
Women's Health Initiative	0	0	0	0	35	0	0	35
Demography of aging	27,458	22,957	6,739	57,154	26,502	21,702	6,587	54,791
Aging economics	16,505	13,140	18,568	48,213	14,051	12,105	18,191	44,347
Other	24,589	29,504	337,363	391,456	18,243	25,030	359,022	402,295
Subtotal	**335,898**	**144,780**	**649,521**	**1,130,199**	**320,930**	**146,411**	**698,338**	**1,165,679**

V. Metabolism, Endocrinology, and Gastrointestinal

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Diabetes	75,476	83,087	132,030	290,593	81,611	85,625	132,660	299,896
Obesity	143,377	98,887	141,955	384,219	141,573	95,688	133,551	370,812
Hepatobiliary diseases	696	877	255,305	256,878	1,512	1,891	242,303	245,706
Thyroid diseases/ conditions	12,149	3,104	821	16,074	12,057	3,067	0	15,124
Fecal incontinence	1,857	237	0	2,094	1,472	164	0	1,636
Irritable bowel syndrome	4,961	806	0	5,767	5,467	607	2,256	8,330
Other	7,338	810	248,280	256,428	1,295	673	123,044	125,012
Subtotal	**245,854**	**187,808**	**778,391**	**1,212,053**	**244,987**	**187,715**	**633,814**	**1,066,516**

VI. Substance Abuse

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Etiology (unspecified)	6,685	7,609	100,487	114,781	6,795	7,989	85,233	100,017
Epidemiology (unspecified)	8,121	5,536	11,034	24,691	29,672	29,836	62,275	121,783
Prevention (unspecified)	3,698	3,111	16,679	23,488	24,716	24,612	44,054	93,382
Treatment (unspecified)	5,139	5,619	22,345	33,103	74,748	77,699	137,550	289,997
Alcohol	17,819	21,501	126,384	165,704	19,602	21,560	119,694	160,856
Illegal drugs	278,514	285,907	488,035	1,052,456	130,090	133,473	229,381	492,944
Prescription drugs	0	0	0	0	8,660	8,878	15,673	33,211
Tobacco products	447	514	26,564	27,525	29,358	30,443	74,933	134,734
Other substances	315	473	6,387	7,175	551	771	6,888	8,210
Co-occurring substance abuse and mental disorders	638	822	1,885	3,345	703	760	2,441	3,904
Subtotal	**321,376**	**331,092**	**799,800**	**1,452,268**	**324,895**	**336,021**	**778,122**	**1,439,038**

VII. Behavioral Studies/Programs

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Violence (including domestic, abused women, spouse abuse, elder abuse, violence against women, trafficking, bullying)	6,458	1,885	24,497	32,840	6,070	2,172	20,925	29,167
Tobacco use cessation	735	132	4,644	5,511	731	172	4,274	5,177
Physical activity/ exercise/nutrition (promoting healthy behavior)	10,073	5,215	206,694	221,982	20,294	8,889	225,374	254,557
Other behavior change/risk modification	11,888	4,674	467,027	483,589	16,207	4,056	471,633	491,896
Caregiving	2,297	951	9,194	12,442	4,394	1,592	9,553	15,539
Other	22,030	44,944	329,521	396,495	19,972	17,749	394,224	431,945
Subtotal	**53,481**	**57,801**	**1,041,577**	**1,152,859**	**67,668**	**34,630**	**1,125,983**	**1,228,281**

VIII. Mental Health

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Etiology (unspecified)	124	3	21,907	22,034	121	0	17,076	17,197
Epidemiology (unspecified)	0	0	51	51	5	6	154	165
Prevention (unspecified)	0	0	2,396	2,396	0	0	1,504	1,504
Treatment (unspecified)	44	0	1,144	1,188	33	65	1,768	1,866
Depression/mood disorders	23,275	3,036	150,906	177,217	20,983	3,152	158,248	182,383
Suicide	1,292	599	17,046	18,937	1,179	624	15,019	16,822
Schizophrenia	2,804	70	141,770	144,644	656	428	130,585	131,669
Anxiety disorders	304	403	38,915	39,622	608	393	37,639	38,640
Eating disorders	5,215	33	4,105	9,353	6,091	0	6,010	12,101
Psychosocial stress	12,609	1,772	21,639	36,020	9,864	2,597	20,235	32,696
Post-traumatic stress disorder (PTSD)	4,593	1,562	15,442	21,597	4,881	2,227	19,686	26,794
Other mental disorders (excluding Alzheimer's)	31,901	6,798	778,260	816,959	32,665	8,165	793,079	833,909
Autism	1,014	31,800	72,466	105,280	3,930	35,052	71,541	110,523
Subtotal	**83,175**	**46,076**	**1,266,047**	**1,395,298**	**81,016**	**52,709**	**1,272,544**	**1,406,269**

IX. Infectious Diseases

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
AIDS/HIV	187,104	72,667	2,273,582	2,533,353	185,339	64,957	2,295,941	2,546,237
Tuberculosis	8,628	11,717	136,475	156,820	8,489	11,522	137,809	157,820
Sexually transmitted diseases (STDs)	35,374	2,499	178,253	216,126	37,256	4,543	185,426	227,225
Topical microbicides	97,138	1,461	3,047	101,646	110,080	1,419	2,257	113,756
Toxic shock syndrome	3,346	0	0	3,346	3,050	0	0	3,050
Tropical diseases (including malaria)	25,072	3,658	435,294	464,024	25,216	4,335	426,811	456,362
Other	2,967	1,076	611,840	615,883	2,278	17,923	526,426	546,627
Subtotal	**359,629**	**93,078**	**3,638,491**	**4,091,198**	**371,708**	**104,699**	**3,574,670**	**4,051,077**

X. Immune Disorders

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Rheumatoid arthritis	36,051	185	147,797	184,033	36,208	0	141,396	177,604
Lupus erythematosus	50,215	2,953	35,290	88,458	49,570	2,570	35,207	87,347
Multiple sclerosis	10,279	11,924	69,314	91,517	7,948	12,069	74,964	94,981
Myasthenia gravis	0	0	5	5	0	0	0	0
Scleroderma	9,986	0	11,425	21,411	11,775	0	8,447	20,222
Sjögren's syndrome	19,750	298	694	20,742	20,074	125	690	20,889
Takayasu disease	0	0	0	0	0	0	0	0
Other	7,335	4,165	279,912	291,412	7,774	3,907	120,810	132,491
Subtotal	**133,616**	**19,525**	**544,437**	**697,578**	**133,349**	**18,671**	**381,514**	**533,534**

XI. Neurologic, Muscular, and Bone

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Trauma research								
Trauma research: brain	11,035	20,442	148,468	179,945	8,667	20,973	170,127	199,767
Trauma research: other neurologic trauma	0	0	18,562	18,562	0	0	12,398	12,398
Trauma research: bone fracture (non-osteoporotic) and muscle injury	18	31	17,435	17,484	367	297	15,238	15,902
Muscular dystrophy	2,782	36,260	26,838	65,880	1,440	36,880	24,348	62,668
Chronic pain conditions	9,138	14,184	107,300	130,622	8,651	14,926	109,675	133,252
Temporomandibular disorders	16,210	0	526	16,736	17,964	0	2,153	20,117
Vulvodynia	1,468	0	0	1,468	2,924	0	227	3,151
Fibromyalgia and eosinophilic myalgia	4,750	0	277	5,027	4,811	0	350	5,161
Migraine	21	21	205	247	37	37	1,001	1,075
Sleep disorders	7,457	8,404	42,829	58,690	7,943	9,048	45,481	62,472
Paget's disease	0	0	735	735	0	0	1,226	1,226
Parkinson's disease	9,714	17,112	106,104	132,930	7,578	17,427	112,247	137,252
Seizure disorders	11,075	19,963	106,654	137,692	8,120	19,749	106,072	133,941
Other	84,561	136,360	1,112,874	1,333,795	62,832	134,313	1,122,735	1,319,880
Subtotal	**158,229**	**252,777**	**1,688,807**	**2,099,813**	**131,334**	**253,650**	**1,723,278**	**2,108,262**

XII. Kidney and Urologic

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Urinary tract infections (cystitis, pyelonephritis)	9,733	546	20,992	31,271	10,540	834	16,001	27,375
ESRD/transplantation	2,745	3,014	80,374	86,133	2,301	2,512	80,185	84,998
Urinary incontinence	9,658	89	0	9,747	8,824	240	260	9,324
Painful bladder, interstitial cystitis	9,224	1,042	0	10,266	9,577	1,064	0	10,641
Other	1,149	8,610	404,623	414,382	942	6,911	439,768	447,621
Subtotal	**32,509**	**13,301**	**505,989**	**551,799**	**32,184**	**11,561**	**536,214**	**579,959**

XIII. Ophthalmic, Otolaryngologic, and Oral Health

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Eye diseases and disorders	30,295	11,923	740,542	782,760	29,327	14,141	742,806	786,274
Ear diseases and disorders	17,617	1,545	207,954	227,116	16,936	1,294	203,127	221,357
Dental and oral health	1,127	1,576	358,935	361,638	514	1,333	359,639	361,486
Other	0	0	719	719	0	0	678	678
Subtotal	**49,039**	**15,044**	**1,308,150**	**1,372,233**	**46,777**	**16,768**	**1,306,250**	**1,369,795**

XIV. Health Effects of the Environment

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Environmental estrogens	8,110	2,496	5,417	16,023	8,560	2,678	9,537	20,775
Health effects of toxic exposure (excluding cancer)	0	5	127,099	127,104	446	0	139,941	140,387
Toxicological research and testing program	0	0	99,421	99,421	0	0	98,172	98,172
Chemical/biological warfare agents	0	0	802	802	0	0	530	530
Other	6	31	1,156	1,193	40	0	3,776	3,816
Subtotal	**8,116**	**2,532**	**233,895**	**244,543**	**9,046**	**2,678**	**251,956**	**263,680**

XV. Cross-Cutting Categories and Special Initiatives

Disease, condition, or initiative	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Treatment, prevention, and services	2,889	2,320	418,736	423,945	2,561	3,257	468,654	474,472
Access to health care and financing	664	697	14,829	16,190	1,008	782	27,908	29,698
Education and training for health care providers	525	143	51,393	52,061	1,253	282	67,371	68,906
Health literacy and bilingual information	1,225	820	24,520	26,565	1,516	869	25,806	28,191
Cultural influences	3,804	1,433	34,338	39,575	2,229	1,944	27,631	31,804
Disability research and services	1,671	2,147	78,765	82,583	1,957	1,851	85,229	89,037
Homelessness	125	79	120	324	586	405	369	1,360
Chronic fatigue syndrome	596	327	2,928	3,851	334	75	2,379	2,788
Breastfeeding	1,387	0	682	2,069	208	0	343	551
Organ donation	103	103	1,197	1,403	0	0	1,448	1,448
Genetic services/ counseling	0	0	7,367	7,367	902	902	12,094	13,898
Unintentional injury	3,333	3,502	19,033	25,868	2,730	2,098	11,757	16,585
Alternative and complementary therapies	37,271	22,596	133,713	193,580	36,940	22,475	151,152	210,567
Health statistics and data collection	1,661	1,755	21,496	24,912	1,664	630	31,840	34,134
Programs/Offices on/ of Women's Health	14,272	17	0	14,289	38,527	0	1,926,897	1,965,424
Global health	24,465	15,122	1,580,171	1,619,758	18,549	4,255	1,719,344	1,742,148
Drug metabolism (sex differences, pregnancy, etc.)	192	192	2,503	2,887	891	891	5,157	6,939
Other cross-cutting[3]	17,376	661	1,729,654	1,747,691				
Subtotal	**111,559**	**51,914**	**4,121,445**	**4,284,918**	**111,855**	**40,716**	**4,565,379**	**4,717,950**

	FY 2011 Women	FY 2011 Men	FY 2011 Both	FY 2011 Total	FY 2012 Women	FY 2012 Men	FY 2012 Both	FY 2012 Total
Total	**3,890,913**	**1,726,445**	**24,800,809**	**30,418,167**	**3,833,095**	**1,708,258**	**25,008,357**	**30,549,710**

[3] Category is no longer valid. Programs/Offices on/of Women's Health acts as a replacement.

Table 2. FY 2011 and FY 2012[1] Summary: NIH Research Budget by Sex

Category	FY 2011, $	FY 2012, $	FY 2011, %	FY 2012, %
Women	3,890,912	3,833,095	12.8	12.5
Men	1,726,445	1,708,258	5.7	5.6
Both	24,800,809	25,008,357	81.5	81.9
Total	30,418,167	30,549,710	100.0	100.0

[1]Dollars in thousands.

VII. Committee Members and ORWH Staff, FY 2011–2012

Advisory Committee on Research on Women's Health, FY 2011

Vivian W. Pinn, M.D., *Chair*
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health

Joyce Rudick, *Executive Secretary*
Director, Programs and Management
Office of Research on Women's Health
National Institutes of Health

Richard Besdine, M.D. *(2015)*
Professor of Medicine and Community Health
Center for Gerontology and Healthcare Research
Brown University

John O. DeLancey, M.D. *(2015)*
Norman F. Miller Professor
Obstetrics and Gynecology
University of Michigan

Francisco Garcia, M.D., M.P.H. *(2014)*
Distinguished Outreach Professor of Obstetrics and Gynecology and Public Health
Director, Center of Excellence in Women's Health
The University of Arizona

Margery L. S. Gass, M.D., NCMP *(2013)*
Executive Director, The North American Menopause Society
Consultant, Cleveland Clinic Center for Specialized Women's Health

Linda C. Giudice, M.D., Ph.D. *(2012)*
The Robert B. Jaffe, M.D., Endowed Professor and Chair
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Ronda S. Henry-Tillman, M.D. *(2014)*
Practice Director, Ladies' Oncology Clinic
Director, Cancer Control
Winthrop P. Rockefeller Cancer Institute
University of Arkansas for Medical Sciences

Paula A. Johnson, M.D., M.P.H. *(2013)*
Executive Director, Connors Center for Women's Health and Gender Biology
Chief, Division of Women's Health
Brigham and Women's Hospital

Karen Kim, M.D., M.S. *(2014)*
Associate Professor of Medicine
The University of Chicago

Susan Kornstein, M.D. *(2015)*
Director and Professor of Psychiatry and Obstetrics-Gynecology
Institute for Women's Health
Virginia Commonwealth University

Valerie Latona *(2015)*
Westfield, NJ

Jon Levine, Ph.D. *(2015)*
Director
Wisconsin National Primate Research Center

Nancy H. Nielsen, M.D., Ph.D. *(2012)*
Senior Associate Dean
School of Medicine and Biomedical Sciences
University at Buffalo, State University of New York

Claire Pomeroy, M.D., M.B.A. *(2014)*
Vice Chancellor, Human Health Sciences
Dean, School of Medicine
Professor of Internal Medicine and Microbiology/Immunology
University of California, Davis

Jeanne Craig Sinkford, D.D.S., Ph.D. *(2013)*
Professor and Dean Emeritus
Howard University College of Dentistry
Associate Executive Director and Director, Center for Equity and Diversity
American Dental Education Association

Farida Sohrabji, Ph.D. *(2013)*
Associate Professor and Associate Department Head
Department of Neuroscience and Experimental Therapeutics
Interdisciplinary Program in Neuroscience
College of Medicine
Texas A&M System Health Science Center

Gary E. Striker, M.D. *(2013)*
Research Professor
Division of Experimental Diabetes and Aging, Department of Geriatrics and Palliative Medicine
Division of Nephrology, Department of Medicine
Mount Sinai School of Medicine

Paul F. Terranova, Ph.D. *(2014)*
Vice Chancellor for Research
Senior Associate Dean for Research and Graduate Education, University of Kansas School of Medicine
The University of Kansas Medical Center

Debra Toney, Ph.D., R.N., FAAN *(2012)*
President, National Black Nurses Association
President, TLC Health Care Service

Advisory Committee on Research on Women's Health, FY 2012

Janine A. Clayton, M.D., *Chair*
Associate Director for Research on Women's Health
Director, Office of Research on Women's Health
National Institutes of Health

Joyce Rudick, *Executive Secretary*
Director, Programs and Management
Office of Research on Women's Health
National Institutes of Health

Richard Besdine, M.D. *(2015)*
Professor of Medicine and Community Health
Center for Gerontology and Healthcare Research
Brown University

John O. DeLancey, M.D. *(2015)*
Norman F. Miller Professor
Obstetrics and Gynecology
University of Michigan

Francisco Garcia, M.D., M.P.H. *(2014)*
Distinguished Outreach Professor of Obstetrics and Gynecology and Public Health
Director, Center of Excellence in Women's Health
The University of Arizona

Margery L. S. Gass, M.D., NCMP *(2013)*
Executive Director, The North American Menopause Society
Consultant, Cleveland Clinic Center for Specialized Women's Health

Ronda S. Henry-Tillman, M.D. *(2014)*
Practice Director, Ladies' Oncology Clinic
Director, Cancer Control
Winthrop P. Rockefeller Cancer Institute
University of Arkansas for Medical Services

Paula A. Johnson, M.D., M.P.H. *(2013)*
Executive Director, Connors Center for Women's Health and Gender Biology
Chief, Division of Women's Health
Brigham and Women's Hospital

Karen Kim, M.D., M.S. *(2014)*
Associate Professor of Medicine
The University of Chicago

Susan Kornstein, M.D. *(2015)*
Director and Professor of Psychiatry and Obstetrics-Gynecology
Institute for Women's Health
Virginia Commonwealth University

Valerie Latona *(2015)*
Westfield, NJ

Jon Levine, Ph.D. *(2015)*
Director
Wisconsin National Primate Research Center

Afaf I. Meleis, Ph.D., Dr.P.S. (hon.), FAAN, FRCN *(2016)*
Margaret Bond Simon Dean of Nursing
Professor of Nursing and Sociology
University of Pennsylvania School of Nursing

Heidi D. Nelson, M.D., M.P.H. *(2016)*
Research Professor, Departments of Medical Informatics & Clinical Epidemiology, and Medicine
Medical Director, Providence Women and Children's Program and Research Center
Co-Director, VA Women's Health Fellowship
Oregon Health & Science University

Claire Pomeroy, M.D., M.B.A. *(2014)*
Vice Chancellor, Human Health Sciences
Dean, School of Medicine
Professor of Internal Medicine and Microbiology/Immunology
University of California, Davis

Jeanne Craig Sinkford, D.D.S., Ph.D. *(2013)*
Professor and Dean Emeritus
Howard University College of Dentistry
Associate Executive Director and Director, Center for Equity and Diversity
American Dental Education Association

Farida Sohrabji, Ph.D. *(2013)*
Associate Professor and Associate Department Head
Department of Neuroscience and Experimental Therapeutics
Interdisciplinary Program in Neuroscience
College of Medicine
Texas A&M System Health Science Center

Gary E. Striker, M.D. *(2013)*
Research Professor
Division of Experimental Diabetes and Aging, Department of Geriatrics and Palliative Medicine
Division of Nephrology, Department of Medicine
Mount Sinai School of Medicine

Paul F. Terranova, Ph.D. *(2014)*
Vice Chancellor for Research
Senior Associate Dean for Research and Graduate Education, University of Kansas School of Medicine
The University of Kansas Medical Center

Gerson Weiss, M.D. *(2016)*
Professor and Chair
Department of Obstetrics, Gynecology and Women's Health
University of Medicine & Dentistry of New Jersey–New Jersey Medical School

NIH Coordinating Committee on Research on Women's Health, FY 2011

Representatives

Lee Alekel, Ph.D.
Program Officer
National Center for Complementary and Alternative Medicine

Margaret V. Ames, Ph.D.
Acting Director
Office of Science Planning and Assessment
National Cancer Institute

Jane C. Atkinson, D.D.S.
Director, Center for Clinical Research
National Institute of Dental and Craniofacial Research

Regan K. Bailey, Ph.D., R.D.
Director, Supplement Intakes Project
Office of Dietary Supplements
Office of Disease Prevention
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Gina M. Brown, M.D.
Director, Women and Girls Section
Office of AIDS Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

John T. Burklow
Director, Office of Communications and Public Liaison
Office of the Director

Janine A. Clayton, M.D.
Acting Director
Office of Research on Women's Health
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Deborah F. Cohen
Director, Postbac and Summer Program Services
Office of Intramural Training and Education
Office of Intramural Research
Office of the Director

Deborah Dozier-Hall, M.S.W.
Assistant Chief, Social Work Department
NIH Clinical Center

Gale A. Dutcher, M.L.S., M.S.
Deputy Associate Director
Specialized Information Services
National Library of Medicine

Paula Flicker, Ph.D.
Program Director
National Institute of General Medical Sciences

Mary M. Gant, M.S.
Interagency Liaison
National Institute of Environmental Health Sciences

Valery Gordon, Ph.D., M.P.H.
Senior Extramural Policy Officer
Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

Eleanor F. Hoff, Ph.D.
Health Science Policy Analyst
Office of Scientific Program and Policy Analysis
National Institute of Diabetes and Digestive and Kidney Diseases

Tanya Hoodbhoy, Ph.D.
Program Director
Office of Strategic Coordination
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Bonnie Kalberer, M.P.H.
Contractor
Office of Science Education
Office of Science Policy
Office of the Director

Tamara E. Lewis-Johnson, M.P.H., M.B.A.
Women's Health Program Manager
Office of Special Populations and Research Training
National Institute of Allergy and Infectious Diseases

Barbara R. Marzetta, M.S.
Deputy Director
Office of Science and Technology
National Heart, Lung, and Blood Institute

Lori Mulligan
Chief, Office of Science Policy and Public Liaison
National Center for Research Resources

Kate Nagy, M.A.
Senior Public Health Analyst
National Institute on Aging

Lisa A. Neuhold, Ph.D.
Retinal Diseases Program Director
National Eye Institute

Kathleen M. O'Leary, M.S.W.
Deputy Chief, Women's Programs
National Institute of Mental Health

Karen L. Parker, Ph.D., M.S.W.
Senior Health Science Analyst and Women's Health Officer
Office of Science Planning and Assessment
National Cancer Institute

Linda Porter, Ph.D.
Program Director, Systems and Cognitive Neuroscience Cluster
Division of Extramural Research and Training
National Institute of Neurological Disorders and Stroke

Svetlana Radaeva, M.D., Ph.D.
Program Director, Division of Metabolism and Health Effects
National Institute on Alcohol Abuse and Alcoholism

Mona Rowe, M.C.P.
Associate Director, Science Policy Analysis and Communication
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Lana O. Shekim, Ph.D.
Director, Voice and Speech Program
National Institute on Deafness and Other Communication Disorders

Michael L. Spittel, Ph.D.
Social Scientist
Office of Behavioral and Social Sciences Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Rachel M. Sturke
Evaluation Officer
Fogarty International Center

Derrick C. Tabor, Ph.D.
Program Official
Centers of Excellence
National Institute on Minority Health and Health Disparities

Anne Tatum
Senior Legislative Analyst
Office of Communications and Public Liaison
Office of the Director

Xenia Tigno, Ph.D., M.S.
Program Director
National Institute of Nursing Research

Bernadette Tyree, Ph.D.
Program Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Cora Lee Wetherington, Ph.D.
Women and Sex/Gender Differences Research Coordinator
National Institute on Drug Abuse

Denise G. Wiesch, Ph.D.
Scientific Review Officer
Epidemiology of Cancer Study Section
Center for Scientific Review

Rosann N. Wise
Program Analyst
National Human Genome Research Institute

Alternates

Diane Adger-Johnson
Minority Health Program Manager
National Institute of Allergy and Infectious Diseases

Marin P. Allen, Ph.D.
Deputy Director
Office of Communications and Public Liaison
Office of the Director

Nalani P. Anand
Fogarty International Center

James M. Anderson, M.D., Ph.D.
Director
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Sanja Basaric
Program Analyst
National Human Genome Research Institute

April L. Bennett
Contractor
National Institute of Environmental Health Sciences

Anissa Brown, Ph.D.
Health Scientist Administrator
Office of AIDS Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Victoria A. Cargill, M.D., M.S.C.E.
Director of Minority Research and Clinical Studies
Office of AIDS Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Paul Cotton, Ph.D., R.D.
Program Director, Division of Extramural Programs
National Institute of Nursing Research

Anthony Demsey, Ph.D.
Director
Office of Extramural Policy
National Institute of Biomedical Imaging and Bioengineering

Dena Fischer, D.D.S.
Program Director
Clinical Research and Epidemiology
National Institute of Dental and Craniofacial Research

Ruth S. Grossman, D.D.S.
Scientific Review Officer
National Institute of Biomedical Imaging and Bioengineering

Mary C. Hanlon, Ph.D.
Health Science Policy Analyst
National Institute of Diabetes and Digestive and Kidney Diseases

Walter Jones
Deputy Director for Management and Diversity Operations
NIH Clinical Center

Robin I. Kawazoe
Deputy Director
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Karin L. Kolsky
Writer and Editor
National Institute on Aging

Donna Krasnewich, M.D., Ph.D.
Program Director
National Institute of General Medical Sciences

Natalie Kurinij, Ph.D.
Health Scientist Administrator
National Eye Institute

Anita M. Linde, M.P.P.
Director
Office of Science Policy Planning
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Lonnie L. Lisle
Office of Health Communication and Public Liaison
National Institute on Deafness and Other Communication Disorders

Sheila A. McClure, Ph.D.
Health Scientist Administrator
National Center for Research Resources

Genevieve A. Medley
Health Science Analyst
National Cancer Institute

Sharon L. Milgram, Ph.D.
Director
Office of Intramural Training and Education
Office of Intramural Research
Office of the Director

Walter Mitton
Community Relations Specialist
Office of Community Liaison
Public Information Office
Office of the Director

Wendy J. Nilsen, Ph.D.
Health Scientist Administrator
Office of Behavioral and Social Sciences Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Samia D. Noursi, Ph.D.
Deputy Coordinator, Women and Sex/Gender Differences Research
National Institute on Drug Abuse

Estella C. Parrott, M.D., M.P.H.
Program Director, Reproductive Sciences Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Rose E. Pruitt
Federal Women's Program Manager
Office of Equal Opportunity and Diversity Management
Office of the Director

Deidra Roach, M.D.
Health Scientist Administrator
National Institute on Alcohol Abuse and Alcoholism

Catherine A. Roca, M.D.
Contractor
National Institute of Mental Health

Louise Rosenbaum, Ph.D.
Science Policy Analyst
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Jacques Rossouw, M.D.
Women's Health Initiative Branch
National Heart, Lung, and Blood Institute

Joan P. Schwartz, Ph.D.
Special Volunteer
Office of Intramural Research
Office of the Director

Susan Scolnik
Program Analyst
National Heart, Lung, and Blood Institute

Elaine Sierra-Rivera, Ph.D.
Scientific Review Administrator and Deputy Chief
Oncology Sciences Integrated Review Group
Center for Scientific Review

Riju Srimal, Ph.D.
AAAS Fellow
Office of Science Policy and Planning
National Institute of Neurological Disorders and Stroke

Nathaniel Stinson, Jr., M.D., Ph.D.
Acting Director, Division of Extramural Activities
National Institute on Minority Health and Health Disparities

Stacy Wallick, M.P.H.
National Institute of Biomedical Imaging and Bioengineering

NIH Coordinating Committee on Research on Women's Health, FY 2012

Representatives

Lee Alekel, Ph.D.
Program Officer
National Center for Complementary and Alternative Medicine

Jennifer Alvidrez, Ph.D.
Health Scientist Administrator
National Institute on Minority Health and Health Disparities

Jane C. Atkinson, D.D.S.
Director, Center for Clinical Research
National Institute of Dental and Craniofacial Research

Gina M. Brown, M.D.
Director, Women and Girls Section
Office of AIDS Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

John T. Burklow
Director, Office of Communications and Public Liaison
Office of the Director

Janine A. Clayton, M.D.
Director
Office of Research on Women's Health
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Deborah F. Cohen
Director, Postbac and Summer Program Services
Office of Intramural Training and Education
Office of Intramural Research
Office of the Director

Caroline H. Dilworth, Ph.D.
Health Scientist Administrator
Division of Extramural Research Training
National Institute of Environmental Health Sciences

Gale A. Dutcher, M.L.S., M.S.
Deputy Associate Director
Specialized Information Services
National Library of Medicine

Paula Flicker, Ph.D.
Program Director
National Institute of General Medical Sciences

Ruth S. Grossman, D.D.S.
Scientific Review Officer
National Institute of Biomedical Imaging and Bioengineering

Eleanor F. Hoff, Ph.D.
Health Science Policy Analyst
Office of Scientific Program and Policy Analysis
National Institute of Diabetes and Digestive and Kidney Diseases

Lydia Mann Kline
Science Policy analyst
Fogarty International Center

Jane Lockmuller, M.S.
Chief, Strategic Planning and Evaluation
National Institute of Allergy and Infectious Diseases

Barbara R. Marzetta, M.S.
Deputy Director
Office of Science and Technology
National Heart, Lung, and Blood Institute

Kate Nagy, M.A.
Senior Public Health Analyst
National Institute on Aging

Lisa A. Neuhold, Ph.D.
Program Director for Fundamental Retinal Processes
National Eye Institute

Kathleen M. O'Leary, M.S.W.
Acting Chief, Women's Programs
National Institute of Mental Health

Karen L. Parker, Ph.D., M.S.W.
Acting Chief, Strategic Coordination Branch and Women's Health Officer
National Cancer Institute

Sylvia L. Parsons
Program Analyst
National Center for Advancing Translational Sciences

Svetlana Radaeva, M.D., Ph.D.
Program Director, Division of Metabolism and Health Effects
National Institute on Alcohol Abuse and Alcoholism

Mona Rowe, M.C.P.
Associate Director, Science Policy Analysis and Communication
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Lana O. Shekim, Ph.D.
Director, Voice and Speech Program
National Institute on Deafness and Other Communication Disorders

Barbara Sorkin, Ph.D.
Director, Botanical Research Centers Program
Office of Dietary Supplements
Office of Disease Prevention
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Michael L. Spittel, Ph.D.
Social Scientist
Office of Behavioral and Social Sciences Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Lisa A. Strauss
Program Analyst
Office of Science Education
Office of Science Policy
Office of the Director

Anne Tatum
Senior Legislative Analyst
Office of Communications and Public Liaison
Office of the Director

Xenia Tigno, Ph.D., M.S.
Program Director
National Institute of Nursing Research

Bernadette Tyree, Ph.D.
Program Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Cora Lee Wetherington, Ph.D.
Women and Sex/Gender Differences Research Coordinator
National Institute on Drug Abuse

Vicky Whittemore, Ph.D.
Program Director, Synapses, Channels, and Neural Circuits
National Institute of Neurological Disorders and Stroke

Rosann N. Wise
Program Analyst
National Human Genome Research Institute

Alternates

Diane Adger-Johnson
Minority Health Program Manager
National Institute of Allergy and Infectious Diseases

Marin P. Allen, Ph.D.
Deputy Director
Office of Communications and Public Liaison
Office of the Director

James M. Anderson, M.D., Ph.D.
Director
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Laura Bartlett
Technical Information Specialist
National Library of Medicine

Sanja Basaric
Program Analyst
National Human Genome Research Institute

Paul Cotton, Ph.D., R.D.
Program Director, Division of Extramural Programs
National Institute of Nursing Research

Anthony Demsey, Ph.D.
Director
Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

Jonelle Drugan, Ph.D., M.P.H.
Science Policy Analyst
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Dena Fischer, D.D.S., M.S.D., M.S.
Program Director
Clinical Research and Epidemiology
National Institute of Dental and Craniofacial Research

Mary M. Gant, M.S.
Program Analyst
National Institute of Environmental Health Sciences

Adrienne Goodrich-Doctor, Ph.D.
Strategic Planning and Evaluation Branch
National Institute of Allergy and Infectious Diseases

Mary C. Hanlon, Ph.D.
Health Science Policy Analyst
National Institute of Diabetes and Digestive and Kidney Diseases

Lauren Hill, Ph.D.
Public Health Analyst
National Institute of Mental Health

Walter Jones
Deputy Director for Management and Diversity Operations
NIH Clinical Center

Robin I. Kawazoe
Deputy Director
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Donna Krasnewich, M.D., Ph.D.
Program Director
National Institute of General Medical Sciences

Natalie Kurinij, Ph.D.
Health Scientist Administrator
National Eye Institute

Anita M. Linde, M.P.P.
Director
Office of Science Policy Planning
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Lonnie L. Lisle
Office of Health Communication and Public Liaison
National Institute on Deafness and Other Communication Disorders

Genevieve A. Medley
Health Science Analyst
National Cancer Institute

Sharon L. Milgram, Ph.D.
Director
Office of Intramural Training and Education
Office of Intramural Research
Office of the Director

Wendy J. Nilsen, Ph.D.
Health Scientist Administrator
Office of Behavioral and Social Sciences Research
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director

Samia D. Noursi, Ph.D.
Deputy Coordinator, Women and Sex/Gender Differences Research
National Institute on Drug Abuse

Estella C. Parrott, M.D., M.P.H.
Program Director, Contraception and Reproductive Health Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Deidra Roach, M.D.
Health Scientist Administrator
National Institute on Alcohol Abuse and Alcoholism

Jacques Rossouw, M.D.
Women's Health Initiative Branch
National Heart, Lung, and Blood Institute

Joan P. Schwartz, Ph.D.
Special Volunteer
Office of Intramural Research
Office of the Director

Elaine Sierra-Rivera, Ph.D.
Scientific Review Administrator and Deputy Chief
Oncology Sciences Integrated Review Group
Center for Scientific Review

Nathaniel Stinson, Jr., M.D., Ph.D.
Acting Director, Division of Extramural Activities
National Institute on Minority Health and Health Disparities

Rachel M. Sturke
Evaluation Officer
Fogarty International Center

ORWH Staff, FY 2011

Vivian W. Pinn, M.D.
Associate Director for Research on Women's Health, NIH
Director, ORWH

Janine A. Clayton, M.D.
Deputy Director

Angela C. Bates
Program Analyst

Lisa Begg, Dr.P.H., R.N.
Director, Research Programs

Sharon E. Gist
Program Specialist

Charles W. Hampp, Jr.
Administrative Technician

Eleanor Z. Hanna, Ph.D.
Associate Director for Special Projects and Centers

Dorie A. Hightower
Communications Director

Sharron Jernigan-Jones
Program Support Assistant

Indira P. Jevaji, M.D.
Senior Medical Officer

Teresa R. Kendrix
Administrative Officer

Joslyn Y. Kravitz, Ph.D.
Program Analyst

Kimberly S. Kurilla-Gray
Secretary to the Director

Nichelle S. Lewis
Executive Assistant

Dennis F. Mangan, Ph.D.
Health Scientist Administrator

Joan D. Nagel, M.D., M.P.H.
Medical Officer

Heidi Rosvold-Brenholtz
Communications Editor

Joyce E. Rudick
Director, Programs and Management

Charles A. Wells, Ph.D.
Senior Advisor to the Director

ORWH Staff, FY 2012

Janine A. Clayton, M.D.
Associate Director for Research on Women's Health, NIH
Director, ORWH

Angela C. Bates
Program Analyst

Lisa Begg, Dr.P.H., R.N.
Director, Research Programs

Mary C. Blehar, Ph.D.
Senior Research Advisor

Sharon E. Gist
Program Specialist

Charles W. Hampp, Jr.
Program Specialist

Indira P. Jevaji, M.D.
Senior Medical Officer

Sharron Jernigan-Jones
Program Support Assistant

Stephanie Joseph
Program Analyst

Teresa R. Kendrix
Administrative Officer

Joslyn Y. Kravitz, Ph.D.
Program Analyst

Kimberly S. Kurilla-Gray
Secretary to the Director

Nichelle S. Lewis
Executive Assistant

Susan E. Maier, Ph.D.
Associate Director for Special Projects

E. Ann Mosher-Paulsen
Public Affairs Specialist

Joan D. Nagel, M.D., M.P.H.
Medical Officer

Susan M. Persons, M.A.
Chief of Staff

Heidi Rosvold-Brenholtz
Communications Editor

Joyce E. Rudick
Director, Programs and Management

Charles A. Wells, Ph.D.
Senior Advisor to the Director

Report of the NIH Institutes and Centers

National Cancer Institute

Executive Summary

Advances in cancer prevention, screening, and treatment have resulted in declining rates of cancer mortality among women in recent years. These rates reflect noteworthy decreases in some of the most common cancers among women, such as lung, breast, cervical, colorectal, and ovarian cancers, as well as non-Hodgkin lymphoma. Deaths from lung cancer have finally begun to decrease in women, after rising continuously for several decades. This trend reflects the decrease in smoking rates over the past 40 years. Cancer incidence rates among women have stabilized over the past few years. Although the incidence of breast cancer has increased slightly, the rate of lung cancer—the leading cause of cancer death among women—has decreased. Despite this progress, cancer continues to take a devastating toll on American women. The most recent figures suggest that approximately 790,740 women in the United States will be diagnosed with cancer in 2012, and 275,370 will die from the disease. Moreover, many women from minority and underserved communities continue to be disproportionately affected by various forms of cancer.

As this report highlights, the National Cancer Institute (NCI) has made notable progress by conducting and supporting research, training, health information dissemination, and other programs with respect to cancer prevention and treatment as well as continuing care of cancer patients. Many of these programs—including clinical, basic, translational, population-based, and dissemination research—address cancers specific to or primarily affecting women, as well as cancers with high incidence or mortality rates among women.

In the past 2 years, NCI-supported clinical researchers have made important strides in identifying better ways to prevent and treat cancers that commonly afflict women. Among the most promising advances was the finding that the drug exemestane (Aromasin®) significantly reduces risk of invasive breast cancer in postmenopausal women at high risk for developing the disease. In addition, through a direct comparison of new detection techniques, the National Lung Screening Trial (NLST) demonstrated a 20 percent reduction in lung cancer deaths among trial participants screened with low-dose helical CT, compared with those who were screened with chest x rays. Other noteworthy findings include results from a bivalent HPV (human papillomavirus) vaccine trial, which revealed that two doses, instead of three, may be sufficient to provide long-term protection against development of cervical cancer.

NCI also is advancing both basic science and translational research projects related to women's health. Many of these projects involve the innovative use of advanced mouse models that mimic human disease. In addition, NCI supports and conducts a number of population-based projects, ranging from studies focused on screening and early detection to studies aimed at identifying risk factors for poor outcomes. Researchers have confirmed that the HPV-16 strain is the dominant strain in the causation of cervical cancer. This finding suggests that screening women for specific HPV strains could identify women most at risk of developing cancer.

NCI remains dedicated to speeding the delivery of knowledge and beneficial interventions to the community to reduce the burden of cancer experienced by women. The NCI Women's Health Officer is dedicated to facilitating communication across the Institute and to promoting collaboration between NCI and other NIH Institutes and Centers, Federal agencies, and nongovernmental organizations. NCI also is committed to disseminating research advances to the scientific community and the public and has numerous resources related to women's health. Additional information about women's health issues related to cancer can

be found on the award-winning NCI Web site (*http://www.cancer.gov*).

Introduction

The American Cancer Society estimated that 275,370 women would die from cancer in 2012. Breast, colorectal, and lung cancers are the most commonly diagnosed cancers among women, collectively accounting for 52 percent of estimated cancer cases in this population. Of these three, breast cancer is the most common, representing 29 percent of all new cases in women. Lung cancer accounts for 14 percent of new cancer cases among women, while colorectal accounts for 9 percent. These same three cancers are also the leading causes of cancer death in women. Although breast cancer is the most commonly diagnosed cancer among women, lung cancer surpasses breast cancer as the leading cause of cancer death in women.

Despite these statistics, significant progress is being made in the fight against cancer. Overall death rates from cancer have continued to decrease in both men and women since the early 1990s. Between 2000 and 2009, cancer death rates in women decreased an average of 1.5 percent per year. Colorectal cancer and non-Hodgkin lymphoma death rates both declined an average of 3.1 percent per year from 2005 to 2009. Stomach cancer death rates decreased 2.8 percent per year; oral cavity and pharynx cancer, 2.2 percent; ovarian cancer, 2.0 percent; breast cancer, 1.9 percent; leukemia, 1.4 percent; cervical cancer, 0.9 percent; and lung cancer, 0.7 percent.

Overall cancer incidence rates among women stabilized between 2000 and 2009. Breast cancer incidence rates increased slightly—an average of 0.9 percent per year from 2005 to 2009. However, there have been declines in other cancers common among women. Between 2005 and 2009, colorectal cancer incidence rates decreased an average of 2.1 percent per year; ovarian cancer and lung cancer incidence rates both decreased by 1.5 percent per year; and cervical cancer incidence rates decreased by 2.6 percent per year. Steady declines in cancer incidence among women also have been observed in other cancer types, such as lymphoma and cancers of the brain, uterus, and stomach.

These data indicate real progress in cancer control. Primary prevention, early detection, and treatment have resulted in the vast majority of changes. Decreases in cervical cancer deaths are due primarily to early detection; incidence rates are expected to drop dramatically in the coming years due to improvements in primary prevention, including development of the human papillomavirus (HPV) vaccine. The decrease in colorectal cancer incidence rates largely reflects increases in screening, which can detect and remove precancerous polyps. Decreases in mortality for many cancers, particularly breast and colon cancers, also can be attributed to improved treatment strategies, such as combination therapy, targeted drugs, and genetic testing. Unfortunately, improvement has not been the case for all cancers. Incidence rates increased between 2000 and 2009 for two HPV-associated cancers (oropharynx and anus). These increases underscore the need for additional prevention efforts for HPV-associated cancers, including efforts to increase vaccination coverage. Moreover, with many minority and underserved women burdened by increased rates of cancer incidence and mortality, improvements have not been equal among all populations.

NCI conducts and supports research, training, health information dissemination, and other programs focused on the causes, diagnosis, prevention, and treatment of cancer, as well as on rehabilitation and continuing care for patients with cancer. NCI supports numerous research programs and projects that address cancers specific to or primarily affecting women, especially those cancers with high incidence or mortality among women, as well as cancers that affect both genders to a similar degree. These research programs and projects focus on the full continuum of the cancer challenge, from prevention to survivorship, and range from molecular and subcellular basic science experiments to population-based studies and community-based interventions.

NCI also is committed to disseminating research advances to the scientific community and to the public, and it has developed numerous resources related to women's

health. The award-winning NCI Web site, Cancer.gov (*http://www.cancer.gov*), is the Institute's central vehicle for dissemination of information to a diverse range of audiences. NCI also provides a Spanish-language version of its Web site, Cancer.gov en Español (*http://www.cancer.gov/espanol*). NCI's Cancer Information Service provides the latest, most accurate information about cancer treatment, clinical trials, early detection, and prevention for cancer patients, their families, and the public. U.S. residents can reach English- or Spanish-speaking NCI information specialists by calling toll-free at 1–800–4–CANCER (1–800–422–6237). An instant-messaging service called LiveHelp is also available on the NCI Web site.

Although far from comprehensive, the following pages provide a representative sampling of the activities and accomplishments of NCI relative to women's health in FYs 2011 and 2012.

NCI Women's Health Officer

The NCI Women's Health Officer facilitates communication across the Institute and promotes collaboration between NCI and other NIH Institutes and Centers, Federal agencies, and nongovernmental organizations. The Women's Health Officer develops and disseminates reports and information on NCI's research and research progress on cancers in women, and she coordinates NCI's responses to agency requests for information.

Accomplishments

This section provides highlights of NCI women's health research administrative supplements and other funded research relevant to women's health. The relationship of each highlight to the goals of the NIH Strategic Plan for Women's Health Research (*http://orwh.od.nih.gov/research/strategicplan/index.asp*), hereafter referred to as Strategic Plan, is noted at the end of the description of each highlight.

Administrative Supplements to NCI-Funded Research Projects: Funding to Advance Research on Cancers in Women

In 2011, the NCI Women's Health Officer and the NCI Office of Science Planning and Assessment (OSPA) launched a program titled "Administrative Supplements to NCI-Funded Research Projects: Funding to Advance Research on Cancers in Women" (*http://grants.nih.gov/grants/guide/notice-files/NOT-CA-12-001.html*). This program was also supported with funds provided by ORWH. During the first year of this administrative supplement program, a total of eight grant supplements were awarded to basic and translational research projects. The research focuses of these grant supplements were wide-ranging.

Basic research projects explored diverse topics, including the role of somatic mutation and gene fusion in ovarian cancer, the characterization of novel viruses from human genital areas, the mechanisms of ceramide synthesis, the effects of stress on immune function in cervical cancer, single nucleotide polymorphisms in anti-inflammatory pathways in ovarian cancer, and the relationship of estrogen metabolites to physical activity in breast cancer. Diverse translational projects focused on the influence of gender on the interrelationship of smoking and mental health and on the feasibility of nurse-patient navigation intervention in lung cancer.

This supplement program was not limited to research projects. In addition to the research grants, four scientific conferences were supported through this funding mechanism. These conferences served as a forum to discuss research on cancer health disparities among women, diagnosis and treatment of pregnancy-related cancer in women, the opportunities in cancer research among women in developing countries, and improved assessment of breast cancer risk and the prevention of the development of breast cancer. In total, $390,783 in grant funding was provided to advance research on cancer in women. Of this, OSPA contributed $250,783, and ORWH provided $140,000.

In its second year, this supplement program continued to focus on advancing cancer research, particularly on distinct characteristics unique to women. Together with ORWH, OSPA supported 10 administrative supplement grants during this cycle; however, in FY 2012, only research grants were supported. Topics were broad in focus and included the study of hormone metabolite concentrations and DNA methylation patterns in women prenatally exposed to diethylstilbestrol (DES); the effects of assisted reproductive technology on development of childhood cancer; defining the microenvironment in breast cancer; the integration of tumor models for predicting response in triple-negative breast cancer; the role of the PI3-kinase (PI3K) signaling pathway in breast and endometrial cancer cells; the relationship of breast cancer subtype, ancestry, and risk factors in Hispanic women; the effectiveness of low-dose tamoxifen in reducing breast cancer risk in Hodgkin lymphoma survivors; and the mechanisms of BRCA1-dependent DNA damage responses. In year 2, OSPA supported $297,650 in research grants, and ORWH provided an additional $150,000 in funding support. For FY 2012, a total of $447,650 in grant support was administered through this supplement program. This program maps to Strategic Plan Goals 1, 3, and 6.

Research Highlights

This section provides highlights of FY 2011 and FY 2012 NCI research relevant to women's health. Highlights are organized by nine disease categories: AIDS-related malignancies, brain cancer, breast cancer, colorectal cancer, Burkitt's lymphoma, cervical cancer, lung cancer, ovarian cancer, and skin cancer. The research highlights are further organized by malignancy type and approach (e.g., biology, prevention, treatment).

AIDS-Related Malignancies

Screening and Treatment

- **AIDS Malignancy Clinical Trials Consortium (AMC).** AMC was established in 1995 to evaluate clinical interventions for the treatment and prevention of malignancies in HIV-infected persons and to investigate the biology of the malignancies in the context of clinical trials. AMC is supporting the two studies described below:

- **Quadrivalent Human Papillomavirus (HPV) Vaccine Among HIV+ Women in India.** India has one of the highest cervical cancer incidence rates in the world, but little is known about the prevalence and incidence of cervical HPV infection in Indian women, and even less is known about HPV infection and cervical intraepithelial neoplasia (CIN) in HIV+ Indian women. A study has been initiated to investigate the effect of the HPV vaccine on HIV viral load and CD4+/CD8+ levels, determine the serologic response of HIV+ women to the vaccine, and evaluate CIN and the spectrum of HPV types at baseline and after 1 year in HIV+ women in Mumbai, India. This study addresses the important problem of HPV-associated cancers in HIV+ women by determining whether the women will benefit from HPV vaccination. This program maps to Strategic Plan Goals 3 and 4.

Screening HIV+ Women for Anal Cancer Precursors. HIV+ women have at least 14 times the risk of developing anal carcinoma as does the general population, despite the widespread use of highly active antiretroviral therapy. Like cervical cancer, anal cancer appears to be preceded by high-grade intraepithelial neoplasia and is strongly associated with HPV infection. Little to no evidence exists to define the optimal screening strategy for anal intraepithelial neoplasia in the context of HIV+ women. A multisite, multidisciplinary study will provide important information regarding the test characteristics, epidemiology, and natural history of anal HPV infection and high-grade anal intraepithelial neoplasia among a cohort of HIV+ women undergoing routine anal cytology testing. The data will then be utilized to perform comprehensive cost-benefit analyses that will direct clinical decisions regarding an optimal anal cancer screening approach for these women. This program maps to Strategic Plan Goals 2 and 3.

Women's Interagency HIV Study (WIHS). WIHS—jointly sponsored by NCI, the National Institute of Allergy and Infectious Diseases (NIAID), and the *Eunice Kennedy*

Shriver National Institute of Child Health and Human Development (NICHD)—was established in 1993 to investigate the impact of HIV infection on women. Participants include over 3,500 HIV+ and HIV- women. Results indicate that Pap test abnormalities are more common among HIV+ than HIV- women; furthermore, HIV+ women treated for cervical intraepithelial neoplasia (CIN) are more likely to experience a recurrence of their precancer than their HIV- counterparts. Other findings are that the 5-year risk of developing cervical cancer among women with normal cervical cytology was similar in HIV+ and HIV- women.

This program maps to Strategic Plan Goal 1.

Infrastructure

Developing Research Capacity in Africa for Studies on HIV-Associated Malignancies. The NCI Office of HIV and AIDS Malignancy and the Fogarty International Center sponsored a training initiative to encourage partnerships between U.S. and African researchers, build multidisciplinary research teams of African investigators, and enhance the capacity for innovative research in Africa. Described below are two awarded grants that focused on women's health issues.

- **Developing Rwandan Research Capacity in Cervical Cancer and Other AIDS Malignancies.** This program proposes to extend the partnership of the Albert Einstein Cancer Center (Bronx, NY) and the National University of Rwanda to develop a multidisciplinary team investigating operational, clinical, and translational questions in cervical cancer in HIV+ women and to extend the population-based cancer registry to allow linkage to an African computerized HIV tracking system. This program maps to Strategic Plan Goals 2, 3, and 4.
- **Zambian Cervical Cancer Research Capacity Initiative.** This project seeks to increase research capacity through collaborations between the University of North Carolina, Chapel Hill, and the Centre for Infectious Disease Research in Zambia. Training will commence in the areas of radiation, cervical cancer screening, oncology, gynecologic oncology, pathology, virology, nutrition, epidemiology, and biostatistics. This program maps to Strategic Plan Goals 3 and 4.

Brain Cancer

Treatment

Possible Inhibitors of Brain Metastasis. Brain metastases are a significant cause of morbidity and mortality for patients with cancer, and yet preventive and therapeutic options remain an unmet need. Research indicated that the addition of the protein pigment epithelium-derived factor (PEDF) rapidly stopped metastasis to the brain in a breast cancer model while helping to protect neurons adjacent to the tumor site. In addition, researchers tested pazopanib, an antiangiogenic drug that significantly reduced occurrence of brain metastases, in HER2+ breast cancer. This program maps to Strategic Plan Goal 1.

Fitzgerald, D. P., Subramanian, P., Deshpande, M., Graves, C., Gordon, I., Qian, Y., … Steeg, P. S. (2012). Opposing effects of pigment epithelium-derived factor on breast cancer cell versus neuronal survival: Implication for brain metastasis and metastasis-induced brain damage. *Cancer Research, 72*, 144–153.

Gril, B., Palmieri, D., Qian, Y., Smart, D., Ileva L., Liewehr, D. J., … Steeg, P. S. (2011). Pazopanib reveals a role for tumor cell B-Raf in the prevention of HER2+ breast cancer brain metastasis. *Clinical Cancer Research, 17*, 142–153.

Breast Cancer

Biology

The Cancer Genome Atlas Publishes Comprehensive Characterization of the Breast Cancer Genome. The Cancer Genome Atlas (TCGA) is a program jointly sponsored by NCI and the National Human Genome Research Institute, with the aim to comprehensively characterize the genomes of more than 25 tumor types. From data generated by TCGA, including single-nucleotide polymorphisms, copy number variation, gene and miRNA expression profiles, epigenomic landscape, and whole-exome or whole-genome

sequencing, researchers were able to confirm and further elucidate four of the standard molecular subtypes of breast cancer: HER2-enriched, luminal A, luminal B, and basal-like (also called triple-negative breast cancer). Researchers hope these findings, as well as the resulting resources provided to the cancer genomics research community, will become the foundation for future breakthroughs. This program maps to Strategic Plan Goal 1.

The Cancer Genome Atlas Finds Genomic Similarities Between Breast and Ovarian Cancers. TCGA recently published genomic data and analysis of samples from 825 breast cancer patients. These data showed that one subtype of breast cancer (basal-like) shares many genetic features with high-grade serous ovarian cancer. This finding suggests that the two cancers may be of a similar genetic origin, which might facilitate evaluation of joint therapies for breast and ovarian cancers. Understanding the similarities between these cancer types will provide researchers with the opportunity to compare treatments and outcomes of both cancers. This program maps to Strategic Plan Goal 1.

Identification of Specific Subtypes of Triple-Negative Breast Cancer that Disproportionately Impact African-American and Hispanic Women. Triple-negative breast cancer (TNBC) lacks hormonal receptors for estrogen and progesterone and for the receptor HER2 (human epidermal growth factor receptor 2). Therefore, therapies that target hormonal receptors (e.g., tamoxifen and aromatase inhibitors) or HER2 (e.g., trastuzumab, lapatinib, and pertuzumab) are not effective in treating this disease, as with tumors that are hormone receptor-positive or HER2+. Chemotherapy can be effective in some women, but many women will suffer disease recurrence after initial therapy. Of the approximately 209,000 cases of breast cancer diagnosed in 2010, it is estimated that 15–20 percent (approximately 31,000–42,000 patients) were classified as TNBC. Groups at higher risk of TNBC include women under 50, African-American and Hispanic women, and women of lower socioeconomic status. Regardless of the stage at diagnosis, women with TNBC have poorer survival than those with other breast cancers of the same stage. Among women with TNBC, the 5-year relative survival was 77 percent, compared with 93 percent for women with other breast cancers. African-American women with late-stage TNBC fared worst, with a 5-year relative survival of only 14 percent.

While TNBC is heterogeneous (not all patients will have the same type of cell abnormalities), about 80–90 percent of TNBC falls into a subcategory called basal-like breast cancer. In 2011, NCI-funded researchers identified six distinct TNBC subtypes, each with specific molecular candidate targets, and developed cell lines for each tumor subtype. These findings may provide biomarkers that can be used for patient selection in the design of clinical trials, as well as a way to measure response to treatment. This study, together with others, has identified several potential targets that may be amenable to treatment. This program maps to Strategic Plan Goal 1 and 2.

Assessment of Kinome Activity Allows Rational Design of Combination Therapies for Breast Cancer. Kinase inhibitors have limited success in cancer treatment because tumors circumvent their action. Using quantitative approaches, Specialized Programs of Research Excellence (SPORE) investigators assessed the activity of 50–60 percent of the expressed cellular kinases in response to MEK inhibition in triple-negative breast cancer. This approach defines mechanisms of drug resistance, potentially allowing individualized rational design of combination therapies for cancer. This program maps to Strategic Plan Goals 1 and 2.

Identifying Mechanisms That Contribute to Resistance to Targeted Therapies: HER2-Amplified Breast Cancers. Trastuzumab is an antibody used to treat women with HER2+ breast cancers. However, not everyone with HER2+ cancer responds to the treatment, and many patients develop resistance to the therapy within 1 to 2 years. Researchers have developed new systems to study when and how resistance to trastuzumab develops. Using these models, they found that loss of the tumor suppressor PTEN function resulted in a dramatic increase in the level of the

cytokine IL-6 produced by breast cancer cells. This inflammation-associated cytokine then promoted the expansion of a population of breast cancer stem cells, which coincided with the development of resistance to trastuzumab. Interruption of the feedback loop with an antibody that blocks IL-6-initiated signaling reduced the population of breast cancer stem cells, blocked the formation of distant metastases, and prevented the development of resistance to trastuzumab. This program maps to Strategic Plan Goals 1 and 2.

Repression of a Cellular Protein Seen in High-Density Breast Tissue as Well as in Breast Tumors. Although high mammographic density is considered one of the strongest risk factors for developing aggressive breast cancer, the genes involved in modulating this clinical feature remain unknown. NCI-funded scientists, using in vitro and in vivo assays as well as experiments employing normal and malignant human breast tissue, have shown that the level of expression of CD36, an important cellular signaling protein, is necessary and sufficient to control two important characteristics that define mammographic density. Modulating the expression levels of this protein in the breast tissue could be a potential strategy to prevent cancer progression in women with high-density breast tissue. This program maps to Strategic Plan Goal 1.

DeFilippis, R. A., Chang, H., Dumont, N., Rabban, J. T., Chen, Y. Y., Fontenay, G. V., … Tisty, T. D. (2012). CD36 repression activates a multicellular stromal program shared by high mammographic density and tumor tissues. *Cancer Discovery, 2*, 826–839.

The Art of Interpreting Epigenetic Activity. To better understand the relationship between a cancer cell's epigenetic activity and its phenotype, researchers undertook a large-scale analysis of DNA methylation patterns in primary invasive breast cancers. Their aim was to understand the changes that developed over time when compared with the epigenetic state of normal mammary tissue. Researchers were able to identify a baseline DNA methylation pattern using normal tissue from numerous unrelated patients. From these data, researchers created an index and ranked cancers in terms of how much they deviated from a "normal" baseline breast methylation profile. This research shows that it is possible to use routine breast pathology samples and evaluate methylation reprogramming (relative to baseline) for both epithelial and non-epithelial tissue constituents to identify clinically and biologically relevant cancer subclasses. This program maps to Strategic Plan Goal 1.

Killian, J. K., Bilke, S., Davis, S., Walker, R. L., Jaeger, E., Killian, M. S., … Meltzer, P. S. (2011). A methyl-deviator epigenotype of estrogen receptor-positive breast carcinoma is associated with malignant biology. *American Journal of Pathology, 179*, 55–65.

New Function for Breast Cancer Gene BRCA1. Scientists have uncovered a new function for BRCA1, a gene most commonly associated with hereditary breast and ovarian cancer. Working on mouse cells, they discovered that BRCA1 suppresses the expression of another gene that codes for a microRNA called miR-155, a known carcinogen. These findings suggest that BRCA1 functions as a tumor suppressor not only by playing a role in DNA repair, as known previously, but also by silencing a gene that can cause cancer when overexpressed. If the BRCA1-associated tumors are confirmed to be dependent upon miR-155, it may be possible to treat hereditary cancers by challenging them with agents that can inactivate miR-155. This program maps to Strategic Plan Goal 1.

Chang, S., Wang, R. H., Akagi, K., Kim, K. A., Martin, B. K., Cavallone, L., … Sharan, S. K. (2011). Tumor suppressor BRCA1 epigenetically controls oncogenic microRNA-155. *Nature Medicine, 17*, 1275–1282.

NCI Mouse Models of Human Cancer Consortium (MMHCC). A wide range of cell and animal models are the mainstays of basic and translational breast cancer research. Despite the reliance on data generated through translational and computational applications of so many varied models, NCI has never undertaken a systematic evaluation of experimental breast cancer models to define how each one relates to human biology. A catalog of such information has substantial potential to benefit the clinical aspects of cancer research. For several years,

MMHCC has been spearheading a research community-wide project to assemble and deploy best practices and standard operating procedures (SOPs) for the use of transgenic mouse models for translational research. However, breast cancer modeling approaches vary widely, so MMHCC is working with two other Division of Cancer Biology programs, the Integrative Cancer Biology Program and the Tumor Microenvironment Network, to extend cancer model best practices and SOPs to human breast cancer cell lines, multicell cultures, and xenografts.

- One MMHCC project developed a new mathematical tool, FOCAL, to comb through the vast amount of genomic data from breast cancer specimens. Data revealed that multiple driver genes exist within the same tumor amplifications or deletions, suggesting that, as tumors grow, these alterations are selected because they have an impact on multiple genes. This same research group also examined genetic heterogeneity among tumor cells within a single tumor. Heterogeneity complicates evaluation of cancer mechanisms and treatment and the interpretation of animal model systems, particularly human-in-mouse xenograft models. Researchers performed single nucleus sequencing on a number of single cells from 10 different cultured human breast cancer cell lines after growth in culture. Even in normal cell lines, up to 25 percent of the cells in the population have different patterns. In a BRCA1 cell line from a typical triple-negative tumor, no two cells had exactly the same profile. This behavior can profoundly affect the tumor biology of human cell lines grown in mice or as three-dimensional cell cultures.
- Another MMHCC project focuses on identifying genes and pathways that are functionally involved in tumor recurrence. Researchers here identified the SPSB1 protein as a functional contributor to breast cancer recurrence. SPSB1 protects cells from apoptosis induced by chemotherapy or HER2/neu inhibition; elevated levels of SPSB1 predict a high probability of relapse in breast cancer patients, specifically in women with ER- and HER2+ breast cancer and independent of tumor grade and basal subtype. This suggests that targeting the SPSB1 pathway may prevent or delay breast cancer recurrence.
- A genetically engineered mouse model of ER+ (luminal) breast tumors is being used to discover therapeutic targets for tumors that recur after initial treatment of estrogen ablation. One interesting lead is emerging, a signal pathway that is activated in 60 to 70 percent of all human ER+ breast cancers; blocking that pathway in the mice results in durable responses. A small preclinical trial is under way, using direct patient xenografts from women with recurrent ER+ tumors, to test potential efficacy in patients.

This program maps to Strategic Plan Goal 1.

Normal Mammary Microenvironment Suppresses the Tumorigenic Phenotype of Mouse Mammary Tumor Cells. Emerging results indicate that signals emanating from a normal mammary microenvironment combine to suppress the cancer phenotype during glandular regeneration. Further study of these signals offers the potential of improved therapeutic possibilities for the control of mammary cancer growth. This program maps to Strategic Plan Goal 1.

Booth, B. W., Boulanger, C. A., Anderson, L. H., & Smith, G. H. (2011). The normal mammary microenvironment suppresses the tumorigenic phenotype of mouse mammary tumor virus-neu-transformed mammary tumor cells. *Oncogene, 30*, 679–689.

Mutation of Thyroid Hormone Receptor-β Predisposes to the Development of Mammary Tumors in Mice. Correlative data suggest that thyroid hormone receptor-β (TRβ) mutations could increase the risk of mammary tumor development. Using a mouse model, researchers showed for the first time that a TRβ mutation promotes the development of mammary hyperplasia through the aberrant activation of signal transducer and activator of transcription 5 (STAT5), thereby conferring a fertile genetic ground for tumorigenesis. This study opens the door for future studies in humans. This program maps to Strategic Plan Goal 1.

Screening

Novel in vivo Imaging of Breast Cancer Markers. Epidermal growth factor receptor (EGFR) and HER2 play an important role in carcinogenesis; overexpression of one or more members of the EGFR family has been shown in a number of malignancies, including breast and ovarian cancers. Researchers have developed a novel method to detect the expression levels of EGFR and HER2 in vivo that could be helpful for detecting and characterizing malignant tumors as well as determining therapy. This program maps to Strategic Plan Goal 3.

Breast Cancer Risk in Asian/Pacific Islander and Hispanic-American Women. NCI's Breast Cancer Risk Assessment Tool (BCRAT) estimates a woman's personal risk of developing invasive breast cancer and is in widespread use by clinicians to counsel their patients. Because BCRAT was initially based on data from White women, NCI researchers developed the Contraceptive and Reproductive Experiences (CARE) model to better predict breast cancer risk in African-American women. Recently, NCI researchers developed a more accurate model for estimating breast cancer risk for Asian and Pacific Islander women that has been incorporated into BCRAT. Work is also under way to improve the model for predicting breast cancer risk in Hispanic women. This program maps to Strategic Plan Goals 3 and 4.

The Early Detection Research Network (EDRN) Breast and Gynecological Cancers Collaborative Group Validates Biomarkers for Breast Cancer. The increase in incidence of breast cancer observed over the past 20 years is almost entirely attributable to improved imaging techniques, which have allowed for the detection of ductal carcinoma in situ (DCIS) and stage I cancer. The large majority of these lesions remain indolent. At the same time, there are many cancers that are being missed by screening mammography, many of which tend to be aggressive disease, such as "interval" and HR-negative or triple-negative breast cancer. The incidence of the latter is significantly higher in premenopausal women, where imaging screening modalities are significantly less effective. Furthermore, about 1–2 percent of women diagnosed and treated for DCIS with surgery will have another DCIS or invasive breast cancer within 5 to 10 years. Finally, the relative risk of developing invasive breast cancer (IBC) after a diagnosis of atypical ductal hyperplasia (ADH) is 2–4 times as great as it is in the general population. To address these issues, investigators in the Breast and Gynecological Cancers Collaborative group of EDRN are working toward the validation of:

- **Tissue-Associated Biomarkers.** It is important to validate tissue-associated biomarkers that identify women diagnosed with ADH or DCIS, as these women are at increased risk of developing IBC and might benefit from risk reduction with the use of chemoprevention agents, such as tamoxifen.
- **Biomarkers for Triple-Negative Breast Cancer (TNBC).** EDRN investigators have teamed up with the goal of developing a blood-based biomarker panel for the routine screening of women over the age of 40 to identify high-risk cases for TNBC for more frequent imaging by mammography and/or magnetic resonance imaging. The overall study design involves the identification of three distinct types of blood-based biomarkers: autoantibodies, protein antigens, and microRNAs. The top-performing markers and their combinations will be further validated in a phase III case-control study for the detection of TNBC using serial blood specimens collected prior to clinical diagnosis from the cohorts of the Women's Health Initiative study, the Risk of Ovarian Cancer Algorithm study, and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

These programs map to Strategic Plan Goals 1 and 3.

Treatment

Trial Suggests New Treatment Option for Some Women with Metastatic Breast Cancer. Results from an NCI-funded phase III clinical trial suggest that, for some women with metastatic breast cancer, combining two drugs that work in different ways to disrupt estrogen's ability to promote cancer growth may delay disease progression and death.

In the SWOG (part of the NCI National Clinical Trial Network) trial, women with hormone receptor-positive metastatic breast cancer treated with the aromatase inhibitor anastrozole (Arimidex) and the antiestrogen fulvestrant (Faslodex) had better progression-free and overall survival than women who were treated with anastrozole alone or anastrozole followed by fulvestrant. Both drugs are already approved to treat metastatic breast cancer. This program maps to Strategic Plan Goal 3.

NCI Facilitates Design and Prioritization of Trials for Breast, Gynecologic Cancers. NCI has formed Scientific Steering Committees (SSCs) for both breast and gynecologic cancers to leverage existing Intergroup, Cooperative Group, SPORE, and Cancer Center structures to develop, evaluate, and prioritize concepts for phase II and large phase III clinical trials. The role of SSCs is to increase information exchange at an early stage of trial development, increase the efficiency of clinical trial collaboration, and reduce redundancy for phase II and III clinical trials. This ensures a nationally coordinated effort to implement optimally designed, high-priority clinical trials. This program maps to Strategic Plan Goal 3.

Limited Efficacy of Antiangiogenic Agents in Treating Breast Cancer. Antiangiogenic agents restrict blood flow, a function that can result in tumor hypoxia and, in turn, stimulate the growth of cancer stem cells (CSC) in the tumor. CSCs have tumor-initiating capabilities and a high metastatic potential. In this study, NCI-funded researchers examined the effect of angiogenesis inhibitors on the growth of human breast cancer cells in culture and in mice. They found that the antiangiogenic agents did increase CSCs in the tumor and suggest that, in order to improve patient outcome, these agents need to be combined with cancer stem cell-targeting drugs. This program maps to Strategic Plan Goal 1.

Conley, S. J., Gheordunescu, E., Kakarala, P., Newman, B., Korkaya, H., Heath, A. N., … Wicha, M. S. (2012). Antiangiogenic agents increase breast cancer stem cells via the generation of tumor hypoxia. *Proceedings of the National Academy of Sciences of the United States of America, 109*, 2784–2789.

Blocking the Growth of Metastases. Survival rates for breast cancer that has metastasized continue to be below 25 percent; thus, understanding and preventing metastasis is critical. Previous studies identified the first metastasis suppressor gene, the human non-metastatic gene 23 (NM23-H1). An inverse relationship between NM23-H1 and expression of lysophosphatidic acid receptor 1 gene (LPA1) has also been reported. However, the effects of LPA1 inhibition on primary tumor size, metastasis, and metastatic dormancy have not been investigated. In two different mouse models, the inhibition of LPA1 with the drug Debio-0719 prevented the growth of metastases. These data suggest that Debio-0719 stands as one of the first compounds to induce metastatic dormancy and holds promise for eventual testing in patients with cancer. This program maps to Strategic Plan Goals 1 and 2.

Marshall, J. C., Collins, J. W., Nakayama, J., Horak, C. E., Liewehr, D. J., Steinberg, S. M., … Steeg, P. S. (2012). Effect of inhibition of the lysophosphatidic acid receptor 1 on metastasis and metastatic dormancy in breast cancer. *Journal of the National Cancer Institute, 104*, 1306–1319.

Targeted Therapies for Triple-Negative Breast Cancer (TNBC). Ongoing clinical trials are examining the role of antiangiogenesis agents, platinum compounds, poly ADP ribose polymerase (PARP) inhibitors, and other targeted agents in TNBC, in addition to molecular profiling to help determine which subtypes of TNBC will respond to the different therapies. NCI intramural researchers identified two genes (CHK1 and RRM1/2) that are intimately related to the growth of TNBC cells in a synergistic manner. Based upon these results, NCI is developing a clinical trial to treat these TNBC patients with drugs that target these genes. This program maps to Strategic Plan Goals 1 and 3.

Genetic Signature Linked to Risk of Breast Cancer Recurrence. The NCI-sponsored Trial Assigning Individualized Options for Treatment (Rx), or TAILORx, for lymph node-negative breast cancer, and Rx for Positive Node, Endocrine Responsive Breast Cancer, or RxPONDER, for lymph node-positive breast cancer, are two of the first trials to

examine a methodology for more accurately determining appropriate cancer treatment. They utilize a molecular profiling test (Oncotype DX) to analyze whether genes that are frequently associated with risk of recurrence for women with early-stage breast cancer can be used to assess the likelihood of recurrence and predict the effectiveness of chemotherapy. TAILORx and RxPONDER seek to incorporate this information into clinical decision making and, thus, spare women unnecessary treatment if chemotherapy is not likely to be of substantial benefit. This program maps to Strategic Plan Goal 3.

Prevention

New Chemopreventive Agents for Breast Cancer. The Division of Cancer Prevention (DCP) completed two phase I studies through the DCP Consortia for Early Phase Prevention Trials in which it examined multiple doses of agents that may reduce the incidence of estrogen receptor (ER)- and ER+ breast cancer. In a phase IB study of atorvastatin, DCP researchers found that atorvastatin significantly reduced C-reactive protein, cholesterol, and low-density lipoprotein, with minimal grade I and II toxicity observed.

DCP also conducted multiple phase II studies examining agents that may prevent ER+ breast cancer. Preliminary results show a statistically significant change in mammographic density in postmenopausal women after 1 year on exemestane and a reduction in PS2, an estrogen response gene. DCP examined the use of local therapy for breast cancer prevention. When comparing transdermal 4-hydroxtamoxifen (4-OHT), an active metabolite of tamoxifen, to oral tamoxifen in women with DCIS, researchers found that while mean plasma 4-OHT levels in 4-OHT and tamoxifen groups were significantly different, the mean breast adipose tissue levels were similar. Both groups had decreased proliferation as measured by KI-37 expression. These results are positive steps forward towards developing agents with a better risk-benefit ratio for breast cancer prevention. This program maps to Strategic Plan Goal 3.

Exemestane Substantially Reduces Breast Cancer Risk. A multicenter study found that the drug exemestane, an aromatase inhibitor, significantly reduced invasive breast cancers in postmenopausal women who were at moderately increased risk for breast cancer. In the MAP.3 trial, which enrolled 4,560 women, only 11 women assigned to exemestane developed an invasive breast cancer, compared with 32 women who took the placebo. Exemestane use also led to a statistically significant reduction in the development of DCIS. Further, the invasive tumors that did develop in women taking exemestane were less aggressive than those in the placebo group. This is the third drug that has been shown to reduce breast cancer risk. This program maps to Strategic Plan Goal 3.

Risk Factors

Study Evaluates Physical Activity and Breast Cancer Risk. Investigators conducted a prospective cohort study of Chinese women aged 40 to 70 years to evaluate their risk of breast cancer in relation to physical activity, including adolescent and adult exercise, household activity, and walking and cycling for transportation. Breast cancer risk was lower for women with the least amount of occupational sitting time and with the highest amount of occupational energy expenditure. Adult exercise at or above the recommended level was associated with lower breast cancer risk in postmenopausal women. This program maps to Strategic Plan Goals 1 and 4.

Genetic Variation Linked to Risk of Breast Cancer. The Cancer Genetic Markers of Susceptibility (CGEMS) project is NCI's major strategic initiative that uses genome-wide association studies (GWAS) to uncover inherited genetic susceptibility for a variety of cancers. CGEMS researchers identified genetic variations in 2 regions of DNA, located on chromosomes 1 and 14, which may be associated with the risk of sporadic breast cancer. Recently, researchers investigated common risk alleles for estrogen receptor-negative (ER-) breast cancer in multiple populations by combining GWAS data from women of African ancestry and European ancestry. They identified a common risk variant for ER- breast cancer at the TERT-CLPTM1L locus on chromosome 5p15. Further study of these regions may help to identify possible mechanisms that contribute to the development of

breast cancer. This program maps to Strategic Plan Goals 1 and 4.

Multigenerational Impact of Diet and Estrogen Exposure on Breast Cancer Risk. The NCI Integrative Cancer Biology Program (ICBP) is administered by the Division of Cancer Biology and supports a number of centers employing a systems biology approach to generate new insights and computational models into the study of cancer. The Georgetown University ICBP Center has developed a novel in vivo model to study the critical role of estrogen on both the risk of developing breast cancer and the risk of developing drug resistance. Georgetown researchers established that in utero estrogen exposures can increase breast cancer risk across generations through estrogen-associated epigenetic modifications. They showed that maternal exposure to exogenous estrogen during pregnancy increases both de novo and acquired resistance to tamoxifen. In contrast, prepubertal exposure to genistein (soy phytoestrogen) reduces tamoxifen resistance and prevents recurrence. This study indicates that maternal exposure to a diet high in fat or external estrogen during pregnancy increases mammary cancer risk in multiple generations of offspring. They observed that a maternal high-fat diet increases mammary cancer risk in the daughters and granddaughters. Maternal estrogen exposure increased the risk in three consecutive generations (daughters, granddaughters, and great-granddaughters), indicating that the effects are transgenerational for the maternal estrogen exposure but multigenerational for the maternal high-fat exposure. This program maps to Strategic Plan Goal 1.

de Assis, S., Warri, A., Cruz, M. I., Laja, O., Tian, Y., Zhang, B., … Hilakivi-Clarke, L. (2012). High-fat or ethinyl-oestradiol intake during pregnancy increases mammary cancer risk in several generations of offspring. *Nature Communications, 3*, 1053.

Molecular Link between BRCA1 Protein Levels and Obesity. Researchers have defined a possible molecular link between breast cancer risk and obesity. The study results show that a protein called C-terminal binding protein acts to control a gene linked to breast cancer risk (BRCA1) in rapidly growing cells by monitoring and responding to how the cells use and store energy (metabolic state). This program maps to Strategic Plan Goal 1.

Di, L. J., Fernandez, A. G., De Siervi, A., Longo, D. L., & Gardner, K. (2010). Transcriptional regulation of BRCA1 expression by a metabolic switch. N*ature Structural & Molecular Biology, 17*, 1406–1413.

Adverse Health Outcomes in Women Exposed in utero to Diethylstilbestrol. A large NCI study of the daughters of women who had been given diethylstilbestrol (DES), the first synthetic form of estrogen, during pregnancy has found that exposure to the drug in utero is associated with many reproductive problems and an increased risk of certain cancers and precancerous conditions. Compared with non-DES-exposed women, as adults, women exposed to DES in utero had eight times the risk of neonatal death, almost five times the risk for preterm delivery, and nearly four times the risk of an ectopic pregnancy. In addition, DES-exposed daughters were twice as likely to experience infertility. Risks of breast cancer or neoplastic cervical lesions were approximately doubled and persisted until age 55. The data also showed a 40-fold increased risk of clear cell adenocarcinoma in women exposed to DES in utero, persisting until at least age 40. This program maps to Strategic Plan Goal 3.

Study of Breast, Ovarian, and Endometrial Cancers in Poland. NCI researchers and external collaborators are conducting a large population-based study in Poland to assess the role of environmental and genetic factors in the risk of breast, ovarian, and endometrial cancers. NCI researchers were among the first to show that nongenetic and genetic risk factors for breast cancer vary by hormone receptor status; data from this study further suggested etiological differences between luminal A and basal tumors. Recently, researchers found that high sex steroid concentrations are more strongly related to ER+/progesterone receptor (PR)+ breast cancers than ER-/PR-. This program maps to Strategic Plan Goals 3 and 4.

Study Evaluates Breast Density as Breast Cancer Risk Factor. NCI researchers and extramural colleagues have undertaken a

study to understand the determinants of breast density and the mechanisms by which it elevates breast cancer risk. Researchers are now comparing novel volumetric density measures with standard area assessments as well as exploring whether regional variation in density is related to risk factors and pathologic diagnosis. In addition, researchers evaluated the relationship between breast density and risk of death from breast cancer and all causes. They found that high mammographic breast density was not associated with risk of death from breast cancer or death from any cause after accounting for other patient and tumor characteristics. Thus, risk factors for the development of breast cancer may not necessarily be the same as factors influencing the risk of death after breast cancer has developed. This program maps to Strategic Plan Goal 3.

Postpartum Breast Remodeling, Lactation, and Breast Cancer Risk. NCI researchers are developing a study that will seek to understand the relationships between lactation, postpartum breast remodeling, and breast cancer risk. The "bench" aims of this project are to develop optimal methods for collecting and fractionating milk into liquid and cellular components. The "bedside" aims of this project focus on evaluating these methods among first-time Black and White mothers of varying ages. The long-term goal is to develop the optimal means for milk collection and processing for large epidemiological studies of the risk of early-onset, aggressive breast cancers. This program maps to Strategic Plan Goal 3.

Müllerian Inhibiting Substance and Cancer Risk. NCI researchers are studying the association between Müllerian inhibiting substance (MIS), a factor that inhibits the growth of mammary ducts, and cancer risk. Recently, researchers demonstrated that MIS is directly associated with breast cancer risk, and they are currently assessing MIS with respect to ovarian and cervical cancer. This program maps to Strategic Plan Goal 1.

Pilot Study to Evaluate Breast Cancer among African Women. There is little information on breast cancer that occurs among African women, although data suggest that, as in African-American women, the cancers that develop among African women tend to occur at younger ages and have worse prognostic features than those occurring among American Caucasians. Given that breast cancer incidence rates are increasing in many African nations and that treatment options are limited in those countries, there is a critical need for better understanding the pathogenesis of breast cancer in Africa and identifying risk factors that might be used in primary prevention among African women. As an initial step in conducting a full-scale molecular epidemiologic study of breast cancer in Ghana, a pilot study will be conducted to determine the feasibility of all phases of the study. The pilot will test the infrastructure needed to conduct a molecular epidemiologic study, determine the number of available cases, define methods for subject recruitment (for both cases and comparison subjects), and assess procedures for collecting questionnaire-based interviews and for processing, storing, and transporting biologic specimens. This program maps to Strategic Plan Goals 3 and 4.

Burkitt's Lymphoma

Risk Factors

Effects of Malaria on Epstein-Barr Virus (EBV) Persistence and Maternal Transfer in Burkitt's Lymphoma. Burkitt's lymphoma has a complex etiology, often involving EBV infection. Preliminary data suggests that repeated infection with Plasmodium falciparum malaria during pregnancy diminishes the infant's ability to control subsequent EBV infections, thus increasing the incidence of endemic Burkitt's lymphoma. Investigators are examining a cohort of pregnant women in Africa to determine if malarial infection affects in utero maternal transfer of EBV-specific antibodies and reduces a child's passive immunity to subsequent EBV infection. Results have potential for quick clinical translation that could result in substantial impact on the prevention and treatment of a deadly childhood cancer. This program maps to Strategic Plan Goals 3 and 4.

Cervical Cancer

Screening

Accurate Detection of Cervical Cancer Using Optical Spectroscopy Reduces Unnecessary Biopsies and Health Care Costs. The screening for cervical cancer in high-resource settings is based on the use of the Pap smear, a cytological sampling of the cervix, followed, if positive, by visualization via colposcopy, and finally by ablation therapy. The whole process, from screening to treatment, can take several weeks and repeated visits to the medical facility. The development of inexpensive miniature optical sensors that probe potentially cancerous tissue in real time would allow for the screening, detection, and possibly treatment of cervical cancer in one visit. A recent study showed that this device had high sensitivity and specificity in detecting diseased tissue, with accuracy similar to colposcopy. The use of this device would eliminate the Pap smear and a repeat visit to the health care facility. In regions of the world where follow-up monitoring and repeated visits constitute a challenge, employing such a device can save lives while controlling health care costs. This program maps to Strategic Plan Goals 2 and 3.

Multi-Society, Evidence-Based Cervical Cancer Screening Guidelines. The American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology, in conjunction with the NCI Division of Cancer Prevention, convened a workshop to develop evidence-based cervical screening guidelines. The resulting consensus guidelines were published in 2012. These screening recommendations for cervical cancer prevention and early detection will have an impact on tens of millions of women in the United States. These guidelines harmonize with separate recommendations put forth by the U.S. Preventive Services Task Force (USPSTF). USPSTF recommends against screening for women under 21 years of age, and it recommends screening in women aged 21 to 65 years with cytology (Pap smear) every 3 years or, for women aged 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and HPV (human papillomavirus) testing every 5 years. This program maps to Strategic Plan Goal 5.

Concurrent Testing for HPV and Cervical Cytology. NCI researchers found that, for women aged 30 and older, a single negative HPV test was sufficient to provide strong reassurance against a diagnosis of cervical cancer over 5 years. HPV testing also resulted in earlier identification of women at high risk of cervical cancer, especially cervical adenocarcinoma, a tumor that is rising in incidence in the United States. Finally, having a normal Pap test and a negative HPV test was associated with about the same cancer risk as a negative HPV test alone. This finding strongly suggests that reserving Pap testing only for HPV+ women could protect women while reducing the number of Pap tests by 95 percent within this population. This program maps to Strategic Plan Goal 3.

Early Detection Research Network-Funded Studies Develop Biomarkers for Cervical Cancer. More than 90 percent of cervical cancer cases are associated with HPV infection. Although a risk factor, detection of HPV DNA in cervical tests by itself is not a sufficient biomarker to indicate the presence of premalignant cervical lesions and their progression to malignancy. Hence, a reliable, noninvasive early detection and risk assessment program is necessary to stratify the female population and identify those with the disease at an early, curable stage, or individuals with premalignant lesions destined to progress to malignancy. During 2011 and 2012, the Early Detection Research Network funded three studies whose focus is to develop such biomarkers:

- **Transrenal Molecular Diagnostic Assay Platform.** This trial will lead to the development of new noninvasive diagnostic assays for the early detection of HPV-related cervical tumors, the monitoring of therapeutic response, and enhanced detection of disease recurrence. A noninvasive, urine-based transrenal DNA (TrDNA) test that detects infection with high-risk HPV strains will be performed in urine collected from women with low-grade squamous intraepithelial cervical lesions, women with high-grade squamous intraepithelial lesions, and women with cancer who visit a cervical cancer high-risk

prevention clinic. The long-term goals of this project are to determine the public health feasibility and medical efficacy of screening a general population for high-risk HPV DNA in urine as a screening test for HPV-associated cervical tumors.

- **HPV 16 DNA Methylation Biomarkers.** In this study, the investigators are validating promising HPV 16 DNA methylation biomarkers that can distinguish between high-grade cervical intraepithelial neoplasia (CIN3) and low-grade CIN1. HPV 16/18 infections can cause cervical cancer, but they are benign and transient in most women. For these women, colposcopy unnecessarily increases the risk of CIN overdiagnosis and overtreatment. A novel secondary screening assay to assess the risk of cervical precancer in HPV 16/18+ women would enable their safe triage to colposcopy. The goal of the funded research is to validate promising HPV 16 DNA methylation biomarkers to ultimately fulfill this unmet need and prevent unneeded colposcopy procedures.
- **Prognostic Biomarkers for the Diagnosis of Some Cervical Cancers.** This DCP-funded study is testing the hypothesis that DNA methylation in specific regions of the E6 and E7 HPV 16 genes is associated with decreased likelihood of developing advanced cervical intraepithelial neoplasia (CIN2 and CIN2+). The investigators have demonstrated that a higher degree of HPV16 E6/E7 DNA methylation assayed in exfoliated cervical cells was associated with a 79 percent reduced likelihood of being diagnosed with CIN. Preliminary studies by the investigators have demonstrated a strong inverse association between folate and risk of developing HPV 16-associated CIN. This study will confirm the association of HPV 16 DNA methylation at specific sites with CIN2 to determine whether increased levels of circulating folate increase further the degree of association of HPV 16 DNA methylation with decreased likelihood of diagnosis of CIN2.

These programs map to Strategic Plan Goals 1 and 2.

Treatment

HPV Vaccine Trial Assessing Duration of Protection, Evaluating Long-Term Effects. NCI researchers are conducting a randomized, controlled phase III clinical trial of the bivalent HPV vaccine (Cervarix®) manufactured by GlaxoSmithKline to prevent HPV 16/18 infections and their associated cervical lesions. The study has confirmed that the HPV vaccine is highly effective in preventing persistent infections with HPV types 16 and 18 and that there is evidence of cross-protection against other cancer-causing HPV types not targeted by the vaccine: HPV types 31, 33, and 45. Vaccination benefits appear to be greatest when the vaccine is given to young women before they have initiated sexual activity. Data from the trial demonstrated that three doses of the HPV vaccine may not be necessary, as similar vaccine efficacy against cervical HPV 16/18 infection was observed among women who received two doses, and even a single dose, of the HPV vaccine. The study has found no therapeutic effect for the vaccine in women previously infected with HPV. This program maps to Strategic Plan Goal 3.

Risk Factors

Effect of Pap Smear Collection and Carrageenan on Cervicovaginal HPV Infection in a Model System. HPV infection is thought to require trauma to the cervicovaginal epithelium. Researchers used a primate model to determine whether a Pap smear, which disrupts the epithelium by design, renders the cervix more susceptible to HPV infection. The findings indicate that a Pap smear might lead to a transiently increased susceptibility to HPV infection and that using a carrageenan-based gel, a sulfonated polysaccharide extracted from red algae, during the examination might mitigate this enhancement. This program maps to Strategic Plan Goal 1.

Roberts, J. N., Kines, R. C., Katki, H. A., Lowy, D. R., & Schiller, J. T. (2011). Effect of Pap smear collection and carrageenan on cervicovaginal human papillomavirus-16 infection in a rhesus macaque model. *Journal of the National Cancer Institute, 103*, 737–743.

Prevention

Population-Based Cohort Studies Focus on HPV. Recently, Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) investigators found that, although women may be infected with multiple HPV types, only one HPV strain, HPV 16, predominated in the discrete cervical biopsies in which precancerous cells were apparent. This discovery confirms the dominant role of the HPV 16 strain in the causation of cervical cancer and contributes to data that indicate that screening women for specific HPV strains could identify those women most at risk of developing cancer. This program maps to Strategic Plan Goal 3.

Lung Cancer

Screening

Lung Cancer Screening Trial Results Show Mortality Benefit with Low-Dose CT. The National Lung Screening Trial (NLST) compared two ways of detecting lung cancer: low-dose helical computed tomography (CT, also known as spiral CT) and standard chest X-ray. Both chest X-rays and low-dose helical CT scans have been used to find lung cancer early, but the effects of these screening techniques on lung cancer mortality rates had not been determined. NLST enrolled more than 50,000 current or former heavy smokers from more than 30 sites across the United States. NLST reported initial trial results in November 2010, showing 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT as compared with those who were screened with chest X-rays. An ancillary finding showed that all-cause mortality (deaths due to any factor, including lung cancer) was 7 percent lower in those screened with low-dose helical CT. A substantial portion of this lower rate was attributable to reduced rate of lung cancer. The possible disadvantages of helical CT include the cumulative effects of radiation and surgical and medical complications in patients who prove not to have lung cancer. These risks must be weighed against the advantage of a significant reduction in lung cancer mortality. This is the first controlled trial to show a decreased mortality from lung cancer from any screening procedure. Despite this success, it still must be emphasized that not smoking is the most effective way to reduce the risk of dying from lung cancer. This program maps to Strategic Plan Goal 2.

Treatment

Studies Exploring Antiestrogen Agents in Treatment of Lung Cancer and Signaling in Lung Cancer. The University of Pittsburgh Lung Cancer SPORE, in collaboration with investigators at the University of California, Los Angeles, and the Translational Oncology Research International network, is involved in two randomized phase II clinical trials for the treatment of non-small cell lung cancer. The first trial studied erlotinib, a tyrosine kinase inhibitor, in combination with fulvestrant, an estrogen receptor inhibitor, in patients with non-small cell lung cancer. The second is studying fulvestrant, the antiestrogen agent anastrazole, and the antiangiogenic drug bevacizumab as a consolidation therapy regimen for postmenopausal women with late-stage non-small cell lung cancer. Both trials collected specimens for biomarker analysis. Results from the two trials will be available in 2013. This program maps to Strategic Plan Goal 3.

Ovarian Cancer

Biology

BRCA1 and BRCA2 Mutations and Ovarian Cancer Survival. NCI researchers conducted a pooled analysis of 26 observational studies of women with ovarian cancer to characterize the survival of BRCA carriers with epithelial ovarian cancer (EOC) compared with those patients without BRCA mutations. Among patients with invasive EOC, having a germline mutation in BRCA1 or BRCA2 was associated with improved 5-year overall survival, and BRCA2 carriers had the best prognosis. This program maps to Strategic Plan Goal 3.

Mechanism Responsible for Transforming Normal Cells Surrounding Ovarian Cancer Cells into Cells that Promote Tumor Growth Identified. Researchers have elucidated the molecular changes that convert normal cells surrounding ovarian cancer cells into ones that promote tumor growth and metastasis. This transformation is the

result of altered expression of three specific small molecules called microRNAs, which are important regulators of cellular functions. Restoring the pattern of expression of these three microRNAs reduced their cancer-promoting characteristics. Targeting microRNAs in the cells that surround the tumor cells may be a promising new therapy for ovarian cancer. This program maps to Strategic Plan Goal 1.

Insights into the Mechanism of Invasion and Metastasis of Ovarian Cancer. IKK-TRϵ was identified previously as a breast cancer oncogene and was associated with poor clinical outcome in ovarian cancer. Researchers found evidence that IKK-ϵ is a key coordinator of invasion and metastasis in ovarian cancer. Inhibition of IKK-ϵ signaling thus emerges as a viable therapeutic strategy in women whose ovarian cancer shows aberrant activation of this pathway. This program maps to Strategic Plan Goal 1.

Hsu, S., Kim, M., Hernandez, L., Grajales, V., Noonan, A., Anver, M., … Annunziata, C. M. (2012). IKK-ϵ coordinates invasion and metastasis of ovarian cancer. *Cancer Research*, *72*, 5494–5504.

Screening

Ovarian Cancer Screening Trial Shows No Benefit of Screening, but Some Harms. The Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial is a randomized controlled trial evaluating screening for four cancer sites. For ovarian cancer, the screening modality was an ovarian cancer cell-specific biomarker, CA125, combined with transvaginal ultrasound (TVU) annually for 6 years. The trial included 78,216 women aged 55 to 74 years who were randomly assigned to undergo either annual screening or usual care. The final results for the ovarian component of PLCO demonstrated no benefit of screening with respect to the primary endpoint of ovarian cancer mortality; after median follow-up of 12.4 years, there were 118 ovarian cancer deaths in the screening arm versus 100 in the control arm. A total of 3,285 women experienced false-positive screens; of these, 1,080 underwent surgical follow-up and 163 experienced at least 1 serious complication. These results show that an annual screening regimen of CA125 and TVU did not reduce ovarian cancer mortality, but it did increase invasive medical procedures and associated harms. This program maps to Strategic Plan Goal 3.

Buys, S. S., Partridge, E., Black, A., Johnson, C. C., Lamerato, L., Isaacs, C., … PLCO Project Team (2011). Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA*, *305*, 2295–2303.

Identification of Biomarkers for Ovarian Cancer. Early Detection Research Network (EDRN) investigators, in collaboration with investigators from the SPORE program, recently completed a clinical trial to identify biomarkers from among a set of more than 65 candidates to detect ovarian cancer prior to clinical diagnosis of the disease. The completed study, however, failed to identify any biomarkers that could reliably detect ovarian cancer more than 6 months before the manifestation of any clinical symptoms of the disease. The single best biomarker remains CA125, which has poor diagnostic performance for premalignant or early-stage disease. Furthermore, its increased levels are found in about 3 percent of postmenopausal women, resulting in a significant number of false positives for this biomarker. Therefore, new biomarkers for ovarian cancer need to be developed, some of which could be coupled with existing biomarkers in highly accurate, multiplexed assays that can identify women at high risk of harboring premalignant or early malignant ovarian lesions. This program maps to Strategic Plan Goal 3.

Validation of Ovarian Cancer Biomarkers. Investigators in the EDRN Breast and Gynecological Cancers Collaborative group have teamed up to validate a large number of promising biomarkers to be used in a screening program to increase the proportion of ovarian cancers detected at an early stage. To achieve ovarian cancer detection at an early stage, this team project is designed to validate top-performing biomarkers and their combinations from among the more than 150 candidates. The plan is to develop highly accurate assays for at least 50 selected candidate protein markers previously identified by

diverse approaches and platforms. Verified biomarkers will then be tested on longitudinally collected samples obtained up to 2 or more years prior to diagnosis from cohorts such as PLCO and the UK Collaborative Trial for Ovarian Cancer Screening. This program maps to Strategic Plan Goal 3.

Using Cervicovaginal Fluids for the Development of Ovarian Cancer Biomarkers. Researchers are investigating a novel approach for the development of ovarian cancer biomarkers by utilizing cervicovaginal fluids, a material that is usually collected during routine Pap tests but discarded. A phase II validation study will be conducted to determine the validity of the discovered biomarkers as a test for ovarian cancer and for distinguishing it from benign adnexal masses. This program maps to Strategic Plan Goal 3.

Treatment

Inhibiting Ovarian Cancer Metastasis by Targeting the Urokinase Plasminogen Activator Receptor. NCI-funded researchers have demonstrated that a protein, urokinase plasminogen activator receptor (u-PAR), is widely expressed on the cell surface of primary and metastatic ovarian cancers. Its ligand is another secreted protein, the urokinase-type plasminogen activator (u-PA). The u-PA/u-PAR interaction plays an important role in tumor cell metastasis. Researchers have shown that using a monoclonal antibody (ATN-658) directed against u-PAR in in vitro ovarian cancer cell lines and in in vitro mouse models reduces the ability of ovarian cancer cells to metastasize. This program maps to Strategic Plan Goal 1.

Kenny, H. A., Leonhardt, P., Ladanyi, A., Yamada, S. D., Montag, A., Im, H. K., … Lengyel, E. (2011). Targeting the urokinase plasminogen activator receptor inhibits ovarian cancer metastasis. *Clinical Cancer Research, 17,* 459–471.

Multidrug Resistance-Linked Gene Signature Predicts Overall Survival of Patients with Primary Ovarian Serous Carcinoma. Scientists found an 11-gene signature that improves prediction of overall survival of ovarian cancer patients whose disease becomes resistant to standard chemotherapy drugs. These 11 new targets offer opportunities for new therapies to improve clinical outcome in ovarian cancer. This program maps to Strategic Plan Goal 1.

Gillet, J. P., Calcagno, A. M., Varma, S., Davidson, B., Bunkholt Elstrand, M., Ganapathi, R., … Gottesman. M. M. (2012). Multidrug resistance-linked gene signature predicts overall survival of patients with primary ovarian serous carcinoma. *Clinical Cancer Research, 18,* 3197–3206.

Risk Factors

Genetic Variants Associated with Risk of Ovarian Cancer. NCI researchers and extramural colleagues conducted a three-phase genome-wide association study to identify single nucleotide polymorphisms (SNPs) associated with variation in the time from diagnosis of invasive epithelial ovarian cancer (EOC) to death. Two SNPs at 19p13.11 (rs8170 and rs2363956) demonstrated genome-wide significance for risk of serous EOC. This program maps to Strategic Plan Goal 1.

Skin Cancer

Risk Factors

SPORE Study Links Indoor Tanning to Basal Cell Carcinoma. A Skin Cancer SPORE investigating the association between indoor tanning and early onset of basal cell carcinoma (BCC) showed that indoor tanning was a strong risk factor for early onset of BCC. The researchers conducted a case-control study of subjects younger than 40 years with BCC and control subjects with minor benign skin conditions. Using multivariate logistic regression with those who never used indoor tanning as the reference group, the investigators reported that indoor tanning was associated with a 69 percent increased risk of early-onset BCC. The association was stronger among women. Risk increased in a dose-dependent manner. In addition, the investigators reported that one-quarter of early-onset BCCs could be prevented if individuals never used indoor tanning salons. This program maps to Strategic Plan Goal 3.

National Eye Institute

Executive Summary

The National Eye Institute (NEI) was created on August 16, 1968, by Public Law 90-489 with the mission to conduct and support research, training, the dissemination of health information, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of blind persons.

The major causes of blindness that affect men and women about equally include glaucoma, macular degeneration, diabetic retinopathy, uveitis, and cataracts; there are several eye conditions that affect women more frequently than men. These conditions are optic neuritis, dry eye, corneal endothelial dystrophy, keratoconus, age-related macular degeneration, idiopathic intracranial hypertension (IIH), and thyroid eye disease.

NEI's research and initiatives in FY 2011–2012 addressed the NIH Strategic Plan for Women's Health Research. For example, they addressed several objectives under Goal 3: "Actualize Personalized Prevention, Diagnostics and Therapeutics for Girls and Women, including:

(7) Conducting developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan (3.1);

(8) Studying sex/gender differences in the aging process (3.6); and

(9) Conducting research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life (3.8)."

NEI studies of hormone factors in such conditions as intracranial hypertension, eye diseases of aging women, and the role of dietary supplements in eye health in aging women are also examples that satisfy the goals and objectives of the Office of Research on Women's Health. Below is a summary of findings from vision research for which significant sex/gender differences were reported during FY2011–2012.

National Eye Institute's Women's Health Research Report

Accomplishments—Highlights

Optic Neuritis

Optic neuritis is an acute debilitating inflammation of the optic nerve that affects more that 25,000 Americans each year, primarily women between the ages of 18 and 45. People with this disease usually have rapid vision loss and ocular pain. The NEI-supported Optic Neuritis Treatment Trial (ONTT) compared oral corticosteroid, intravenous steroid followed by oral corticosteroid, and placebo for the treatment of new cases of optic neuritis. At present, the Longitudinal Optic Neuritis Study (LONS), which follows patients originally enrolled in ONTT, is under way. Taken together, these studies have provided well-established guidelines for treating optic neuritis and established an association between optic neuritis and multiple sclerosis. Results from the ONTT showed that oral corticosteroid, the most common treatment of the disease, when used alone is ineffective in treating the disease and actually increases a person's risk for future attacks; whereas intravenously administered corticosteroids promote more rapid recovery and do not increase the rate of recurrence. However, results from LONS demonstrate that this treatment, although accelerating visual recovery, provides no long-term benefit to vision, and not treating is a viable option. Based on data collected from 2 years of follow-up of patients enrolled in the ONTT, researchers found that treating first-time optic neuritis patients with a combination of intravenous and oral corticosteroids lowers their risk of developing multiple sclerosis in the short term. The results from this research offered the first scientific evidence that intravenous corticosteroids help to delay the short-term progression of multiple sclerosis. However,

long-term follow-up provided by LONS revealed that the effect of corticosteroids in reducing the rate of development of multiple sclerosis was diminished after 3 years of follow-up. This study also demonstrated that the presence of multiple enhancing lesions on the brain MRI (magnetic resonance imaging) scan performed at the time optic neuritis was diagnosed was the single most important predictor of the development of multiple sclerosis within 5 years, and confirmation of these results was provided by LONS. LONS investigators have completed 15-year follow-up examinations of enrolled patients and are in the process of analyzing study data.

Dry Eye

Tears are necessary to maintain the health and comfort of the eye. A lack of sufficient tear fluid is a very common and frequently debilitating condition. Dry eye can result from insufficient secretion of fluid by the lacrimal glands, or from defects in the surface of the eye, mucin or mucous production, or the lipid or fatty components of the tear film. Lacrimal insufficiency is especially associated with immune system disorders, e.g., in Sjögren's syndrome, but it also occurs in association with aging, nerve dysfunction, radiation therapy, and with antidepressant and antipsychotic drug therapy. It is characterized by complaints of eye irritation, eye pain, foreign-body sensation, chronic red eyes, photophobia, fluctuation in vision, or loss of vision.

Lacrimal insufficiencies affect roughly 2 million Americans, and dry eye is the most common complaint of patients in the ophthalmologist's office, with 10 percent to 20 percent of adults in the United States suffering from it. It appears to be more common in women, particularly postmenopausal women, than in men.

Corneal Endothelial Dystrophy

Corneal endothelial dystrophy is a slowly progressing disease of the endothelium that usually affects both eyes and is more common in women than men. Although physicians can often see early signs of the disease in people in their 30s or 40s, the disease rarely affects vision until people reach their 50s or 60s.

The corneal endothelium is a layer of cells that line the inner surface of the cornea. The endothelial cells are responsible for pumping fluid out of the cornea. The cornea is normally clear despite being bathed in tears on the outer surface and in aqueous humor on the inner surface. This clarity is maintained by the endothelial cell layer. If endothelial cells are diseased or absent, permanent corneal edema, loss of corneal transparency, and blindness may eventually occur.

NEI-supported scientists are attempting to determine why endothelial function deteriorates following cell loss, age, or trauma. Delineating the optimal conditions for the tissue culture of corneal endothelium will help evaluate the problems involved in transplanting these cultured cells and assuring their survival. With further refinement of endothelial culture techniques it will be possible to determine whether cell-cycle stimulatory and inhibitory factors arise from other cells and whether the endothelium can be induced to repair itself. Parallel gene therapy studies are being pursued in animals with the aim of developing vectors to deliver factors therapeutically to the eyes of patients with the disease.

Keratoconus

Keratoconus arises when the middle of the cornea thins and gradually bulges outward, forming a rounded cone shape. This abnormal curvature changes the cornea's refractive power, producing moderate to severe distortion (astigmatism) and blurriness (nearsightedness and farsightedness) of vision. These changes may also disrupt the normal light-conducting arrangement of corneal protein, causing swelling and a sight-impairing scarring of the tissue. Keratoconus has become better understood though investigations into the genetic predisposition of the disease, detection of early forms of the disorder through computerized analysis, and advances in understanding the enzymology that underlies corneal thinning. Microarray technology is proving to be highly valuable in developing profiles of diseased tissue and comparing them to those of normal tissue.

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study is an NEI-supported multicenter, observational study designed to characterize the progression of keratoconus over a broad spectrum of disease severity. Information on participants' vision, quality of life, corneal shape, and corneal scarring was collected to characterize the disease throughout its course and to identify risk factors and protective factors that determine the severity and progression of the disease. Study findings demonstrate an association between corneal scarring and decreased vision in keratoconus. A causal connection between wearing a contact lens and corneal scarring was found, suggesting that modifying the lens fit can reduce this risk factor. Investigators are continuing to analyze data and publish study results.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is not only the leading cause of blindness in patients over the age of 65 but is now also the most common cause of blindness in the United States. The incidence of AMD continues to rise in the population as the result of the increasing percentage of elderly persons, with women at 50 percent greater risk than men.

The macula is a specialized region near the center of the retina that is responsible for the high-resolution vision that permits activities such as reading. Degeneration of this region is believed to be the result of a complex set of interactions involving genes/gene products and environmental factors. A high priority has been placed on identifying predisposing genes and their products and then determining what environmental factors cause these gene products to produce the disease or protect against it. One of these factors may be estrogen. According to a recent report in the Archives of Ophthalmology that looked at AMD in women participating in the Nurses' Health Study, women who received hormone replacement therapy after menopause had a 34 percent higher risk of early AMD but a 48 percent lower risk of the late-stage neovascular form of the disease. These findings suggest a role for estrogen in the pathogenesis of AMD that requires further research in specific early and late signs of disease.

The Age-Related Eye Disease Study (AREDS) is a multicenter clinical trial/epidemiologic study designed to assess the clinical course, prognosis, and risk factors for AMD and to evaluate the effects of antioxidants and zinc in slowing the progression of the disease. The study demonstrated that high-dose antioxidant supplements (beta-carotene, vitamins C and E, and zinc) can slow the progression of AMD. Data from AREDS and other studies suggest that lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids might also have benefit in AMD and cataracts. A second study, AREDS 2, is currently under way to test this hypothesis. A multicentered clinical trial, The Complications of Age-related Macular Degeneration Prevention Trial, assessed the safety and efficacy of laser treatment in preventing vision loss in patients in whom the disease is manifested bilaterally. This study recently reported that low-intensity laser treatment was ineffective in preventing complications of AMD or loss of vision.

Idiopathic Intracranial Hypertension

The incidence of idiopathic intracranial hypertension (IIH), which typically occurs in women of childbearing age, is 1/100,000 in normal-weight women and 20/100,000 in obese women. The disease is characterized by an increase in intracranial pressure (>250 mm H2O); the cause is unknown but involves obstruction of cerebral venous outflow. This, in turn, results in transient blurred vision, diplopia, and permanent vision loss. The role that obesity and hormonal changes play in contributing to this disorder is currently being investigated. While some medications and surgical treatments are available, there is no consensus on treatment strategies.

Thyroid Eye Disease

Thyroid eye disease is a manifestation of Graves' disease. The latter is an autoimmune disease that causes hyperthyroidism and tends to affect 2 percent of all women (7:1 ratio of women to men) between the ages of 20 and 40. Excessive thyroxine causes swelling of the muscle and other tissues around the eye, resulting in proptosis (bulging of the eye), corneal exposure, optic nerve

compression, and ultimately loss of vision. Current treatments for thyroid eye disease are only marginally effective, and therefore research into its pathogenic mechanisms and investigations seeking new therapeutic targets are under way.

Glaucoma

Primary open angle glaucoma (POAG) is a leading cause of irreversible blindness worldwide, and yet its pathogenesis remains unknown. The Nurses' Health Study (NHS), supported by various branches of the NIH, has contributed considerably to research on POAG. The NHS started in 1976 when 121,000 registered female nurses from across the United States agreed to complete biennial questionnaires regarding their lifestyle and health. Among women 65 years of age or older, entering menopause at age 54 years or later was associated with a 47 percent reduced risk of POAG compared with entering menopause between 50 and 54. In addition, postmenopausal hormone (PMH) use consisting of estrogen and progesterone was associated with a 42 percent reduced risk of high-tension POAG (IOP [intraocular pressure] >21 mm Hg at the time of diagnosis). Circulating estrogen strongly modulates the expression of endothelial nitric oxide synthase (NOS3). In a gene association study involving participants in the NHS and the Health Professionals Follow-up Study, significant relationships between common NOS3 gene variants and POAG were found in women, but not in men. Furthermore, significant interactions between four NOS3 gene variants and PMH use in high- tension POAG were noted. Finally, anthropometric studies indicated an inverse relation between body mass index (BMI) and the risk of the normal-tension variant of POAG (IOP=21 mm Hg at diagnosis) in women, but not in men. Perhaps higher circulating estrogen levels in women who have a higher BMI contribute to this inverse relationship. Collectively, these data support the notion that circulating estrogen levels play a role in the pathogenesis of POAG.

Women in the NHS and the Genetic Etiologies of POAG (GEP) study contributed DNA specimens to a project aimed at discovering new genes for POAG. The GEP uses a clinic-based sample of POAG cases and controls located mostly in New England. Specimens from NHS and GEP contributed to a genome-wide association study (GWAS) of POAG as part of the Glaucoma Genes and Environment Initiative (GLAUGEN). The NEI funded the formation of the GLAUGEN case-control study group, while the National Human Genome Research Institute supported genotyping efforts. Genotyping in GLAUGEN is complete, quality control filters have been applied, and data analysis is ongoing. A second GWAS within the NEI Glaucoma Human Genetics Collaboration (NEIGHBOR), which consists of approximately 2,000 POAG cases and 2,000 controls, is currently under way. The NEIGHBOR consortium is headquartered at Harvard University and Duke University, with contributing centers at the University of Pittsburgh, University of West Virginia, Johns Hopkins University, University of Miami, University of Michigan, University of California, San Diego, and Stanford University. Vanderbilt University serves as a data analysis center for the NEIGHBOR project. The high-throughput genotyping efforts in GLAUGEN and NEIGHBOR will help define the genetic architecture of POAG. Participants in the Women's Health Study (WHS) will serve to confirm some of the new gene discoveries in GLAUGEN and NEIGHBOR. The WHS consists of over 26,000 women who completed a genome-wide scan and have completed biennial questionnaires regarding lifestyle behavior and health. The identification of POAG cases in WHS is ongoing.

Initiatives

The NEI and the National Advisory Eye Council (NAEC) have established in their strategic plan, "A National Plan for Eye and Vision Research," goals and objectives as well as research priorities for improving visual health and preventing blindness, including research into diseases that have a higher incidence and prevalence among women than among men. These include studies on:

- Optic neuritis—Research priorities are to develop an animal model of this disease to better understand the pathogenesis of

the disorder, to develop immunomodulating therapies to limit optic nerve damage from inflammation, and to understand the relationship between optic neuritis and multiple sclerosis.

- Dry eye—The overall objective is to determine the role of sex hormones in lacrimal gland function. A body of experimental evidence supports the notion that androgen sex hormones and prolactin modulate lacrimal gland function, thus providing an explanation for the observed gender bias of this condition and suggesting hormone modulation as a possible treatment.
- Corneal endothelial dystrophy—Research priorities are aimed at understanding the biologic and functional structures of endothelial cells.
- Keratoconus—An overarching objective is to understand the genetic basis of kerataconus. Identification of gene loci and their encoded proteins should provide clues to the pathogenesis of the disease and suggest new therapies.
- Age-related macular degeneration—Research priorities are aimed at identifying the cellular, molecular, and systemic factors that are involved in the pathophysiology of AMD. Because of the complexity of this disease, studies that use a combination of epidemiology, basic cellular and molecular biology approaches, and genetics are being pursued.
- Glaucoma—Functional tests used to measure vision loss due to glaucoma can be affected by estrogen. Moreover, the thickness of retinal nerve fiber layers appears to be influenced by estrogen levels. A longitudinal study is being conducted to determine the effects of female hormones on these measures of glaucomatous damage.
- Cataracts—A role for estrogen in the pathophysiology of cataract formation has been observed. However, the evidence is unclear as to whether this role is protective or deleterious. Studies are under way to determine how estrogen influences the development of cataracts.

The Women's Health Initiative Observational Study affords the NEI the opportunity to pursue epidemiologic studies in women-only cohorts. This has allowed gender-specific analyses of risk factors in major blinding and debilitating diseases. Approximately 2,000 women from 3 sites participating in the Women's Health Initiative Observational Study were enrolled in the Carotenoids in Age-Related Eye Disease Study (CAREDS). Women aged 50–79 were selected to participate in the study if their dietary intake of lutein plus zeaxanthin was judged to be either high or low. The presence of AMD was assessed by fundus photography. Findings from the CAREDS study include the following:

- Diets rich in lutein and zeaxanthin among women aged less than 75 years may be protective against intermediate AMD.
- High serum concentrations of vitamin D (25 OH) D among women aged less than 75 years may be protective against intermediate AMD.

The NEI has funded a Clinical Study Planning Grant to design a clinical trial examining the role of essential fatty acids (EFA) in the treatment of moderate to severe dry-eye disease (DED). Despite being a widespread, growing problem with serious consequences, at present DED is inadequately treated. Because EFAs have been shown in laboratory studies, animal models, and in some human studies to ameliorate inflammatory reactions and are widely available over-the-counter they are gaining in popularity as a treatment to combat or prevent diseases associated with inflammation, including DED. But as with any treatment, results of a large, randomized double-blind clinical trial are needed to assess efficacy and safety. The current project is attempting to lay the groundwork for a definitive trial.

The NEI is working with the National Institute of Dental and Craniofacial Research and the ORWH to enhance research opportunities in the diagnosis, epidemiology, and treatment of Sjögren's syndrome.

- The NEI is cofunding a NIDCR initiative for the development of an International Sjögren's Syndrome Registry. The ultimate

goal of the registry is to promote cutting-edge research in the area of Sjögren's syndrome, with emphases on diagnosis, epidemiology, causes, prevention. and treatment. The coordinating center is at University of California, San Francisco, and multiple international sites (USA, Argentina, China, Denmark, Japan, and United Kingdom) have been established. There is a plan to add India as a site pending approval of the Indian government. All sites have started accruing patients, which includes the use of the standardized "Baseline Eye Exam Form" and a "Baseline Eye Exam Standard Operating Procedures" developed by the consortium.

- The NEI is working with the ORWH to evaluate different diagnostic and treatment options for idiopathic intracranial hypertension (IIH) and thyroid eye disease (Graves' disease).

The NEI is supporting the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC), which is prepared to conduct clinical studies on two neuro-ophthalmology-related diseases that occur predominantly in women. These are IIH and thyroid eye disease (Graves' disease). The objective is to provide a unique opportunity to recruit and study enough hard-to-find patients to generate statistically significant findings about the utility of different diagnostic and treatment options.

National Heart, Lung, and Blood Institute

Executive Summary

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives. To achieve this vision, NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, encourages the training and mentoring of emerging scientists and physicians, and communicates research advances to the public. NHLBI creates and supports a robust, collaborative research infrastructure in partnership with private and public organizations, including academic institutions, industry, and government agencies. NHLBI collaborates with patients, families, health care professionals, scientists, professional societies, patient advocacy groups, community organizations, and the media to maximize the use of research results and leverage resources to address the public health needs of the Nation.

NHLBI places high priority on enhancing the health of women by reducing the burdens of cardiovascular, lung, and blood diseases. As articulated in its Strategic Plan (*http://apps.nhlbi.nih.gov/strategicplan*), the Institute's broad goals are to improve understanding of the molecular and physiological basis of health and disease and use that knowledge to develop better approaches to disease diagnosis, treatment, and prevention; to improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis, and treatment; and to generate a clearer understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

For many years the NHLBI has been diligent in ensuring that its clinical research projects include adequate representation of women and that its overall research portfolio addresses gaps in knowledge of how to diagnose, prevent, and treat disease in women. This effort has included not only careful monitoring of recruitment for clinical trials and other studies but also the support of certain studies conducted entirely in cohorts of women.

In addition to supporting its own extensive portfolio of activities of importance to women's health, NHLBI has, since FY 1998, borne administrative responsibility for the NIH Women's Health Initiative. Recent activities are described herein.

This report also highlights a variety of research results, new programs and solicitations, and educational activities in areas of women's health that align with the Institute's mission. Especially noted are NHLBI's efforts to explore sex differences in the basic biology and physiology of the cardiovascular and respiratory systems and the etiology, pathology, and outcomes of diseases.

NHLBI Entities with a Designated Focus on Women's Health

The NIH Women's Health Initiative is administered by the NHLBI through its Division of Cardiovascular Sciences.

The NHLBI Office of Communications has responsibility for The Heart Truth.

Accomplishments

The Women's Health Initiative

The Women's Health Initiative (WHI) is a major long-term research program designed to address the most frequent causes of death, disability, and diminished quality of life in postmenopausal women: cardiovascular disease (CVD), cancer, and osteoporosis. WHI enrolled more than 160,000 women in clinical trials and an observational study, all of which have been completed.

The original protocol allowed for follow-up until March 2005, but participants were subsequently invited to enroll in the WHI Extension Study for continued observation through 2010.

A further 5-year extension began October 1, 2010, with more than 93,000 enrollees. Its main objectives are to take advantage of the large WHI cohort to explore factors contributing to CVD burden in aging women; increase data sharing; launch a new generation of ancillary studies, consortium studies, and clinical trials; and increase mentoring of new investigators. Extensive work has been performed to validate clinical outcomes found in databases of the Centers for Medicare & Medicaid Services against those reported in the WHI, with an eye toward future clinical research and health care utilization studies.

The WHI Long Life Study, launched in 2012, conducted in-person visits with 8,000 older WHI participants. The data and blood collected in this study will establish a new baseline from which numerous studies on aging and health/disease can be initiated. A brief clinical assessment will be conducted on all participants, including an assessment of functional status. A closely related ancillary study, Objective Physical Activity and Cardiovascular Health in Women Aged 63 and Older, has been funded. Its goals are to increase understanding of the health of aging women and, specifically, to shed light on the association of physical activity with CVD events and total mortality.

The WHI has also provided support for solicited research using blood, DNA, and other biological samples and clinical data from WHI participants. The studies help explain the clinical trial findings and will investigate the influence of genetic and biological markers on common diseases affecting postmenopausal women. For instance, a study initiated in FY 2011 is examining plasma samples of participants in the WHI hormone therapy trials (see below) to look for proteins believed to be linked to coronary heart disease (CHD) and stroke. Investigators will evaluate how these biomarkers change as a result of postmenopausal hormone therapy and how the changes relate to the observed effects of postmenopausal estrogen and estrogen plus progestin (E+P) on the risk for CHD and stroke.

(This work is supported through PAS-10-226, Advancing Novel Science in Women's Health Research, cosponsored by ORWH.)

A solicitation for research projects focused on systems biology and CVD and aging was released in 2012, with an anticipated award date in early 2013.

The WHI included two randomized clinical trials of postmenopausal hormone therapy—a study of E+P in women who had an intact uterus and a study of estrogen alone in women who had undergone a hysterectomy. Both were designed to test the hypothesis that long-term use of hormone therapy could reduce risk of CHD. The E+P trial was halted ahead of schedule in July 2002. Compared

with women taking a placebo, participants taking hormones experienced higher rates of heart attack, stroke, blood clots, and invasive breast cancer. Although the women taking hormones had a lower incidence of colon cancer and fewer hip fractures, the overall balance of risks and benefits was unfavorable. In March 2004, the estrogen-alone trial also was halted ahead of schedule. After an average of nearly 7 years of treatment, estrogen therapy had no effect on CHD risk, but it increased risk of stroke and of blood clots in the legs. No evidence of elevated breast cancer risk was found, and a favorable effect on bone health emerged. On balance, however, the trial indicated that postmenopausal hormone therapy should not be prescribed for the prevention of chronic disease. Following release of these findings, use of postmenopausal hormone therapy in the United States declined dramatically.

Subsequent analysis of additional data from women enrolled in the E+P trial showed that the elevated breast cancer risk at the end of the trial decreased rapidly after hormone therapy was stopped. The declines in breast cancer incidence were unrelated to changes in the frequency of mammograms. Continued study of the cardiovascular effects of postmenopausal hormone therapy confirmed the short-term risks associated with E+P treatment. Researchers reported a trend toward an increased risk of heart disease during the first 2 years of hormone therapy among women who began therapy within 10 years of menopause and a more marked elevation of risk among women who began hormone therapy more than 10 years after menopause.

Investigators have published new data on health outcomes experienced by women in the estrogen-alone trial. This report of follow-up after the trial was halted includes nearly 4 additional years, for an average total of 11 years. Investigators found that the excess risks of stroke and of blood clots disappeared during follow-up. Estrogen use during the trial did not significantly affect the subsequent risk of death, CHD, colorectal cancer, or hip fractures; moreover, it was associated with a statistically significant decrease in the risk of breast cancer. Health outcomes were better for younger women than for older women—women in their 50s had reduced risks of heart attack, overall illness, and death, whereas women in their 70s fared worse on several measures of health. This study provides important new information to guide treatment decisions, particularly for younger women who have had a hysterectomy and contemplate short-term use of estrogen to relieve menopausal symptoms.

LaCroix, A. Z., Chlebowski, R. T., Manson, J. E., Aragaki, A. K., Johnson, K. C., Martin, L., … Wactawski-Wende, J.; WHI Investigators. (2011). Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: A randomized controlled trial. *JAMA, 305*, 1305–1314.

Analysis of WHI data continues to yield numerous publications on health issues of concern to postmenopausal women, such as CHD, heart failure, hypertension, nutrition, venous thromboembolism, diabetes, breast and other cancers, osteoporosis, and cognitive function.

The Heart Truth®

The Heart Truth is a national campaign to promote heart disease prevention among women. Its objectives are to raise awareness that heart disease is a serious health issue for U.S. women, increase knowledge of the risk factors that render women susceptible to heart disease, and encourage women to talk to their doctors, learn their personal risk, and take action to reduce it. The campaign uses the iconic Red Dress® to impart the message "Heart Disease Doesn't Care What You Wear—It's the #1 Killer of Women." Sponsored by NHLBI, The Heart Truth collaborates closely with other components of HHS, including CDC and the HHS Office on Women's Health.

The Heart Truth conducts outreach to engage partners in community, corporate, and media sectors that count women among their core audience and can amplify the campaign's messages and support national promotional programming and outreach. To date, the campaign has established partnerships with more than 50 corporations, including Burlington Coat Factory, Diet Coke, Johnson & Johnson,

General Mills, TimeWarner, Swarovski, Albertsons, and American Express. Through its partnerships, the campaign has secured promotional programming that reaches millions of women via on-pack promotions and advertising with Diet Coke, Cheerios, Campbell's Soups, Bobbi Brown, Hamilton Beach, and Celestial Seasonings. The campaign has ongoing relationships and outreach programs with more than 25 national and local community organizations, including WomenHeart: the National Coalition for Women with Heart Disease, the American Heart Association, the American College of Cardiology, the General Federation of Women's Clubs, and Hadassah. It has several women-of-color and faith-based initiatives with organizations such as The Links, Inc.; the National Black Nurses Association; the Association of Black Cardiologists, Inc.; the National Coalition of Pastors' Spouses; and the National Latina Health Network. It has developed partnerships with numerous media outlets or publications over the years, including Newsweek; Glamour; Lifetime; Essence; Siempre Mujer; Woman's Day; AOL Inc.; Time, Inc.; Prevention; and BET Networks.

As part of a public-private partnership between NHLBI and the Foundation for the National Institutes of Health, the Community Action Grant Program empowers community organizations to assist women—especially those of color, low income, or rural residence—in identifying personal risk factors for heart disease and motivating them to take steps to lower their risk. The Heart Truth Champions Program, supported by the HHS Office on Women's Health, trains and equips health educators and women's health advocates to plan and implement heart health awareness and education programs in their communities.

Over the past decade, The Heart Truth has produced a comprehensive set of educational materials to help women talk with their doctors and control risk factors for heart disease, with these materials including a wallet card, the "Healthy Heart Handbook for Women," a speaker's kit, fact sheets, and information graphics. In addition, the campaign launched and maintains a Web page (*http://www.hearttruth.gov*) that includes resources and a National Wear Red Day online toolkit to encourage individuals and organizations nationwide to share The Heart Truth and Red Dress activity ideas. The campaign also created a faith-based toolkit for women to use as a guide for conducting The Heart Truth activities in their communities. Most recently, the campaign has expanded its reach via social media, including Facebook and Twitter.

(These activities address the NIH Strategic Plan for Women's Health Research, Goal 5: Develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health and wellness research; Objective 5.3: Expand strategic alliances and partnerships with key national and international organizations to maximize the communication and impact of women's health research.)

Cardiovascular Diseases

Statistics on Sex and Gender Similarities and Differences

Recent national health statistics provide the following snapshot of sex/gender similarities and differences in CVD:

- Diseases of the heart constitute the leading cause of death for both women and men in the United States, accounting for 24 percent of deaths among women and 25 percent among men. The age-adjusted death rates (per 100,000 population) attributed to heart disease are 143 for women and 225 for men.
- Age-adjusted death rates for CHD, the most prevalent form of heart disease in the United States, are 85 for women and 151 for men. The median age at death from CHD is 84 for women and 76 for men.
- Sex/gender differences are apparent in other measures of CHD prevalence. Angina pectoris affects slightly more women than men under the age of 65 but more men (9 percent) than women (7 percent) at ages 65 and over. Emergency department visit rates (per 10,000 population, age-adjusted) for CHD are 21 for women and 30 for men. The percentage

of patients under age 65 hospitalized for acute myocardial infarction who die before discharge is markedly higher in women (6 percent) than men (3 percent); among those aged 65 or older, it is slightly higher in women (11 percent) than men (10 percent).

- Cerebrovascular disease (stroke) constitutes the third most common cause of death for women in the United States (6 percent of deaths) and the fifth most common cause of death for men (4 percent of deaths). Age-adjusted stroke death rates (per 100,000 population) are 38 for women and 39 for men. The median age at death from stroke is 84 in women and 78 in men.

Heart diseases and cerebrovascular diseases share many risk factors such as hypertension, dyslipidemia, smoking, diabetes, and obesity. Prevalence data for such risk factors in the United States by sex are the following:

- Hypertension—32 percent of women and 34 percent of men
- High LDL (low-density lipoprotein ["bad"]) cholesterol—39 percent of women and 32 percent of men; low HDL (high-density lipoprotein ["good"]) cholesterol—12 percent of women and 32 percent of men
- Cigarette smoking—17 percent of women and 21 percent of men
- Diabetes (physician-diagnosed)—8 percent of women, 9 percent of men; prediabetes—31 percent of women, 46 percent of men
- Obesity—36 percent of women, 34 percent of men

Women's Ischemia Syndrome Evaluation (WISE)

In 1996, the NHLBI began WISE, a study of over 900 women referred for angiography because they had experienced symptoms such as chest pain and shortness of breath that suggested they might have CHD. The study originally found that half of the women did not have coronary artery obstructions, and yet many of them continued to have debilitating symptoms or went on to have heart attacks. Recent NHLBI-funded work has extended these observations. For example, researchers used intravascular ultrasound to study coronary artery morphology in 100 women whose angiograms had shown no significant obstructions. They found evidence of atherosclerosis in coronary segments of 79 percent of the women. Risk factors for CHD, especially age, were strongly correlated with the amount and extent of atherosclerosis.

Khuddus, M. A., Pepine, C. J., Handberg, E. M., Bairey Merz, C. N., Sopko, G., Bavry, A. A., … Anderson, R. D. (2010). An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: A substudy from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *Journal of Interventional Cardiology, 23*, 511–519.

Another study examined levels of dehydroepiandrosterone sulfate (DHEA-S), which is secreted primarily by the adrenal glands and is the most abundant endogenous steroid hormone in women and men. Women who had the lowest DHEA-S levels had greater CVD mortality and all-cause mortality than women with higher levels, suggesting that DHEA-S might be predictive of CVD in women or a possible therapeutic target.

Shufelt, C., Bretsky, P., Almeida, C. M., Johnson, B. D., Shaw, L. J., Azziz, R., … Bairey Merz, C. N. (2010). DHEA-S levels and cardiovascular disease mortality in postmenopausal women: Results from the National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *The Journal of Clinical Endocrinology & Metabolism, 95*, 4985–4992.

Heart Attack in Young Women

Young women hospitalized with heart attacks are twice as likely as young men to die before discharge, but the reasons for this gender difference are unknown. An NHLBI-funded observational study titled Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) is examining factors that may predispose

younger women to having heart attacks and experiencing poorer outcomes. The study is following 2,000 women and 1,000 men, all of them 18–55 years of age, who were hospitalized with a heart attack. The researchers are collecting data on biologic, demographic, psychosocial, environmental, and behavioral factors that may affect CHD risk and recovery after a heart attack. They also are seeking to determine whether women and men receive different care following a heart attack. The trial is expected to conclude in 2013. (*http://clinicaltrials.gov/ct2/show/NCT00597922*)

The Women's Health Study (WHS)

The WHS is a randomized, placebo-controlled clinical trial that was designed primarily to evaluate the use of low-dose aspirin and vitamin E to prevent CVD and cancer. About 40,000 women who were 45 years of age or older were enrolled from 1992 to 1995 and followed for 10 years. In FY 2005, the WHS was extended through 2010 to enable further evaluation of clinical issues related to CVD risk in women. The WHS constitutes a rich source of data for exploring a range of important research questions, and many significant findings have been reported.

Investigators have found that dietary marine, but not plant-based, omega-3 (n-3) fatty acids may influence the development of type 2 diabetes. The study involved 36,328 women who participated in the WHS and were followed from 1992 to 2008. During an average follow-up of more than 12 years, 2,370 of them were diagnosed with type 2 diabetes. Those who consumed the highest levels of marine n-3 fatty acids had the highest risk of developing the disease. The relation between consumption of marine omega-3 fatty acids and diabetes was observed in both hypertensive and nonhypertensive women and in those who reported infrequent fish consumption. The results indicate that further studies may be needed to determine risks versus benefits of omega-3 fatty acids.

Djoussé, L., Gaziano, J. M., Buring, J. E., & Lee, I. M. (2011). Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes (2011). *American Journal of Clinical Nutrition, 93*, 143–150.

A study of the relationships between work-related stress and CVD has shed light on the long-term effects of job strain and job insecurity in women. It found that women with highly demanding jobs were about 40 percent more likely to experience a CVD event than were women with less demanding jobs, regardless of their perceived control in the job setting. On the other hand, job insecurity did not appear to increase CVD risk. Given the high number of women in the workplace, the results suggest that strategies to reduce job strain may play an important role in reducing CVD in women.

Slopen, N., Glynn, R. J., Buring, J. E., Lewis, T.T., Williams, D. R., & Albert, M. A. (2012). Job strain, job insecurity, and incident cardiovascular disease in the Women's Health Study: Results from a 10-year prospective study. *PLOS ONE, 7*, e40512.

One of the largest genetic studies involving WHS participants is the Women's Genome Health Study (WGHS), which is performing blood-based analyses to identify genetic factors that influence disease susceptibility. Its goal is to improve understanding and prediction of CVD development and outcomes as well as of health conditions that constitute major CVD risk factors (e.g., hypertension, metabolic syndrome). WGHS also seeks to evaluate genotype-phenotype interactions and shed light on interrelationships among multiple CVD risk factors in the prediction of CVD events. A recent study focused on hypertension, building upon previous genome-wide association studies that found multiple loci that appear to be associated with blood pressure levels. In an effort to validate these findings by replication in a single large, homogeneous, population-based cohort, investigators examined the association of numerous single-nucleotide polymorphisms, all established in previous studies, with blood pressure in 23,019 women from WGHS. They validated most of the previously studied loci and found a new locus in a region adjacent to a gene called BLK-GATA4. The results of this study suggest the possibility of genetic screening to detect the risk for hypertension in women as well as new targets for treatment strategies.

Ho, J. E., Levy, D., Rose, L., Johnson, A. D., Ridker, P. M., & Chasman, D. I. (2011). Discovery and replication of novel blood pressure genetic loci in the Women's Genome Health Study. *Journal of Hypertension, 29*, 62–69.

Abdominal Aortic Aneurysm

Abdominal aortic aneurysms (AAAs) are characterized by localized ballooning of the abdominal aorta, which may rupture, potentially leading to death in minutes. AAAs are more common in men than in women, but the reasons for this differential are not well understood. In one study, investigators induced experimental AAA formation in male and female mice by using a protein from pigs called pancreatic elastase. AAA development was much less common in females than in males. When the experiment was repeated using female mice deficient in plasmin activator inhibitor-1 (PAI 1), the females developed AAA at a rate similar to that in the male mice, suggesting that PAI-1 protects females from AAA in this model and plays a role in the sex differences observed in the development of AAA. In a second study, investigators found that exposing 1-day-old female mice to a single dose of testosterone rendered them much more likely to develop AAA as adults.

DiMusto, P. D., Lu, G., Ghosh, A., Roelofs, K. J., Su, G., Zhao, Y., … Upchurch, G. R. Jr. (2012). Increased PAI-1 in females compared with males is protective for abdominal aortic aneurysm formation in a rodent model. The American Journal of Physiology—Heart and *Circulatory Physiology, 302*, H1378–1386.

Zhang, X., Thatcher, S. E., Rateri, D. L., Bruemmer, D., Charnigo, R., Daugherty, A., & Cassis, L. A. (2012). Transient exposure of neonatal female mice to testosterone abrogates the sexual dimorphism of abdominal aortic aneurysms. *Circulation Research, 110*, e73–85.

(This research addresses the NIH Strategic Plan for Women's Health Research, Goal 1: Increase sex differences research in basic science studies; Objective 1.4: Include sex parameters in the design of experiments using animal models.)

Implantable Cardioverter Defibrillators (ICDs)

ICDs, normally placed in the chest or abdomen, are programmed to detect arrhythmias and then deliver a substantial electrical shock to restore normal heart rhythm. Research has shown that women, more than men, tend to develop significant anxiety in anticipation of the electrical shocks. The Female-Specific Education, Management, and Lifestyle Enhancement for Implantable Cardioverter Defibrillator Patients (FEMALE-ICD) Study evaluated the effectiveness of a women-specific psychosocial group intervention to alleviate such distress. It found that women who received education about ICDs, cognitive behavioral therapy strategies, and group social support had lower shock anxiety and greater device acceptance. The study suggests that such interventions should be considered as part of the overall treatment plan for women receiving ICDs.

Vazquez, L. D., Conti, J. B., & Sears, S. F. (2010). Female-specific education, management, and lifestyle enhancement for implantable cardioverter defibrillator patients: The FEMALE-ICD study. *Pacing and Clinical Electrophysiology, 33*, 1131–1140.

Cardiomyocyte Function

Investigators used magnetic resonance imaging (MRI) to evaluate sex-based differences in cardiomyocytes (heart muscle cells). In a study of the left ventricle of the heart in 60 normal adult volunteers (32 women, 28 men), researchers measured the contractile characteristics of the cardiomyocytes and found that the cells in women had a greater average change in length and circumference during contraction than those in men. This finding sheds light on the differences between women and men in pathologic changes that occur during the onset and development of cardiac disease. Further work may ultimately provide explanations for sex differences in CVD outcomes.

Lawton, J. S., Cupps, B. P., Knutsen, A. K., Ma, N., Brady, B. D., Reynolds, L. M., & Pasque, M. K. (2011). Magnetic resonance imaging detects significant sex differences in human myocardial strain. *BioMedical Engineering OnLine, 10*, 76.

Right Ventricular Structure and Function

Investigators in the Multi-Ethnic Study of Atherosclerosis (MESA) have found sex- and race-based differences in the structure and function of the right ventricle (RV) of the heart. The RV is the chamber that sends deoxygenated blood to the lungs, where it becomes oxygenated. Using cardiac MRI, investigators measured the RV mass, volume, and ejection fraction in 4,123 men and women who were free of clinical CVD. They found that the men studied had greater RV mass and larger RV volume than the women, but the women typically had a larger ejection fraction. Black participants had lower RV mass than Whites, and Hispanics had higher RV mass than Whites. The results suggest that sex and race differences in RV morphology might explain some of the differences observed in CVD manifestations among population subgroups.

Kawut, S. M., Lima, J. A., Barr, R. G., Chahal, H., Jain, A., Tandri, H., … Bluemke, D. A. (2011). Sex and race differences in right ventricular structure and function: The multi-ethnic study of atherosclerosis-right ventricle study. *Circulation, 123*, 2542–2551.

Heart Transplant Donor–Recipient Matching

For some patients with conditions such as advanced coronary artery disease, cardiomyopathy, heart valve disease, or congenital heart defects, the only hope for survival may be a heart transplant. Although prior studies have attempted to understand the relationship between the sex of the donor and the sex of the recipient in terms of how it affects posttransplant survival, results have been inconclusive. In a recent study, investigators analyzed the outcomes for 60,584 adult recipients of heart transplants performed between 1990 and 2008. They concluded that higher success rates are obtained when the sex of the donor and recipient are matched. Women who received hearts from female donors had 10 percent lower mortality than women who received hearts from male donors. Similarly, men had better survival rates when receiving hearts from male, rather than female, donors. These results add to the body of knowledge about sex-related differences in heart transplantation outcomes.

Khush, K. K., Kubo, J. T., & Desai, M. (2012). Influence of donor and recipient sex mismatch on heart transplant outcomes: Analysis of the International Society for Heart and Lung Transplantation Registry (2012). *The Journal of Heart and Lung Transplantation, 31*, 459–466.

Psychosocial Factors in Heart Disease

Growing evidence indicates that psychosocial factors play an important role in the development of heart disease in women. Investigators conducted an analysis of available data from previous studies that included at least 100 women in order to evaluate negative effects related to emotions, stress, and social relationships as well as the effects of positive psychological factors. Results of the analysis showed that factors such as depression, anxiety disorders, suppression of anger, and the stress associated with relationships or family responsibilities were all linked to elevated risk of heart disease in women. Furthermore, positive psychological factors and supportive relationships were found to be associated with decreased risk. The investigators also found that factors such as general anxiety, hostility, and work-related stress were less likely to be associated with heart disease in women than in men. Results of this analysis may be beneficial in identifying women at higher risk for heart disease and in developing positive psychological strategies to help lower the risk for women.

Low, C. A., Thurston, R. C., & Matthews, K. A. (2010). Psychosocial factors in the development of heart disease in women: Current research and future directions. *Psychosomatic Medicine, 72*, 842–854.

Intimate Partner Violence and Hypertension

An analysis of data from 51,434 women enrolled in the Nurses' Health Study II has shed light on the effects of emotional abuse, physical abuse, and sexual abuse on the development of high blood pressure/hypertension. Although 22 percent of participants reported being physically hurt and 10 percent

reported being forced into sexual activities during adulthood by an intimate partner, neither physical nor sexual abuse was associated with hypertension. However, women who reported severe emotional abuse had a 24-percent higher rate of hypertension than women unexposed to emotional abuse. The results provide further impetus for development of strategies to prevent abuse of women and mitigate its effects.

Mason, S. M., Wright, R. J., Hibert, E. N., Spiegelman, D., Forman, J. P., & Rich-Edwards, J. W. (2012). Intimate partner violence and incidence of hypertension in women. *Annals of Epidemiology, 22*, 562–567.

Over-the-Counter Phytoestrogens and CVD Risk

Although a number of women use over-the-counter phytoestrogens not only to relieve menopausal vasomotor symptoms but also to protect against CVD, efficacy data are lacking. Use of genistein, the most common soy-derived phytoestrogen, appears to have some beneficial influence on vascular reactivity and endothelial function in healthy women but perhaps not in women with insulin resistance. A new research project titled Phytoestrogens, Insulin Resistance, and Endothelial Function will study the effects of genistein on microvascular reactivity both in healthy women and in women with insulin resistance. The results should help women make better-informed choices about using phytoestrogens.

(This award resulted from the solicitation PAS-10-226, Advancing Novel Science in Women's Health Research, cosponsored by ORWH.)

Long QT Syndrome

Certain genetic mutations found in patients with long QT syndrome type 1 (LQT1), a rare inherited disorder that affects heart rhythm, are associated with a particularly high risk of sudden death. LQT1 is more prevalent in women than in men, but young men have the highest mortality rate overall. The syndrome can be caused by numerous different mutations that affect an ion channel found on heart muscle cells. Although all mutations affect the same channel, their specific effects on channel function vary. Researchers gathered genetic and clinical data from 387 patients with LQT1, measured the effects of 17 different LQT1 mutations on ion channel function, and correlated the findings with patient outcomes. Mutations that caused the ion channel to open more slowly than normal were associated with a higher risk for sudden death than mutations that did not affect the rate of channel opening. Risk assessment for patients with LQT1 is currently based on factors such as age, gender, and the heart's electrical activity. The new findings should enhance risk assessment for LQT1 patients and help doctors identify patients who might benefit from closer follow-up and more aggressive treatment.

Jons, C., O-Uchi, J., Moss, A. J., Reumann, M., Rice, J. J., Goldenberg, I., … Lopes, C. M. (2011). Use of mutant-specific ion channel characteristics for risk stratification of long QT syndrome patients. S*cience Translational Medicine, 3*, 76ra28.

Preeclampsia

Investigators have found a link between preeclampsia and reduced activity of an enzyme called corin. Pregnant women with preeclampsia had lower uterine corin levels than women with normal pregnancies. The researchers also identified two mutations in the corin gene that reduce enzyme activity in preeclamptic patients. Using genetically engineered mice, investigators determined that corin was involved in new blood vessel formation at the maternal-fetal interface of the placenta and that loss of corin from the uterus led to impaired blood vessel formation, which caused preeclampsia-like symptoms in mice. Preeclampsia is diagnosed when a pregnant woman develops high blood pressure and protein is found in the urine after 20 weeks of pregnancy. It occurs in about 10 percent of all pregnancies and, if left untreated, can develop into eclampsia, which may lead to seizures and death of the mother and/or fetus. The study results could lead to new approaches, specifically those targeting corin, for the treatment of preeclampsia.

Cui, Y., Wang, W., Dong, N., Lou, J., Srinivasan, D. K., Cheng, W., … Wu, Q.

(2012). Role of corin in trophoblast invasion and uterine spiral artery remodeling in pregnancy. *Nature, 484,* 246–250.

(This research addresses the NIH Strategic Plan for Women's Health Research, Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women; Objective 3.4: Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.)

Weight Perception

Investigators in the META-Health Study (Morehouse and Emory Team Up to Eliminate Cardiovascular Health Disparities) examined gender and racial differences in obesity, with an eye toward understanding its very high prevalence in Black women. In particular, they considered the extent to which Black and White women and men differed in the accuracy of their perceptions of their own body weight. Participants were asked to describe themselves as underweight, about the right weight, overweight, or obese, and the results were compared with an objective assessment that categorized their weight as normal, overweight, or obese based on body mass index (BMI) or waist circumference. Blacks were far more likely than Whites to underestimate their weight status, even when sociodemographic characteristics, lifestyle factors, and medical history were taken into account, and most of the racial difference was attributed to weight misperception by the Black women in the study. The findings suggest a need to identify the cultural, social, and environmental factors that give rise to this discrepancy in recognizing overweight or obesity and to develop suitable targets for intervention.

Hendley, Y., Zhao, L., Coverson, D. L., Din-Dzietham, R., Morris. A., Quyyumi, A. A., … Vaccarino, V. (2011). Differences in weight perception among blacks and whites. *Journal of Women's Health (Larchmont), 20,* 1805–1811.

Diet, Physical Activity, and Quality of Life

A study of employees in small blue-collar and service industry worksites in Seattle, WA, has provided information about how dietary behaviors, physical activity, and BMI relate to weight-specific quality of life and work productivity. Investigators collected information on participants' intake of fruits and vegetables, behaviors such as fast-food consumption, physical activity, height and weight, and scores on measures of quality of life and work limitations. They found that higher BMI was associated with lower quality of life in both women and men, but it was associated with productivity loss only in women. Men who ate while doing another activity had reduced quality of life, whereas women who did so had reduced productivity. Fast-food meals were associated with reduced productivity in men only. The results add to existing evidence about the deleterious effects of obesity in the workplace and reinforce the need for gender-specific investigations to inform the development of effective interventions.

Cash, S. W., Beresford, S. A., Henderson, J. A., McTiernan, A., Xiao, L., Wang, C. Y., & Patrick, D. L. (2012). Dietary and physical activity behaviours related to obesity-specific quality of life and work productivity: Baseline results from a worksite trial. *British Journal of Nutrition, 108,* 1134–1142.

Caffeinated Beverages and Cognitive Decline

Investigators examined the relationship between caffeine consumption and cognitive performance in 4,809 participants, 65 years of age or older, who were enrolled in the Cardiovascular Health Study. A food-frequency questionnaire was used to determine caffeine consumption, and Modified Mini-Mental State exams measured cognitive function. After factors such as age, education, smoking, diabetes, hypertension, and depression were taken into account, the study found somewhat lower rates of cognitive decline for some levels of coffee and tea consumption in women, but no consistent effect in men. Further study is needed to determine whether the results seen in women were caused directly by caffeine consumption or influenced by other, undetermined factors.

Arab, L., Biggs, M. L., O'Meara, E. S., Longstreth, W. T., Crane, P. K., & Fitzpatrick, A. L. (2011). Gender differences in tea,

coffee, and cognitive decline in the elderly: The Cardiovascular Health Study. *Journal of Alzheimer's Disease, 27,* 553–566.

Lung Diseases

Chronic Obstructive Pulmonary Disease (COPD)

Chronic lower respiratory diseases, which include COPD and asthma, constitute the fourth most common cause of death for both women and men in the United States, accounting for 6 percent of deaths among women and 5 percent among men. Age-adjusted death rates per 100,000 population are 38 for women and 49 for men. The median age at death from COPD is 79 for women and 78 for men.

A recent analysis of data from the WHS has shed light on the relationship between intake of antioxidants and development of chronic lung disease. Investigators conducted an analysis of 38,597 women without chronic lung disease at baseline to test the effect of vitamin E supplementation on the risk of developing chronic lung disease, including COPD and asthma. During 10 years of follow-up, 3.9 percent of women assigned to take vitamin E pills reported first occurrences of diagnosed chronic lung disease, compared with 4.4 percent of women who were given placebo pills. This reduction of about 10 percent in the risk of chronic lung disease was independent of cigarette smoking, age, randomized aspirin assignment, multivitamin use, or dietary intake of vitamin E, suggesting that vitamin E supplementation may be beneficial for some women in reducing COPD risk.

Agler, A. H., Kurth, T., Gaziano, J. M., Buring, J. E., & Cassano, P. A. (2011). Randomised vitamin E supplementation and risk of chronic lung disease in the Women's Health Study. *Thorax, 66,* 320–325.

The COPD Learn More Breathe Better® campaign, led by NHLBI in partnership with professional societies and advocacy organizations, is directed toward women and men over 45 years of age. The campaign seeks to increase awareness of COPD and understanding that the disease is treatable, and it encourages people at risk to get a simple breathing test and talk with their doctors about treatment options. It emphasizes that COPD is now as much of a problem for women as for men and that former or current smokers and people with risk associated with genetics or environmental exposures are particularly vulnerable. The Breathe Better Network supports organizations representing States, cities, and communities that are engaged in COPD education and awareness through the campaign.

Asthma

In childhood, boys have a higher rate of asthma than girls, but after puberty, females are more likely to be affected. New research has found that the sex differences in asthma, and possibly other airway diseases, may be due to the effect of the female hormone progesterone (P4) on the mucociliary apparatus of the airway. Investigators isolated human airway epithelial cells from male and female lung transplant donors and examined how P4 altered the movement of the cilia, which are found on the cell surface and which normally clear mucus from the airway. They found that P4 attached itself to receptors on the cell surface and slowed the motion of the cilia in both male and female cells. Moreover, the P4 inhibition of ciliary motion was reversed by adding the active form of estrogen,17β-estradiol. The results suggest that female hormones can influence the function of airways cilia, both negatively and positively, and may contribute to the disparity between men and women in asthma prevalence.

Jain, R., Ray, J. M., Pan, J. H., & Brody, S. L. (2012). Sex hormone-dependent regulation of cilia beat frequency in airway epithelium. *American Journal of Respiratory Cell and Molecular Biology, 46,* 446–453.

Blacks, especially Black women, fare worse than Whites on all measures of asthma morbidity, but the reasons for this disparity are not well understood. Previous studies of children have identified psychosocial factors such as experiencing violence and living in inner-city neighborhoods as having a role in asthma prevalence and severity, but similar studies are lacking in adults. An NHLBI-funded project begun in FY 2012 will assess the contribution of psychosocial factors, including violence, racism, depression,

neighborhood socioeconomic status, racial segregation, and urbanicity, to the high incidence of asthma in Black women. The study will use data from the Black Women's Health Study, a cohort established in 1995 that includes about 59,000 Black women from across the United States. Results are expected to improve understanding of the risk factors associated with adult asthma, identify reasons for racial and sex disparities in its appearance, and inform the development of effective preventive strategies at individual and societal levels.

Lymphangioleiomyomatosis (LAM)

LAM is a rare lung disease that affects women of childbearing age almost exclusively, causing abnormal muscle-like cells to grow out of control in certain organs or tissues, especially the lungs, lymph nodes, and kidneys. Over time, the LAM cells can proliferate throughout the lungs and destroy normal tissue, leading to shortness of breath, cough, chest pain, and, in many cases, eventual respiratory failure. Research has linked some cases of LAM with tuberous sclerosis complex, a genetic disorder characterized by formation of noncancerous tumors throughout the body.

A clinical trial has found that sirolimus, a drug currently used to prevent transplant rejection, can improve lung function and quality of life in individuals with LAM. Participants in the study took daily oral doses of sirolimus or placebo for 12 months and had their lung function measured at regular intervals. The sirolimus group had stable lung function during the treatment period, whereas lung function declined about 12 percent in the placebo group. After sirolimus treatment was stopped, however, the rate of decline in lung function was similar in both groups, suggesting that continuous use is necessary to maintain effectiveness. The sirolimus group also showed other clinical improvements and reported a greater ability to carry out day-to-day functions and a better quality of life.

McCormack, F. X., Inoue, Y., Moss, J., Singer, L. G., Strange, C., Nakata, K., … Trapnell, B. C.; National Institutes of Health Rare Lung Diseases Consortium; MILES Trial Group. (2011). Efficacy and safety of sirolimus in lymphangioleiomyomatosis. *New England Journal of Medicine, 364*, 1595–1606.

Researchers who developed a mouse model of LAM found a combination drug treatment that appears to be able to prevent, and to some degree reverse, lung damage caused by LAM in that model. When mice received injections of cells lacking the tuberous sclerosis complex 2 (TSC2) gene, their lungs developed LAM-like lesions, suggesting that lung destruction in LAM is specifically associated with loss of TSC2 function. A regimen of two drugs, sirolimus and simvastatin (a commonly used cholesterol-lowering drug), prevented growth of lung lesions and lung destruction and caused a dramatic regression of established lung lesions in the mice. The study suggests the possibility of cellular therapy to restore TSC2 function in LAM patients, as well as the use of drug therapy to prevent lung damage and reverse or attenuate existing disease.

Goncharova, E. A., Goncharov, D. A., Fehrenbach, M., Khavin, I., Ducka, B., … Krymskaya, V. P. (2012). Prevention of alveolar destruction and airspace enlargement in a mouse model of pulmonary lymphangioleiomyomatosis (LAM). *Science Translational Medicine, 4*, 154ra134.

Sarcoidosis

Sarcoidosis is a disease of unknown cause that leads to persistent inflammation, often resulting in the formation of lumps called granulomas. It can affect any organ of the body, but it most often initiates in the lungs, skin, or lymph nodes.

An analysis of data from the Black Women's Health Study (see above) has confirmed previous reports of relatively high rates of sarcoidosis among Black women and provided new information about the disease's clinical characteristics. An annual incidence of 71 per 100,000 and an overall prevalence of 2 percent were found in the study cohort. Most of the women with sarcoidosis had both pulmonary and extrapulmonary involvement, with the most common extrapulmonary sites being lymph nodes, skin, and eyes. The study also revealed that prednisone was the most commonly used medication, followed by

inhaled corticosteroids. Continued follow-up of the cohort is expected to provide a better understanding of risk factors associated with sarcoidosis in general and, particularly, in Black women.

Cozier, Y. C., Berman, J. S., Palmer, J. R., Boggs, D. A., Serlin, D. M., & Rosenberg, L. (2011). Sarcoidosis in black women in the United States: Data from the Black Women's Health Study. *Chest, 139*, 144–150.

Blood Disorders

Hormone-Induced Thrombosis

Women have special concerns throughout their lives involving increased risk of thrombosis (blood clots). Oral contraceptives, pregnancy, and postmenopausal hormone therapy all confer a heightened risk of deep vein thrombosis and pulmonary embolism, and other factors have also been implicated in the higher susceptibility of women.

NHLBI convened a working group in September 2012 to discuss current knowledge and future research needs regarding hormone-induced thrombosis in women. The meeting brought together basic and clinical scientists, epidemiologists, and physicians with expertise in coagulation science, hematology, epidemiology, and obstetrics/gynecology, including reproductive endocrinology and maternal-fetal medicine.

ORWH Director Dr. Janine Austin Clayton addressed the group and summarized the NIH strategic plan for advancing women's health research. Discussions were organized by three topics: pregnancy and assisted reproductive technologies, indications for hormonal therapy in nonpregnant women, and mechanisms of hormone-induced thrombosis. The recommendations of the working group included analysis of existing study data (e.g., from the Women's Health Initiative) to identify thrombotic risks, mechanistic studies of the natural effects of hormones on tissues from healthy women, identification of biomarkers of thrombotic risk associated with hormone therapy in nonpregnant women, evaluation of the influences of route of estrogen administration and formulation on hormone-induced thrombosis, study of mechanisms involved in pregnancy-associated risk of thrombosis, and development of female animal models for preclinical studies.

Sleep Disorders

Sleep Deprivation and Hypertension

Work supported by a new exploratory/developmental research grant is investigating neurovascular mechanisms that may be responsible for sex differences in the responses of blood pressure to sleep deprivation. The investigators hypothesize that sleep deprivation raises blood pressure much more strongly in women than in men and that the sex difference is linked to sympathetic neural activity. Early results in healthy young adults showed that blood pressure and heart rate were higher in both men and women following 24-hour sleep deprivation, but women and men exhibited different patterns of muscle nerve activity and hormone levels. The results may help suggest a mechanism to explain the strong association of hypertension with sleep deprivation in women.

Carter, J. R., Durocher, J. J., Larson R. A., DellaValla, J. P., & Yang, H. (2012). Sympathetic neural responses to 24-hour sleep deprivation in humans: Sex differences. *The American Journal of Physiology—Heart and Circulatory Physiology, 302*, H1991–1997.

Circadian Rhythms and Sleep Patterns

Research findings have shed light on the observation that women are generally more likely than men to describe themselves as "morning persons." A study of adults confined for weeks to a sleep laboratory that shielded them from cues about the time of day demonstrated that women's internal circadian clocks run somewhat faster than men's. On average, women in the study completed their daily cycle 6 minutes earlier than men, and 35 percent of women, compared with 14 percent of men, had a cycle shorter than 24 hours. This phenomenon may help to explain sex differences in sleep duration and also offer clues to the higher prevalence of insomnia that has been observed in women.

Duffy, J. F., Cain, S. W., Chang, A. M., Phillips, A. J., Münch, M. Y., Gronfier, C., …

Czeisler, C. A. (2011). Sex difference in the near-24-hour intrinsic period of the human circadian timing system. Proceedings of the *National Academy of Sciences, 108*(Suppl 3), 15602–15608.

Sleep-Disordered Breathing in Pregnancy Outcomes

In a study of more than 1,700 singleton (i.e., 1 fetus) pregnancies, researchers found that pregnancy tripled the prevalence of loud, frequent snoring (a hallmark symptom of sleep-disordered breathing) in mothers-to-be. Moreover, women who began snoring for the first time during pregnancy were 2.4 times as likely to develop gestational hypertension and 1.6 times as likely to develop preeeclampsia as were women who did not snore during pregnancy or who had snored prior to pregnancy. The increased risk of preeclampsia was independent of other factors, including age, race, prepregnancy BMI, excess weight gain, number of previous pregnancies, smoking status, educational level, and family history of gestational hypertension or preeclampsia. New-onset snoring is quite common in pregnancy—one-fourth of participants in this study reported it—and so identifying and treating sleep-disordered breathing in pregnant women may constitute an important public health measure to reduce the rates of gestational hypertension and of preeclampsia, with their associated risks to mother and child.

O'Brien, L. M., Bullough, A. S., Owusu, J. T., Tremblay, K. A., Brincat, C. A., Chames, M. C., … Chervin, R. D. (2012). Pregnancy-onset habitual snoring, gestational hypertension, and preeclampsia: Prospective cohort study. *American Journal of Obstetrics & Gynecology, 207*, 487.e1–487.e9.

A new NHLBI-funded study will explore the relationship between sleep abnormalities and pregnancy outcomes using the NICHD-initiated Nulliparous Research Network of 10,000 pregnant women. The study's goals are to characterize sleep patterns during pregnancy, assess the extent to which self-reported measures of sleep correlate with objectively derived measures, and determine the relationships between sleep disorders or poor sleep quality and cardiovascular and metabolic disorders of pregnancy.

(These studies address the NIH Strategic Plan for Women's Health Research, Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women; Objective 3.4: Expand research on pregnancy related conditions, such as pre-eclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.)

Sex/Gender Differences

As noted under "Accomplishments," researchers are uncovering a number of gender differences with regard to various aspects of cardiovascular, lung, and blood diseases and sleep disorders. The findings encompass differences in risk factors, symptoms, diagnosis, response to preventive and therapeutic interventions, and prognosis. The long-running Framingham Heart Study continues to yield comparisons of CVD risk in three generations of women and men, and the Jackson Heart Study and the Hispanic Community Health Study are expected to provide sources of data on gender differences in minorities.

Initiatives

Request for Applications

Clinical Trials Planning Studies for Rare Thrombotic and Hemostatic Disorders. This program supports phase III multicenter investigator-initiated clinical trials focused either on rare hemostatic and thrombotic disorders or on more common hemostatic and thrombotic disorders that occur rarely in special patient populations, such as neonates, children, and pregnant women. (RFA-HL-12-023)

Program Announcements

Etiology and Pathophysiology of Sleep Disordered Breathing (SDB) in Pregnancy. This announcement encourages studies of the etiology of SDB during pregnancy; the link between SDB and maternal heart, lung, and blood pathophysiology; the effect of SDB on placental development and function and associated adverse pregnancy outcomes; and the contribution of SDB to conditions in the intrauterine environment that result in altered

fetal development and predispose offspring to obesity, metabolic, and cardiovascular disease. (PA-11-122 with NICHD, NINR)

Effects of Secondhand Smoke on Cardiovascular and Pulmonary Disease Mechanisms. The purpose of this funding opportunity announcement (FOA) is to encourage research to better characterize the dose-response relationship between secondhand smoke (SHS) exposure and the cardiovascular and pulmonary diseases by improving our understanding of the mechanisms by which SHS contributes to these diseases. (PA-11-244 with NIEHS)

Conferences, Working Groups

Mechanistic Perspectives on How Sex Hormones Induce Thrombosis in Women, September 13–14, 2012. The goal of this workshop was to set forth strategies to determine the mechanistic link between thrombosis and sex hormones in women.

Special Populations

Racial and Ethnic Minorities

Recent U.S. health statistics provide the following snapshot of racial/ethnic similarities and differences in the burden of those leading causes of death that are relevant to the NHLBI mission:

- Diseases of the heart account for 24.0 percent of deaths (first, or leading cause) in White women, 24.4 percent (first) in Black women, 21.0 percent (second) in Hispanic women, 21.7 percent (second) in Asian or Pacific Islander women, and 17.1 percent (second) in American Indian or Alaska Native women.
- Cerebrovascular disease (stroke) accounts for 6.3 percent (fourth) of deaths in White women, 6.4 percent (third) in Black women, 6.0 percent (third) in Hispanic women, 8.4 percent (third) in Asian or Pacific Islander women, and 4.3 percent (seventh) among American Indian or Alaska Native women.
- Chronic lower respiratory diseases account for 6.4 percent of deaths (third) in White women, 2.9 percent (sixth) in Black women, 3.2 percent (seventh) in Hispanic women, 2.6 percent (eighth) in Asian or Pacific Islander women, and 4.7 percent (sixth) among American Indian or Alaska Native women.

The NHLBI supports an extensive portfolio of studies focused on the health issues of racial and ethnic minorities and on disparities that exist between minority and majority populations. Of particular relevance are large epidemiological studies that enable detailed study of diseases and their associated risk factors in defined groups:

- The Jackson Heart Study, initiated in 1998, addresses CVD prevalence, severity, and mortality among Black women and men living in the Jackson, MS, area.
- The MESA (Multi-Ethnic Study of Atherosclerosis), initiated in 1999, is investigating the prevalence, correlates, and progression of subclinical CVD in a cohort that includes Whites, Blacks, Hispanic, and Asian Americans.
- The Hispanic Community Health Study, initiated in 2006, is collecting data on a wide variety of conditions—including heart disease, stroke, asthma, COPD, sleep disorders, dental disease, hearing disorders, diabetes, kidney and liver disease, and cognitive impairment—in Latinos. Participants are Mexican Americans, Puerto Ricans, Cuban Americans, and Central/South Americans.

Lesbian Health

A recent report provided new information about the use of complementary and alternative medicine (CAM) by lesbian women. The work involved an analysis of data from the NHLBI-supported Epidemiologic Study of Health Risk in Women (ESTHER), a large cross-sectional study examining risk factors for CHD among lesbian and heterosexual women living in the Pittsburgh, PA, area. The study found a high prevalence of having ever used CAM (50 percent) among participants, and a significantly higher prevalence in lesbians (57 percent) than in heterosexual women (41 percent). Other correlates of CAM use included White race, higher educational achievement, large-city residence, perceived

discrimination in a health care setting, spirituality, and a history of diagnosed mental illness. Because some alternative medicines may cause serious side effects if taken in conjunction with prescription medication, the findings suggest that physicians should inquire about the CAM usage of their women patients, especially those who are lesbians.

Smith, H. A., Matthews, A., Markovic, N., Youk, A., Danielson, M. E., & Talbott, E. O. (2010). A comparative study of complementary and alternative medicine use among heterosexually and lesbian identified women: Data from the ESTHER Project (Pittsburgh, PA, 2003–2006). *Journal of Alternative and Complementary Medicine, 11*, 1161–1170.

Career Development Initiatives

Mentored Career Development Award to Promote Faculty Diversity/Re-Entry in Biomedical Research. The purpose of this award is to advance the awardee's career development trajectory by strengthening research capacity, publishing, and other scholarly activities; improve success and retention in a research career; promote scientific collaborations that lead to acquisition of new skills or research in other fields of scholarly interest; and increase the number of highly trained investigators who are from diverse backgrounds underrepresented in research areas of interest to NHLBI or who wish to reenter their research careers after a hiatus due to family circumstances. (RFA-HL-11-022 and RFA-HL-12-030)

National Institute on Aging

Executive Summary

The National Institute on Aging (NIA) conducts and supports a diverse portfolio of research on older women's health, including studies on Alzheimer's disease and other dementias, menopause and menopausal hormone therapy, osteoporosis, physical disability, and other diseases and conditions. During FY 2011–2012, NIA-supported researchers made important progress in a number of women's health-related areas, including those described below:

Reproductive Health and Menopause. Research continued through the Study of Women's Health Across the Nation (SWAN) and other studies on health across the menopausal transition. For example, SWAN investigators have found from observational studies that major depressive disorder may be associated with heavy menstrual bleeding at midlife; moderate wine consumption may protect midlife women from development of the metabolic syndrome; and perimenopausal women who experience hot flashes have higher levels of N-terminal telopeptide (Ntx), a marker of bone turnover, than women without hot flashes. In addition, a variety of interventions for the most common symptoms of the menopausal transition are currently under study through the MS FLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) initiative, and investigators in that study found in a randomized clinical trial that healthy menopausal women taking a commonly prescribed dose (10–20 mg/day) of the antidepressant escitalopram had fewer and less severe hot flashes, reduced insomnia, increased sleep quality, and better overall quality of life than those taking a placebo.

Cognitive Health and Alzheimer's Disease. Although in previous studies menopausal hormone therapy has been associated with an increased risk of cognitive decline and dementia, questions remain as to whether a "window of opportunity" exists during which menopausal hormone therapy may exert a protective effect on the brain, after which such treatment may be ineffective with regard to cognition. NIA-supported investigators continue to study the effects of different forms of menopausal hormone therapy on cognition, as well as the mechanisms through which estrogen and related hormones work on the brain.

Sex and Gender Differences. American women lag significantly behind their counterparts in other higher-income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly compared with other industrialized countries. An NIA-sponsored National Research Council panel found strong evidence that smoking is responsible

for a good deal of the divergence in female life expectancy. Other factors, including obesity, diet, exercise, and economic inequality, may also play a role, but this evidence is less clear cut. Investigators have continued to explore the reasons behind the sex differentials in disability and mortality across the lifespan, including divergent levels of longevity among women in high-income nations.

New and ongoing research initiatives focusing on women's health include the following:

- A solicitation for research applications to study the etiology and/or mechanisms regulating bone mass that are regulated by a "central relay" in the brain;
- The Women's Health Initiative Study of Cognitive Aging, (WHISCA), which is investigating both on trial and long-term post-trial effects of exposure to menopausal hormone therapy on cognitive aging within the context of the Women's Health Initiative Memory Study and the Women's Health Initiative (WHI) more generally;
- A Specialized Center of Research on Sex Differences, cofunded by ORWH, to explore the intersection of sex, vascular dysfunction, and cognitive decline; and
- The SWAN Sleep Study, in which investigators from four SWAN sites are examining sleep patterns and various factors that may affect sleep during the menopausal transition.

In addition, NIA supports a number of communication and education activities related to women and aging, career development activities, and research on the specific health concerns of minority women.

Introduction

Older women outnumber older men in the United States, and the proportion of the population that is female increases with age. In 2010, women accounted for 57 percent of the population aged 65 or over and for 67 percent of the population aged 85 or over. Despite living longer, however, older women are more likely than men to report depressive symptoms or limitations in physical function and to live alone (a potential indicator or risk factor for isolation, lack of caregivers, and lack of support); in addition, they live in poverty at a disproportionately high rate (Federal Interagency Forum on Aging-Related Statistics, 2012). Furthermore, American women lag significantly behind their counterparts in other higher-income nations in terms of longevity, and since 1980, the pace of gains in life expectancy of older U.S. women has slowed markedly compared with other industrialized countries (Crimmins, Preston, & Cohen, 2011). In fact, their life expectancy has fallen 3 to 5 years behind other developed nations, including France, Italy, Spain, Switzerland, Australia, and Japan (Woolf, & Aron, 2013).

NIA supports a diverse portfolio of research on older women's health, including studies on the following topics:

- Cognitive and emotional aging;
- Alzheimer's disease and other types of dementia;
- Menopause and menopausal hormone therapy;
- Osteoporosis and hip fracture;
- Physical disability;
- Caregiver burden;
- Decline in function of older women;
- Age-related muscle loss;
- Cancer in older women;
- Demography and economics of aging;
- Ovarian hormone influences on brain structure and function;
- Premature ovarian failure; and
- Sex differences in aging and age-related health conditions.

The women's health liaison in the Office of Planning, Analysis, and Evaluation coordinates communication and reporting on NIA activities related to women's health and serves as liaison to the NIH Coordinating Committee on Research on Women's Health. Recent accomplishments in women's health, as well as ongoing and new research initiatives with a particular emphasis on women, are described below.

Accomplishments

Women's Aging and Health: Findings from the Study of Women's Health Across the Nation

NIA's flagship study of women's health is SWAN, an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from premenopause to postmenopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the premenopausal to perimenopausal to postmenopausal transition in Caucasian, African-American, Chinese, Japanese, and Hispanic women. Selected findings from SWAN in FY 2011–2012 include those described in the paragraphs below.

Depression. Although the majority of women do not become depressed at midlife, depressive symptoms and major depressive disorder are more common in perimenopausal women than in premenopausal women, and some studies have suggested an increased risk of depressive symptoms in the postmenopausal period as well. SWAN investigators have found that major depressive disorder may be associated with heavy menstrual bleeding at midlife; women who undergo a hysterectomy with or without bilateral oophorectomy (removal of the ovaries) in midlife do not experience more negative mood symptoms in the years after surgery than women who undergo natural menopause; and midlife women with a previous history of both depression and an anxiety disorder have the greatest likelihood of experiencing reduced quality of life during the menopause transition, even when they are not currently depressed or anxious.

Obesity and the Metabolic Syndrome. SWAN investigators found that women who drank wine in moderation (about one glass per day) were less likely to develop the metabolic syndrome, a precursor to heart disease and diabetes, than women who consumed either more, very little, or no wine. Greater exposure to discrimination was associated with a greater amount of fat around the internal organs in middle-aged African-American and White women; reports of discrimination were not associated in SWAN with other types of fat surrounding the waist. Mothers without cardiovascular disease who did not breastfeed were significantly more likely to retain abdominal fat than were mothers who consistently breastfed.

Cardiovascular Disease. Development of tiny deposits of calcium in the walls of the coronary arteries, or coronary calcification, is an early sign of coronary heart disease. In FY 2011–2012, SWAN investigators made several discoveries regarding coronary calcification at midlife. For example, they found that for women going through menopause, involvement in rewarding multiple roles was associated with a decreased risk of coronary calcification. They also found that varying levels of sex hormone binding globulin (SHBG) and free androgen (as quantified by the Free Androgen Index, or FAI) were associated with arterial calcification, but obesity status influenced the role that these hormones played. In nonobese women, higher SHBG and lower FAI were associated with greater extent of calcification, while in obese women, lower SHBG was associated with greater extent of calcification. SWAN investigators also found that lower levels of estradiol and SHBG and higher FAI and follicle-stimulating hormone levels were associated with increased subclinical atherosclerosis progression in women during the menopausal transition; these findings were independent of systolic blood pressure and body mass index (BMI). Finally, midlife overweight/obese women with healthy cardiometabolic profiles had lower levels of subclinical cardiovascular disease than at-risk overweight/obese women, but the former group had significantly higher levels of subclinical disease than did healthy normal-weight women.

Vasomotor Symptoms. SWAN investigators found that perimenopausal women with menopausal hot flashes had higher levels of Ntx, a marker of bone turnover, than perimenopausal women without menopausal hot flashes. Hot flashes were also associated with greater thickness of the intima media, an indicator of subclinical cardiovascular disease; an increased number of markers of insulin

resistance; and adverse changes in inflammatory and hemostatic markers. Interestingly, a higher percentage of body fat, larger BMI, and bigger waist circumference were associated with fewer hot flashes among the older women (age >59) in the sample. Associations between body fat and hot flashes were limited to Caucasian women, however. Finally, the investigators found that estradiol and SHBG may play a partial role in age and racial/ethnic variations in relationships between body composition and hot flashes.

Sleep. In SWAN, women with sleep-disordered breathing and light sleep were significantly more likely to have the metabolic syndrome than were women with no sleep disturbances. Beta EEG (electroencephalogram) power in nonrapid eye motion (NREM) and REM sleep—a marker of disturbed sleep quality—was higher in late perimenopausal and postmenopausal women than in premenopausal and early-perimenopausal women. The investigators found limited evidence for associations between EEG sleep measures and nocturnal vasomotor symptoms (VMS) or symptoms of depression or anxiety. EEG sleep measures were largely not associated with VMS and mood symptoms across all racial/ethnic groups, although having more frequent nocturnal VMS was associated with longer sleep time.

Nonhormonal Treatment for Menopausal Symptoms. Researchers with the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) Network, a multisite research network designed to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition, found in a randomized clinical trial that healthy menopausal women taking a commonly prescribed dose (10–20 mg/day) of the antidepressant escitalopram had fewer and less severe hot flashes than those taking a placebo. Escitalopram was also shown to reduce insomnia, increase sleep quality, and improve overall quality of life among women going through the menopausal transition. However, among women whose hot flashes improved with escitalopram, approximately one-third quickly relapsed after discontinuation of the medication. Those with pretreatment insomnia and those with a weaker response to escitalopram may be at greatest risk for relapse after discontinuation of treatment.

Alzheimer's Disease

Alzheimer's disease (AD), the most common cause of dementia among people age 65 and older, is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. Estimates of how many people in the United States currently have AD differ substantially, with numbers ranging from 2.4 million to 5.1 million, depending on how AD is measured. But scientists agree that unless the disease can be effectively treated or prevented, the numbers will increase significantly if current population trends continue (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). Risk of developing AD at any specific age is similar for women and men, but because women live longer, there are significantly more women with AD, and in a recent epidemiologic study, the overall lifetime risk of developing AD for a woman was nearly twice that for a man (32 percent versus 18 percent) (Hebert, Scherr, McCann, Beckett, & Evans, 2001). However, in a recent study, amnestic mild cognitive impairment (MCI), often a precursor condition to AD, was more common in men than in women, suggesting that sex differences in the disease course may exist; for example, the investigators hypothesized that women may transition from MCI to dementia later in life than men but do so more abruptly (Petersen, et al., 2010).

Sex Differences in Risk for Age-Related Cognitive Decline and Cognitive Impairment. In one NIA-supported observational study, consumption of caffeine via coffee and tea was associated with a reduced risk of age-related cognitive decline in women but not in men. In a study of men and women with atherosclerosis, women consistently outperformed men on multiple tests of cognitive function, even when the investigators controlled for education and vascular function, suggesting that sex differences in cognition are not due to differences in vascular health. In addition, several studies

identified endogenous risk factors for AD and cognitive decline, as shown below:

- Increased levels of adiponectin, a hormone derived from visceral fat, are an independent risk factor for all-cause dementia and AD in women.
- Men with amnestic and nonamnestic MCI demonstrated higher fasting plasma insulin than cognitively normal men, while women with amnestic MCI (the subtype most likely to convert to AD) had lower fasting plasma insulin. The apolipoprotein E (APOE) ϵ4 genotype, a strong risk factor for AD, may influence the relationship between sex and insulin.
- The effects of APOE ϵ4 itself appear to be largely sex neutral; however, its association with decline in verbal memory and learning appears to be stronger in women.

The Menopausal Transition, Menopausal Hormone Therapy, and Cognitive Health

Although the number of women prescribed menopausal hormone therapy (MHT) continues to decline, a recent nationally representative survey showed that over 8 million American women continue to use MHT, with women over age 60 continuing to account for over a third of MHT use in the United States. Meanwhile, the long-term effects of estrogen-containing MHT on cognition, including the association between MHT use and Alzheimer's disease, remain the subject of intense scientific scrutiny. The question of whether MHT promotes, protects against, or does not influence risk of cognitive decline and/or Alzheimer's and related dementias has proven to be extremely complex, with timing and duration of treatment, specific hormones prescribed, and environmental factors all implicated to some degree in each woman's individual risk profile.

Observational studies have long suggested that the use of estrogen-containing MHT is associated with a reduced risk of Alzheimer's disease. However, among participants in the Women's Health Initiative Memory Study (WHIMS), conjugated equine estrogens plus the progestin (progesterone-related hormone) medroxyprogesterone acetate (CEE/MPA) increased risk of dementia, although not risk of mild cognitive impairment, in women aged 65 years and above. While the WHI Study of Cognitive Aging (WHISCA) showed that CEE/MPA worsens verbal memory, it found that CEE alone had no influence on cognition. These findings have been replicated in several randomized clinical trials. The apparent negative effect of CEE/MPA on verbal memory does not appear to be age dependent. Studies testing the long-term effects of natural estrogen and progesterone on dementia and cognitive outcomes are in progress.

For example, a study testing the effect of the natural estrogen 17β-estradiol suggested that the cognitive outcome depended on the formulation of hormone used. NIH-supported investigators found that women aged 49–68 who were at risk of Alzheimer's disease and who took 17β-estradiol scored higher on measures of verbal memory than did women who took CEE, regardless of age, IQ, years of education, risk factors for Alzheimer's, history of estrogen exposure, concurrent progesterone use, or natural or surgical menopause status. This study thus suggests that the use of natural estrogen supports cognitive function, although further research is needed to confirm and extend these findings.

In 2012, results were released from the KEEPS (Kronos Early Estrogen Prevention Study) Cognitive and Affective Study, which is the first multisite, randomized, placebo-controlled, double-blind, parallel-group design clinical study to address major issues related to use of menopausal hormone therapy raised by WHI and WHIMS. The KEEPS Cognitive and Affective Study compared the effects of conjugated equine estrogens (CEE—Premarin®), transdermal 117β-estradiol (t-E2—Climara®), and placebo on comprehensive measures of cognition and mood in recently menopausal women over 4 years of treatment. All the women received cyclical micronized progesterone (Prometrium®). The women who received oral CEE demonstrated significant improvement in symptoms of depression and anxiety/tension, and trends for benefit were seen on symptoms of anger/hostility and self-reported recall for information contained in printed material. The women who received the t-E2 patch showed an increase

in memory complaints, but the complaints were not supported by results of the actual memory tests. Although the study did not evaluate the potential effects of menopausal hormone therapy on risk for Alzheimer's disease, it will be important to follow the participants over time to determine whether hormone therapy started during early menopause could slow the decline in memory commonly seen with getting older or delay the onset, slow the progression, or reduce the risk of Alzheimer's disease.

In the past several years, NIH-supported investigators have begun to explore whether hormone use by younger postmenopausal women near the time of menopause reduces risk of dementia or whether the negative findings of WHIMS should be generalized to younger women. Some research suggests that MHT may be beneficial if taken during a critical window near menopause but that when initiated in later life it may be associated with increased risk. Recent results from the NIH-supported Cache County Study on Memory Health and Aging support this window-of-opportunity hypothesis: In this study, women who used any type of HT within 5 years of menopause had 30 percent less risk of Alzheimer's disease, especially if use was for 10 or more years. By contrast, Alzheimer's risk was not reduced among those who had initiated HT 5 or more years after menopause. Instead, rates were increased among those who began estrogen-progestin compounds within the 3 years preceding the Cache County Study baseline evaluation.

Evidence suggests that initiation of some forms of HT early in the perimenopausal or postmenopausal stage might confer benefit to verbal memory and the neural systems underlying memory, whereas late-life initiation confers no benefit. In a study from the NIA Intramural Research Program, postmenopausal women who had initiated HT during the perimenopausal period performed better on a verbal memory task than did women who had never used HT. In addition, when the women underwent brain imaging, perimenopausal HT users showed increased activation in the left hippocampus and decreased activation in the parahippocampal gyrus compared with women who had never used HT. Each of these patterns of activation was associated with better memory performance on the imaging memory task.

A January 2010 conference, which brought together experts in the field of aging and endocrinology to discuss the development of translational research models, focused on the critical period to achieve optimal neuroprotection with hormone/estrogen therapy. The papers presented at this meeting appeared in the March 16, 2011, special issue of Brain Research, "The Window of Opportunity: Menopause and Hormone Replacement Therapy." In March 2012, NIA funded a follow-up window-of-opportunity workshop to provide an authoritative update on new science and to review the results of WHIMS. The main goal of the workshop was to determine whether the data support or reject the hypothesis of a window of opportunity for HT in the treatment/prevention of cognitive decline in postmenopausal women. Brain Research will publish the outcomes of this meeting as a special edition in 2013.

Sex Differences: Behavioral and Social Research

Sex Differences in Stress Response. This NIA-supported study examined the brain mechanisms involved in stress effects while male and female participants were engaged in a risky decision task. The researchers found that under acute stress, men worked more quickly to gain greater rewards, while women worked more cautiously, earning fewer rewards. Gender-specific patterns of brain activation were also revealed.

Sex Differences in the Long-Term Health Impacts of Early Adversity. Using data from a unique sample of rhesus macaques randomized at birth to mother-rearing, peer-rearing, or surrogate-rearing conditions, NIA-supported investigators found novel evidence of a causal link between early social environments and sex differences in physical and mental health later in life. All monkeys were put in a single mixed social group between the ages of 6 and 12 months and underwent behavioral observation and physical exams 4 times per year. Males raised with peers or surrogates had significantly more frequent episodes of physical illness and

exhibited more behavioral stereotypy (e.g., rocking, pacing, and digit-sucking behaviors, all similar to behaviors found in autism), with those raised by surrogates being most disadvantaged. Females were most adversely affected by being reared by peers, exhibiting far greater prevalence of wounds and hair loss associated with the greater amount of aggression exhibited in peer groups. This novel demonstration of gender-specific adverse consequences of early social deprivation has the potential to inform how such processes operate in humans, with implications for prevention and intervention efforts.

Relationship Between Socioeconomic Status (SES) and Health and Survival. An analysis of the National Health Interview Survey Linked Mortality Files found that for both men and women there was an educational gradient in self-reported health as adults, with higher levels of education associated with better health, but the gradient was steeper for women than for men. Women reported worse health than men, but this difference was virtually erased for those with tertiary education. There was also a very steep educational gradient in mortality rates, but here the sex difference was reversed, with education reducing adult mortality more steeply for men (who had higher mortality rates) than for women. Increasing educational attainment for the adult population as a whole might reduce these gender gaps. A separate analysis found gender differences indicating lower estimated health among women than men on physical, psychosocial, and pain dimensions of commonly used summary measures of health-related quality of life. Sociodemographic and SES variables, especially income and marital status, explained much of the gender differences, emphasizing the impact of SES disparities on the well-being of women.

Initiatives

Ongoing Research Initiatives

Menopause and Beyond: The Study of Women's Health Across the Nation. SWAN is an ongoing cohort study evaluating longitudinal changes in biological, behavioral, and psychosocial parameters in women as they transition from premenopause to postmenopause. The goal of SWAN is to characterize the biological processes, health effects, psychosocial influences, and sequelae of the premenopausal to perimenopausal to postmenopausal transition in Caucasian, African-American, Chinese, Japanese, and Hispanic women. SWAN is unique in that the period of follow-up spans the menopausal transition, the final menstrual period, and postmenopause in order to characterize how the menopausal transition influences health outcomes at older ages. Over the 18 years of the study, SWAN investigators have collected a wealth of clinical data and biospecimens that represent an important research resource for further studies of menopause. A 2011 special issue of Obstetrics and Gynecology Clinics of North America highlighted key research findings from SWAN.

Funded initially in 1994, SWAN is a cooperative agreement consisting of seven clinical field sites, a central reproductive hormone laboratory, a coordinating center, an advisory panel, and a repository of blood, urine, and DNA specimens. The study is sponsored by NIA, the National Institute of Nursing Research, and ORWH, and it supports Objective 3.1 of the NIH Strategic Plan for Women's Health Research: "Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan."

The SWAN Sleep Study. SWAN investigators from four sites are examining sleep patterns and factors that may affect sleep during the menopausal transition. Although sleep disruptions, insomnia, and breathing-related sleep disorders increase as women age, little is known about how sleep changes as women progress through the menopausal transition. The goals of Sleep I, the baseline phase, were to:

(1) Characterize sleep disturbances in a large, multiethnic sample of midlife women;

(2) Identify relationships among menopausal characteristics (for example, vasomotor symptoms and bleeding) and sleep disturbances;

(3) Evaluate the influence of psychobiological factors on the sleep-menopause relationship; and

(4) Establish baseline data for Sleep II, the longitudinal phase of this research study.

The major goals of Sleep II, which is in progress, are to identify:

(1) Potential predisposing, precipitating, and perpetuating factors for chronic sleep disturbances during the menopausal transition; and

(2) Adverse effects of sleep disturbances on subsequent health status during the early postmenopausal period.

MsFLASH Network. In 2008, NIA, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Complementary and Alternative Medicine (NCCAM), and ORWH, established the MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) initiative, a multisite research network to conduct clinical trials of promising treatments for the most common symptoms of the menopausal transition. The MsFLASH network is composed of five clinical research centers and a data coordinating center. Different treatment approaches are being studied for their efficacy against hot flashes and night sweats in diverse groups of women in trials with either placebo or usual-care control groups. Investigators are also looking at effects on other symptoms at middle age, including sleep disturbance, mood disorder, vaginal dryness, and sexual function. A number of different treatments are being studied, including antidepressants, yoga, low-dose estrogen gel, and exercise.

Hormones, Menopause, and the Aging Brain. NIA-supported investigators continue to study the mechanisms through which estrogen and related hormones work on the brain, as well as the effects of different forms of menopausal hormone therapy on cognition. These efforts support the Strategic Plan Objective 1.5: "Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders." Ongoing initiatives exploring the effects of age-related hormone changes and menopausal hormone therapy on the brain include the following:

- **Women's Health Initiative Memory Study.** NIA supports the continued cognitive follow-up of women who participated in WHIMS, an ancillary study to the WHI randomized clinical trials of the effects of postmenopausal hormone therapy on a variety of health outcomes in older women. In addition, WHIMS investigators are performing cognitive assessments of women who were aged 50–54 when they participated in the WHI randomized hormone trials and are now almost 70 years of age.
- **The Women's Health Initiative Study of Cognitive Aging (WHISCA).** While WHIMS focuses on the effects of menopausal hormone therapy on the risk and progression of Alzheimer's disease and other dementias, WHISCA assesses the effects of hormone treatment on memory, cognition, and mood in nondemented WHIMS volunteers aged 65 or older who had been randomized to hormone therapy or placebo within the WHI trial. More than 12,000 longitudinal assessments have been performed for 2,302 WHISCA participants. In addition to allowing assessment of hormonal effects on cognitive aging, this database permits more general investigation of risk and protective factors for cognitive decline in older women. Because almost half of the women have also participated in the WHIMS-Magnetic Resonance Imaging study, this database also allows investigation of variation in brain volumes and brain lesion burden in relation to cognitive change.
- **Basic studies of hormones and the brain.** Ongoing studies on steroid hormone neurobiology may provide insights into the basis of differences between basic science outcomes and clinical trial outcomes in hormone therapy regimens and thereby lay the groundwork for more informed approaches to hormone use in humans in order to help promote successful brain

aging. Active studies during FY 2011–2012 included:

(1) The elucidation of a neurobiological framework for the complex clinical issues surrounding the neurobiology of menopause and postmenopausal cognitive impairment, from signaling mechanisms of estrogen to an indepth structural and functional assessment of the effects of estrogen on the circuits regulating reproductive function and cognition;

(2) A long-term project to determine the mechanisms and long-term consequences of estrogen on mitochondrial function and metabolism in the brain;

(3) A study exploring how changes in estrogen receptor expression interact with changes in estrogen levels to influence cognitive function; and

(4) A study of the cellular and molecular functions of brain estrogen receptors alpha and beta and how loss of their functions causes neurodegeneration in Alzheimer's disease.

Study of Osteoporotic Fractures. In FY 2011–2012, NIA continued to support the multicenter Study of Osteoporotic Fractures (SOF), which has collected 20 years of prospective data about osteoporosis that has served as the basis for many findings about osteoporosis and aging in women aged 65 or over. In addition to fractures, SOF has tracked cases of breast cancer as well as total and cause-specific mortality. The data include measures of bone mineral density, hormones, strength and function, cognition, sleep, medication use, health habits, and much more. Although initially most of the participants were Caucasian, in 1997 SOF enrolled an additional 662 African-American women, who are now seen with the original cohort. The participants, who are now in their 80s and 90s, continue to be assessed every 2 years, and data are available to qualified researchers for further analysis.

Early Versus Late Intervention Trial with Estradiol (ELITE). Understanding the effect of menopausal hormone therapy on the progression of subclinical atherosclerosis, especially in young postmenopausal women, continues to be an important public health issue. Investigators with ELITE are evaluating whether 17β-estradiol (estrogen) will reduce the progression of early atherosclerosis if initiated soon after menopause when the vascular endothelium (lining of blood vessels) is relatively healthy versus later when the endothelium has lost its responsiveness to estrogen. The investigators are also testing whether 17β-estradiol will reduce the progression of cognitive decline if initiated soon after menopause.

Ovarian Cancer Pathogenesis and Drug Resistance. NIA intramural investigators are working to elucidate the pathogenesis of ovarian cancer, one of the most common gynecological malignancies in women, with particular attention being paid to a family of proteins known as claudins. Evidence is mounting that the proteins claudin-3 and claudin-4 may represent useful markers for the detection and diagnosis of ovarian cancer. The same research team is also identifying genes associated with resistance to drugs that are commonly used to treat ovarian cancer.

Mechanisms Mediating Changes in Central Regulation of Bone Mass. Recent basic research findings have indicated that the regulation of bone mass is highly complex, involving not just the bones themselves but also a "central relay" involving serotonergic neurons in the brain. Several ongoing studies are exploring the etiology and/or mechanisms regulating bone mass that are ruled by a central relay. These studies will significantly enhance our understanding of the integrated nature of the age-related changes in bone mass, and in all likelihood they will identify novel therapeutic targets to prevent bone loss in older women and men.

Sex and Gender Analyses

NIA supports research to identify and elucidate sex and gender differences in aging and age-related disease and dysfunction. New and ongoing initiatives, which are broadly responsive to Objective 3.6, "Study sex/gender

differences in the aging process," include the following:

- A large program project grant that innovatively combines informative animal models, high-quality human data, and sophisticated demographic analyses to generate a deeper understanding of the basis for sex differences in health and survival as well as opportunities to reduce these differences.
- A Specialized Center of Research (SCOR) on Sex Differences, cofunded by ORWH, explores the intersection of sex, vascular dysfunction, and cognitive decline by focusing on women who have experienced a hypertensive pregnancy event, preeclampsia, and menopause. These studies will identify which women might benefit from early treatments to sustain cognitive health across their life transitions.
- Several 2012 program announcements soliciting research applications on the biodemography of aging. Biodemography, the integration of demographic and biological theory and methods, provides an innovative tool for understanding the impact of aging on health and longevity. Investigators will use evolutionary and life history theories as a framework for investigating individual and population-level factors that underlie changes in lifespan and healthy life expectancy, including sex and population differentials in late-life frailty and mortality.
- A collaboration with the National Academy of Sciences (NAS) to identify and explain cross-national, sex-specific differences in mortality at older ages. U.S. life expectancy (at birth and older ages), particularly for White women, has lagged behind other wealthy nations since 1980. A recent NAS panel sponsored by NIA determined that past smoking rates are a major reason for shorter lifespans in the United States than in other high-income countries and that the nation's obesity rates also appear to be a significant factor. The summary report from the National Research Council, which also identified research gaps, is called "Explaining Divergent Levels of Longevity in High-Income Countries" (NRC, 2011) and is available at *http://www.nap.edu/catalog.php?record_id=13089*. A volume of background scientific papers, "International Differences in Mortality at Older Ages: Dimensions and Sources" (NRC, 2011), is available at *http://www.nap.edu/catalog.php?record_id=12945*.

Sex and gender analyses are included in many NIA clinical studies, and several focus specifically on sex and gender differences in older age. These include the following:

- A survey of racial/ethnic and sex differences in behavior patterns such as smoking, physical activity, use of preventive services, alcohol use, and sleep duration among U.S. adults;
- A study of the effect of early-life SES on all-cause, cardiovascular, and cancer mortality in later life as well as gender and race differences in this effect; and
- A study to examine whether the rate of telomere shortening in leukocytes is (a) associated with risk of insulin resistance in adults, and (b) forecasts mortality in the elderly; the study is also examining whether the rate of telomere attrition is faster in men than in women and in postmenopausal women than in premenopausal women.

Communications and Education Initiatives

Many of the topics covered by NIA publications are of special interest to women, including a new AgePage on fatigue, an AgePage on osteoporosis, and "Hormones and Menopause: Tips from the National Institute on Aging." The Institute's booklet "Menopause: Time for a Change" remains the NIH's primary source of detailed information on the menopausal transition. Women are often the caregivers of people at the end of life, and NIA redesigned and updated a 68-page booklet to tackle some of these difficult issues. Another NIA booklet, "End of Life: Helping With Comfort and Care," provides advice and resources to help caregivers find hospice care, learn what

happens at the time of death, obtain support for managing grief, and more.

Being physically active is vital to maintaining health and independence as women age. Go4Life®, the exercise and physical activity campaign from NIA, helps people age 50 and older fit physical activity into daily life. The Go4Life Web site (*http://go4life.nia.nih.gov*) offers sample exercises, motivational tips, and free resources to help women (and men) get ready, start exercising, and keep going. Go4Life works with a variety of organizations, including government agencies, corporations, nonprofits, community groups, employers, and others to reach out to the public with evidence-based campaign messages and materials.

NIA continues to complement its research initiatives by supporting two information centers for older people and their families, the public, health care providers, and others interested in health and aging. The NIA Information Center responds to inquiries received on its toll-free phone number and distributes NIA's free publications on a variety of topics, which can be viewed on the Web at *http://www.nia.nih.gov/health/publication*. The NIA Alzheimer's Disease Education and Referral (ADEAR) Center provides free information and publications for families, caregivers, and professionals on research, diagnosis, treatment, patient care, caregiver needs, and education and training related to Alzheimer's disease via its toll-free phone number and also online at *http://www.nia.nih.gov/alzheimers*.

Health Disparities

Demographic projections predict a substantial change in the racial and ethnic makeup of the older U.S. population, heightening the need to examine and reduce differences in health and life expectancy. NIA is committed to addressing health disparities, with many initiatives supported in partnership with the National Center on Minority Health and Health Disparities. Minority aging research is conducted throughout the Institute's programs, and much of this research has relevance to the health needs of minority women. Examples of current programs and projects include the following:

- The Study of Women's Health Across the Nation (SWAN), which explores a number of health parameters among Caucasian, African-American, Chinese, Japanese, and Hispanic women.
- The MsFLASH (Menopause Strategies: Finding Lasting Answers for Symptoms and Health) initiative, which has successfully recruited sufficient numbers of African-American women to gather baseline data to analyze for differences by race and ethnicity in perimenopause/menopause characteristics.
- The Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) study, a community-based research effort designed to focus on evaluating health disparities in minority and socioeconomically diverse populations.
- A study to increase the understanding of how women of different ethnicities in their 40s and early 50s develop the metabolic syndrome, and also to learn more about hormonal changes and other factors during the menopausal transition that contribute to women's increased risk of the metabolic syndrome.
- A clinical trial of vitamin D supplementation to prevent osteoporosis in older African-American women.

Career Development

NIA actively encourages the participation of women in its training and career development initiatives. In addition, the Institute supports a research study examining the barriers that women face in careers in biomedical research in universities and research centers, and it cofunds the University of Maryland's Building Interdisciplinary Research Careers in Women's Health Program, which has a research emphasis on women and aging.

References

Crimmins, E. M., Preston, S. H., & Cohen, B. (Eds); National Research Council (U.S.) Panel on Understanding Divergent Trends in Longevity in High-Income Countries. (2011). *Explaining divergent levels of longevity*

in high-income countries. Washington, DC: The National Academies Press.

Federal Interagency Forum on Aging-Related Statistics. (2012). *Older Americans 2012: Key indicators of well-being.* Washington, DC: U.S. Government Printing Office. Retrieved from *http://www.agingstats.gov*

Hebert, L. E., Scherr, P. A., Bienias, J. L., Bennett, D. A., & Evans, D. A. (2003). Alzheimer disease in the U.S. population: Prevalence estimates using the 2000 census. *Archives of Neurology, 60,* 1119–1122.

Hebert, L. E., Scherr, P. A., McCann, J. J., Beckett, L. A., & Evans, D. A. (2001). Is the risk of developing Alzheimer's disease greater for women than for men? *American Journal of Epidemiology, 153,* 132–136.

National Research Council. (2011). *Explaining divergent levels of longevity in high-income countries.* Washington, DC: The National Academies Press.

National Research Council. (2011). *International differences in mortality at older ages: Dimensions and sources.* Washington, DC: The National Academies Press.

Petersen, R. C., Roberts, R. O., Knopman, D. S., Geda, Y. E., Cha, R. H., Pankratz, V. S., … Rocca, W. A. (2010). Prevalence of mild cognitive impairment is higher in men: The Mayo Clinic Study of Aging. *Neurology, 75,* 889–897.

Woolf, S. H., & Aron, L. (Eds); Panel on Understanding Cross-National Health Differences Among High-Income Countries, Committee on Population, Division of Behavioral and Social Sciences and Education, National Research Council, Board on Population Health and Public Health Practice, & Institute of Medicine. (2013). *U.S. health in international perspective: Shorter lives, poorer health.* Washington, DC: The National Academies Press.

National Institute on Alcohol Abuse and Alcoholism

Executive Summary

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the primary U.S. agency for conducting and supporting research on the causes, consequences, prevention, and treatment of alcohol abuse, alcoholism, and alcohol problems. NIAAA provides leadership in the national effort to reduce alcohol-related problems by doing the following:

- Conducting and supporting alcohol-related research in a wide range of scientific areas, including genetics, neuroscience, epidemiology, prevention, and treatment.
- Coordinating and collaborating with other research institutes and Federal programs on alcohol-related issues.
- Collaborating with international, national, state, and local institutions, organizations, agencies, and programs engaged in alcohol-related work.
- Translating and disseminating research findings to health care providers, researchers, policy makers, and the public.

According to the U.S. Centers for Disease Control and Prevention (CDC), excessive alcohol consumption is the number three cause of preventable death in the United States. Untreated alcohol problems cost the United States an estimated $184.6 billion dollars per year in health care, business, and criminal justice costs, and they cause more than 100,000 deaths annually. Studies indicate that women consume lower levels of alcohol and are less likely than men to drink daily or to engage in binge patterns of use. For example, in 2011, an estimated 47.1 percent of females aged 12 or older were current drinkers, a rate well below that for males (56.8 percent). However, women are more sensitive than men to the physiological effects of alcohol, achieve higher blood alcohol concentrations, have a higher risk for the development of alcohol-related diseases, and show a higher vulnerability to alcohol dependence.

NIAAA-funded preclinical studies in animal models have begun to reveal the mechanisms underlying sex/gender differences in drinking behaviors and related problems. In the past two fiscal years, the following scientific areas related to Goal 1 of the NIH Strategic Plan for Women's Health Research have experienced significant advances in knowledge: the role of sex hormones on immune responses, tissue injury/repair, and the neurobiology of alcohol dependence and withdrawal; genetic mechanisms mediating differential susceptibility to the teratogenic effects of ethanol (alcohol); fetal programming of stress and hormonal responses after exposure to prenatal ethanol; and ethanol effects on gender differences in HIV infection.

NIAAA also maintains a strong program of research that examines how the presence of other medical conditions, along with environmental and social factors, can lead to different patterns of alcohol abuse and health vulnerabilities in girls and women throughout their lives. Scientists now recognize that human biology and behavior continue to change throughout life, which in turn affects individuals' drinking patterns and their decisions to alter drinking habits or to seek help for alcohol-use problems. A lifespan perspective will allow researchers to identify how the emergence and progression of drinking behavior are influenced by changes in biology, psychology, and in exposure to social and environmental inputs over a person's lifetime, and vice versa. This approach will help discover life-stage-appropriate strategies for developing individualized prevention and treatment programs for girls and women that fulfill Strategic Plan Goal 2.

The following report highlights NIAAA's recent activities and accomplishments in biomedical and behavioral research related to women's health. The accomplishments fall into four major research categories:

(1) Gender differences;

(2) Alcohol, pregnancy, and fetal alcohol spectrum disorders;

(3) Treatment of women with alcohol-use disorders; and

(4) Alcohol and violence.

The accomplishments described below are further identified where appropriate by their correspondence to specific goals and objectives of the NIH Strategic Plan for Women's Health Research.

Accomplishments

Gender Differences

Alcohol and Breast Cancer (cofunded by ORWH) (Objective: 1.7). Alcohol consumption is associated with an increased incidence of breast cancer. The association with alcohol is particularly pronounced in hormone-dependent breast cancers, and so cancers that are associated with alcohol consumption are more likely to be estrogen receptor positive. A common hallmark of cancer cells is over-induction of polymerase III (Pol III), which is involved in expression of nonprotein-coding RNAs such as transfer RNAs (tRNAs). Dysregulation of Pol III might mean greater translation of all proteins, a condition that is associated with cell transformation. Alcohol induces Pol III transcription, and it does so to a greater extent in cancer cells than in healthy cells. Furthermore, alcohol induction of Pol III depends on estrogen receptor function, and the combination of estrogen plus alcohol synergistically increases the induction of Pol III activity. This research project is investigating the mechanism by which alcohol increases the incidence of breast cancer, by looking at the interaction of alcohol with estrogen receptor signaling. Understanding the mechanism by which alcohol enhances tumor formation may lead to insights on prevention and therapeutic approaches and may inform women's decisions about drinking alcohol.

Neuroendocrine Effects of Alcohol on Puberty (Objective: 1.7). This research is intended to further identify consequences of alcohol consumption with regard to hormonal events and their actions that can alter female pubertal maturation. The studies are a logical extension of previous work and dissect out the effects of chronic and acute alcohol consumption upon the factors that regulate hypothalamic hormone release. Recent studies have demonstrated the importance of hypothalamic glial-neuronal communications for the activation of LHRH

(luteinizing hormone-releasing hormone) secretion at puberty. An important observation has been the role of alcohol in blocking IGF-1 (insulin-like growth factor 1), estradiol, and TGF-1 (transforming growth factor 1) release from hypothalamic astrocytes as the mechanism responsible for the inhibitory actions of alcohol on hypothalamic LHRH release. Progress from the studies described is relevant to child health from a standpoint of identifying mechanisms associated with alcohol-induced deficiencies during adolescent female development and provides important insights into alcohol-induced disturbances of a broad spectrum of other reproductive processes and pathologies.

Alcohol-Induced Bone Resorption: The Role of Oxidative Stress (Objective: 1.7). Chronic alcohol abuse results in osteoporosis and increased fracture risk in both premenopausal and postmenopausal women. This research using animal models has demonstrated that alcohol treatment results in analogous bone loss and reduced mineral density in rats and mice. These outcomes were found to result from an imbalance between the actions of osteoclasts, which remove old bone, and osteoblasts, which are responsible for forming new bone. The researchers have shown that, in cycling female rats and mice, alcohol-enhanced bone resorption is associated with increased osteoclast cell numbers and the induction of specific signaling factors (e.g., RANKL) in bone marrow and significantly reduced plasma estradiol concentrations. In contrast, in pregnant females where plasma estradiol levels remained elevated (and unaffected) by alcohol consumption, alcohol-induced bone loss was significantly attenuated. Finally, these studies demonstrated that estradiol replacement prevents alcohol-induced bone loss by opposing the induction of RANKL mRNA in osteoblasts and ethanol-induced osteoclastogenesis. Thus, these studies offer a window into the mechanisms by which chronic alcohol consumption exacerbates osteoporosis and fracture risk in women while also suggesting a protective role for estrogens.

Females Are More Susceptible than Males to Alcohol-Induced Activation of the Stress Axis (Objective: 1.5). Brain injury is among the most prominent effects of prolonged alcohol use or abuse, and evidence suggests that females may be more sensitive than males to the neurotoxic effect of prolonged alcohol intake. Thus, examination of biochemical pathways may be of value in identifying therapeutic targets to be exploited in treating alcohol-related brain injury. This proposal examines the hypothesis that alcohol-induced activation of the stress (hypothalamic pituitary) axis promotes NMDA receptor-mediated seizures and/or neurotoxicity during alcohol withdrawal in a sex-dependent manner. Using in vitro and in vivo rodent models, this study will determine whether alcohol exposure activates the glucocorticoid receptor and increases the expression of the polyamine-sensitive subunit (NR2B) of the NMDA receptor. This will promote NMDA channel opening and neuronal excitation and neurotoxicity in a glucocorticoid receptor-dependent manner. These findings may suggest a role for glucocorticoid receptor antagonists in the treatment of ethanol detoxification or the maintenance of abstinence, especially in females.

Role of Gonadal Hormones in HPA Responses to Alcohol Administration (Objective: 1.2). Maladapation of the stress response can cause long-term health problems. The hypothalamus-pituitary-adrenal (HPA) axis responds differently in males than it does in females to stressors and to alcohol. The purpose of this project is to investigate whether gonadal hormones determine the response of the HPA axis to alcohol. If ovarian hormones produce greater modification of alcohol activation of the HPA axis in women than testicular hormones do in men, that may explain some of the differences between the sexes that are seen in responses to alcohol. Results would permit the development of sex-specific treatments for alcohol abuse.

Alcohol, Puberty, and Sex Differences in Alcohol Intake (Objective: 1.5). Despite the marked hormonal and neural changes associated with puberty and the other physiological transitions of adolescence, little is known about how these factors might contribute to the ontogeny of sex differences in ethanol intake and sensitivity. This proposal examines the organizational and activational effects of

the rise in gonadal hormones at puberty on the expression of sex differences in ethanol intake, ethanol sensitivity (indexed by ethanol-induced social suppression), and ethanol stress interactions using a rat model. To date, notable activational effects of gonadal hormones are evident among males in terms of ethanol intake and preference, with perhaps some role played by ovarian hormones among females in the elevation of stress hormone levels following ethanol challenge and in social interactions. Differences between males and females in their response to kappa receptor stimulation may be a neural contributor to ethanol-related sex differences. This research will increase our understanding of the role of pubertal hormones in promoting the emergence of sex-typical patterns of alcohol use, consequences, and abuse.

Sex Differences in Learning and Memory in the Adolescent Rat: Role of Gonadal Hormones (Objective: 3.1). Adolescence represents a critical window of vulnerability for initiating alcohol use, and in a large number of cases, it is a period of increasing alcohol intake. It is well documented that adolescents differ from adults in their sensitivity to alcohol. Research has shown that male rats exposed to alcohol during adolescence exhibit significant deficits in spatial learning and memory that persist into adulthood. Alcohol consumption in female adolescent rats also causes profound deficits in spatial learning and memory, but deficits in females do not persist beyond the alcohol-exposure period. This proposal will explore the nature, mechanisms, and consequences of alcohol exposure during adolescence on learning and memory in male and female rats, and it will also examine the influence of pubertal gonadal hormones on sex differences in alcohol-use behaviors. The overarching goal is to determine whether, during adolescence, pubertal gonadal hormones influence alcohol-induced behavioral deficit by modulating the NMDA receptor. Understanding age-related changes in the brain as it transitions from adolescence to adulthood, and the effects of pubertal gonadal hormones on alcohol-induced behavioral deficits, will provide clues as to why the adolescent period is particularly vulnerable to use and abuse of alcohol, and it should lead to novel therapeutic targets that may be used for prevention and/or treatment of adolescent alcohol use and abuse.

Neurophysiological and Behavioral Factors Underlying Attention to Alcohol Cues in Mexican-American College Freshmen Women (Objective: 3.9). This recently funded study will focus on investigating attentional changes to alcohol in first-generation Mexican-American women during their freshman year of college. The transition from a traditional home environment to a college campus, where drinking alcohol may be much more prevalent, provides an opportunity to study shifts in perceptions, acculturation, and neurophysiological responses relative to drinking. The study will measure attention to alcohol cues (e.g., picture of a glass of wine) at baseline and again near the end of the freshman year of college. Event-related brain electrical activity will be recoded to track the brain's neurophysiological response to alcohol cues during the first year in a college environment. This study will also test whether the P300 electrical brain wave could be used as a neurophysiological marker of risk for subsequent alcohol abuse in this unique population of women. Understanding the neural and behavioral changes related to exposure to alcohol cues will be important for the design of attention training programs to prevent or treat abusive drinking of alcohol.

Gender and Genetic Effects on Sleep/Wake Parameters Following Ethanol Exposure. This project examines the effect of gender or gender in combination with genetic variation on the severity of alcohol-induced disruption in sleep. Both gender and alcohol exposure influence sleep function, and this investigation examines the additional impact of gender on alcohol-induced sleep. The resulting data will indicate whether sleep disruption may be greater in male or female alcoholics. Because sleep disruption is a contributing factor to relapse, the determination of which gender is more affected by alcohol-induced sleep disruption could identify the processes promoting a sex-specific mechanism in relapse.

Alcohol, Puberty, and Adolescent Brain Development. The onset of puberty and the

emergence of cyclic patterns of hormone secretion may influence the response to alcohol and alcohol consumption. Gonadal steroids may reduce sensitivity to alcohol and thereby reduce the alcohol-induced signals that lead to a reduction in consumption. Determination of the role of increased hormone secretion during puberty in alcohol consumption can identify the processes accounting for the sex differences in adult patterns of drinking. These findings would also identify critical periods of vulnerability during which alcohol exposure may produce long-term consequences in a sex-dependent manner.

Impact of Sex Hormones on the Social Aspects of Drinking (cofunded by ORWH). Social context has a significant impact on alcohol drinking and substance abuse, particularly in teens and young adults who have friends who drink. At the same time, alcohol consumption promotes social bonding. Thus, socially induced drinking and alcohol-induced social bonding create a potentially dangerous feedback loop with implications for making a transition to unhealthy drinking patterns in social settings. This study uses a mouse model of conditioned partner preference to explore substance abuse in a social context. Previous work demonstrated alcohol-induced social preference in female mice. The current studies extend this finding to explore conditioned partner preference in males and females with and without gonadal steroid hormones to understand how ethanol and other drugs interact with steroid hormones to affect neural systems for affiliative behavior. The information gained will help combat unhealthy patterns of social drinking and drug use.

Acute Ethanol Responses in *Drosophila* Are Sexually Dimorphic. There are well-documented sex differences in the way alcohol (ethanol) affects the health and behavior of men and women. In general, men drink greater quantities of alcohol and have a higher incidence of alcohol-use disorders than women. Women, on the other hand, suffer from more severe physical consequences resulting from heavy drinking, including end-organ damage, and become more impaired than men during heavy-drinking episodes. This study uses the fruit fly, *Drosophila,* as a model organism to uncover genes that underlie sex differences in alcohol responses. Alcohol affects fruit flies similarly to humans, where low doses induce hyperactivity and high doses induce sedation. Female flies display decreased alcohol hyperactivity and are less resistant to the sedative effects of alcohol than are male flies. This sex difference in alcohol response is mediated by the sex determination gene transformer (tra) through a signaling pathway that involves another *Drosophila* gene named fruitless (fru). This is the first study to define alcohol-responsive genes that differentially affect alcohol sensitivity in male and female *Drosophila*. This study is important because it points to novel drug targets that could be useful in tailoring medications based on sex.

Adolescent Alcohol Exposure Alters the Rat Adult Hypothalamic-Pituitary-Adrenal Axis Responsiveness in a Sex-Specific Manner. Alcohol abuse and dependence are significant societal problems, especially during adolescence. Determining the long-term impact of adolescent alcohol exposure is critical for developing interventions to treat alcohol-related disorders. One possible persistent long-term effect of adolescent alcohol exposure is adaptation of the HPA axis, the system that mediates responses to stressors. During the adolescent period, females demonstrate a more prominent stress response than do males. Recent evidence shows that adolescent alcohol exposure increases the stress hormone vasopressin in male rats, whereas in adult males challenged with alcohol, a different stress hormone (CRF) is altered. Conversely, adult females do not show significant changes in CRF following alcohol challenge; instead they display increased vasopressin levels. These stress hormone effects were blunted experimentally by adolescent alcohol exposure in both male and female rats. These findings suggest that adolescent alcohol exposure may produce long-lasting changes in stress responsiveness to a subsequent alcohol challenge in adulthood, and this effect is different for males and females.

Gender Differences in Brain Structure and Function in Chronic Alcoholism (Objective: 1.2). This study has been funded for many years to investigate the changes in

brain structure and cognitive and affective behaviors associated with the development of chronic alcoholism. Based on emerging findings from this study showing differences between men and women, the investigators will now focus on gender differences and their potential causative role in the trajectory toward chronic alcoholism. The study will measure differences in the structural integrity of the brain and in functional activation (changes in brain blood flow) during performance of emotional or affective behaviors, reward processing, and conative (i.e., intentional) behaviors. The guiding hypothesis is that alcoholic men and women differ in the structural integrity of certain brain areas and that there will be different patterns of functional brain activation during performance of the behavioral tasks. Understanding the neurobehavioral consequences of chronic alcoholism in terms of gender differences may help in the recognition of predisposing risk factors that are gender specific.

Gender Differences and Menstrual Cycle Effects on Brain Neurotransmitter Levels and Cognitive Functioning (Objective: 3.5). This recently funded study will investigate differences in the levels of the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate in the hippocampus of the brain and their relationship to spatial and verbal learning and memory (functions dependent on the hippocampus) in young adult males and females. The study will also test women in both the follicular phase (low hormone levels) and the mid-luteal phase (high hormone levels) of the menstrual cycle to investigate possible changes in GABA and glutamate levels and memory function influenced by hormonal changes. This information, particularly on the influence of the menstrual cycle in females, will be used to design a longitudinal study of changes in neurochemistry (e.g., neurotransmitter levels) and hippocampal-mediated learning and memory functions in alcoholic men and women. Knowledge of the neurochemical correlates of hippocampal memory and learning could be useful as markers of recovery during abstinence from alcohol and as potential predictors of risk for relapse.

Brain Imaging of Appetitive Decision Making in Alcohol-Dependent Young Women. NIAAA funded an application to study the interaction between alcohol and the brain processes underlying sexual decision making that may bias alcohol-dependent women toward risky sexual behavior. Whether a woman's hormonal state is likely to be a relevant factor mediating alcohol and brain interactions, possibly creating windows of acute vulnerability for young women, will also be investigated. Using functional magnetic resonance imaging (fMRI), this study will test the hypothesis that alcohol-dependent young women have a more sensitized reward brain circuitry in general and that the hormonal state close to ovulation further enhances vulnerability to sexual risk taking. An understanding of menstrual cycle interactions with neural activation and sexual decision making in alcohol-dependent and nondependent women can enhance our ability to intervene to promote safer sexual behavior in at-risk young women.

Genetic Factors Play a Role in Alcohol Problems in Young Women (Objective: 3.1). Although many studies have determined the degree to which genetic factors contribute to alcoholism in males, there is a paucity of data on how genetic factors play a role in vulnerability towards alcoholism in women. NIAAA is supporting a research study that aims to identify the genetic factors that contribute to alcoholism in women and how certain environmental exposures influence vulnerability. This study is a prospective analysis of a birth cohort of female-like-sex twin pairs born in Missouri to Missouri-resident parents. During previous years of funding, information was obtained from twin pairs who were in adolescence. The focus of the current funding is on female twin pairs who have reached young adulthood. Recent findings have identified genes involved in serotonin neurotransmission as contributing to vulnerability to alcoholism in these young women. In addition, it was found that the involvement of peers in substance use and abuse modifies genetic influences on regular substance involvement in these young women. This work has significant implications for understanding the risk factors associated with alcohol use and abuse

specifically in women, who have traditionally been an understudied population. Finally, the information gained from this study will help the design of better treatments for women with alcohol problems and thus improve public health.

Mechanisms for Estrogen-Dependent Myocardial Depressant Effect of Ethanol (cofunded by ORWH) (Objective: 1.7). Moderate alcohol consumption provides cardioprotective effect in men, but surprisingly it may cause cardiotoxicity in women. The underlying mechanism of this phenomenon is incompletely understood. This study, which uses rats as an animal model, is examining the innovative hypothesis that the female hormone estrogen (17-Beta-estradiol, or E2) induced myocardial accumulation of ethanol-derived acetaldehyde (ACA) due to upregulated catalase activity may be the culprit. Accumulation of ethanol-derived ACA creates a conducive microenvironment for paradoxical transformation of E2 into a proinflammatory hormone, which may be the basis for the cardiotoxicity of ethanol in females. Given the steady rise in acute alcohol consumption, especially by young women, the proposal is clinically relevant. The study addresses how estrogen converts the ethanol-induced cardioprotection into cardiac repression in females and provides a plausible explanation of the disappointing outcome of estrogen therapy in clinical studies. Mechanistic insights by identification of the estrogen receptor subtype(s) implicated in the higher physiological activity of the cardioprotective enzyme myocardial mit-ALDH2 in females will also be sought. The studies will advance our understanding of the molecular mechanisms for the E2-dependent myocardial dysfunction due to acute alcohol consumption and may lead to identification of novel targets for therapeutic interventions in treatment and/or prevention of cardiovascular abnormalities caused by alcohol in females.

Alcohol, HIV Infection, and Host Defense. Worldwide, nearly 50 percent of the more than 30 million people with HIV infection are women. Epidemiologic data shows a greater susceptibility of women to HIV through heterosexual contact. However, risk factors for HIV infection in women are not well understood. Evidence from the rhesus macaque simian immunodeficiency virus (SIV) model of HIV supports the idea that alcohol abuse is a significant environmental risk factor for HIV infection in women.

Alcohol Use, Pregnancy, and Fetal Alcohol Spectrum Disorders (FASD)

Trajectory of FASD Across the Lifespan: New Understandings in Intervention (Objective: 3.3). Because of the high prevalence of FASD in some South African communities and because extensive epidemiological studies are still ongoing there, it became possible to institute and to evaluate prevention interventions developed to reduce FASD in these communities. Furthermore, new research trials and etiologic research can now be instituted in a systematic, productive, and potent manner for a refined understanding of FASD across the lifespan and to inform basic science. Improved understandings about the specific characteristics and patterns of FASD in these South African populations have broad implications for public health in almost every human population. This continuing project seeks to implement:

(1) Early intervention research (developmental and nutritional) for children as young as 24 months that may reduce or ameliorate many of the negative effects of prenatal alcohol exposure in an already-identified cohort of children (FASD and controls);

(2) A comparative study of results from alcohol biomarker (EtG and FAEE) tests and self-reported alcohol use in the prenatal period; and

(3) A detailed case-control study of maternal nutrition in the prenatal period.

Collaborative Initiative on FASD (Objective: 3.5). Ongoing research is being carried out within this consortium, which is comprised of multiple international sites with high incidence of fetal alcohol syndrome (FAS) and FASD. A Ukrainian cohort of moderate-to-heavy-drinking women and controls has been established to examine the role of nutritional factors in alcohol-related birth outcomes. Longitudinal follow-up includes expanded prenatal ultrasound

measures and both a physical examination and neurobehavioral testing of the offspring. An embedded study examines the effects of maternal micronutrient status and other markers of oxidative stress at mid-pregnancy and in the third trimester and is also looking at the effects of maternal vitamin and mineral supplementation on the growth, neurobehavioral development, and alcohol-related physical features of the alcohol-exposed offspring. In addition, some consortium members are developing animal models of FAS and FASD with aims of clarifying mechanisms, improving diagnostic methods, identifying genetic and molecular markers of these disorders, and testing potential interventions. The long-term goals of this research consortium are to refine the diagnostic criteria for FAS/FASD, explore the underlying mechanisms of the disorder, and develop therapeutic interventions to provide relief to those affected with the most debilitating features of the disease.

Differences in the Serotonin System in Animals Exposed to Prenatal Ethanol (Objective: 1.2). Prenatal ethanol exposure may affect an individual's brain function later in life, and some effects may be specific to females. NIAAA is funding a research program to investigate fetal programming of the stress and hormonal response after exposure to prenatal ethanol. Adult female rats that were exposed to ethanol prenatally exhibit an altered stress hormone response to drugs that attach to the serotonin receptor in the brain. Males show no hormonal effect of these drugs. Publications from this research report long-term effects on the brain stress system of prenatal ethanol exposure that differ between males and females. The changes induced by prenatal ethanol exposure may alter the way women respond to stress later in life, and these changes may have implications for depression and other related mental health disorders.

Prenatal Alcohol Exposure Among High-Risk Populations: Relationship to Sudden Infant Death Syndrome and Stillbirth (Objective: 3.3). A cooperative agreement has been funded by NIAAA, NIDCD, and NICHD to conduct community-linked studies on the underlying causes of sudden infant death syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and FAS, and the role of prenatal alcohol exposure. The Prenatal Alcohol in SIDS and Stillbirth (PASS) Network consists of two comprehensive clinical sites in the Northern Plains and Western Cape of South Africa, a developmental biology and pathology center, a physiology assessment center, and a data coordinating and analysis center. At the time of this report, the PASS Network has enrolled nearly 8,500 pregnant women (toward an enrollment goal of 12,000) in a comprehensive longitudinal cohort study in which their infants will be followed for up to 1 year. In parallel, the network is conducting a retrospective study to obtain additional SIDS cases occurring within the catchment areas that would not have been captured in the prospective study. Additionally, embedded studies have been designed to explore the role of (under-) nutrition in exacerbating the effects of maternal alcohol exposure on fetal and offspring development. The long-term goals of this initiative are to decrease fetal and infant mortality and to improve child health in the affected communities.

Neurocircuit Targets of In Utero Ethanol Intoxication and of Therapies for FASD (Objective: 3.2). There are currently no treatments to prevent or reverse cognitive deficits in children that were caused by ethanol intoxication during pregnancy. One NIAAA-funded project aims to identify and test therapies that could protect the developing brain from ethanol injury and preserve cognitive functioning in children at risk for FASD. One possible mechanism for these learning and memory deficits is a defect in the signaling of GABA, one of the major neurotransmitters in the brain. A recent study found that during a period equivalent to human third-trimester brain development, binge-like intoxication in rat pups distorted maturation of GABA synapses in certain brain regions. This action could be largely prevented by finasteride, a drug that blocks formation of modulators of the GABA synapse. This work has the potential to provide a model for testing treatments aimed at offering hope for preventing or limiting cognitive injury in children with FASD.

Maternal Uterine Vascular Origins of FASD. Our understanding of the mechanisms by which alcohol damages the developing fetus remains limited. This study explores the maternal uterine origins of FASD and devises strategies for developing a future proteomic biomarker(s)/unique signature profile for maternal alcohol consumption. In particular, these researchers will examine the effects of chronic alcohol binges on nitric-oxide-related signaling cascades in the uterine endothelium and associated structures during pregnancy. Findings from this study will enhance our understanding of the effects of alcohol on maternal-fetal vascular adaptations and address their relative contributions to the pathogenesis of FAS/FASD.

Alcohol's Effects on Teratogenesis (Objective: 3.2). Women who consume alcohol during pregnancy place their offspring at risk for a number of teratogenic effects. In the United States, an estimated 130,000 women per year expose their fetuses to high levels of alcohol, and the estimated associated costs are $4 billion–$11 billion. Genetic factors, both maternal and fetal, are known to play a role in susceptibility to ethanol-related teratogenesis. NIAAA is currently supporting a study on the genetic mechanisms mediating differential susceptibility to the teratogenic effects of ethanol. A maternal effect mediating different teratogenic outcomes following prenatal ethanol exposure has been identified using mouse models. The study has examined genomic imprinting as an epigenetic mechanism for the teratogenic effect. Researchers in this study have examined DNA methylation, histone modifications, and changes in gene expression (of several imprinted genes known to play a role in growth and development) in embryos and placentas following prenatal ethanol exposure. In addition, the researchers have examined global gene expression changes in fetuses exposed to alcohol in utero. These epigenetic modifications and/or gene expression changes identified in imprinted genes following prenatal alcohol exposure in mice can be potential targets for future human studies. The study of a methyl-supplementation diet on the teratogenic effects of ethanol may allow for the design of rational treatment and, ultimately, prevention strategies.

Treatment of Women with Alcohol Use Disorders

Prenatal Drinking and Knowledge of FAS: A Randomized Trial in Russia (Objective: 3.9). The overarching aim of this study is to reduce risk for alcohol-exposed pregnancy (AEP) and alcohol-related neurodevelopmental disorder (ARND)/FASD by testing a prevention model specifically targeted to large numbers of women in obstetrics and gynecology clinics in Russia. The study will conduct a randomized trial to determine whether physicians, trained to conduct a brief motivational intervention, can foster:

(1) Changes in childbearing-aged Russian women's health beliefs regarding risk for AEP; and

(2) Greater reduction of women's AEP risk behaviors (e.g., through abstinence from alcohol and consistent contraception use) compared with standard obstetrics and gynecology care.

Preliminary studies have suggested that while many Russian women reduce alcohol consumption after they recognize they are pregnant, prior to the diagnosis of pregnancy, few of them recognize the risks of combining alcohol use with the potential to become pregnant. Therefore, substantial numbers of women of childbearing age may be at high risk for fetal alcohol exposure during the early weeks of pregnancy. Knowledge gained from the study can contribute to FASD prevention research throughout the world.

Testing Cognitive Behavior Therapy (CBT) Models and Change Mechanisms for Alcohol-Dependent Women. There is limited research on alcohol-dependent women and, in particular, on the change mechanisms that enable alcohol-dependent women to reduce drinking and maintain sobriety. Furthermore, there is a paucity of clinical research to develop and test cost-effective group therapy models for alcohol-dependent women. One ongoing study is adapting an existing Individual Female-Specific Cognitive Behavioral Therapy (I-FSCBT) approach to treating women with alcohol dependence to a group format (G-FSCBT) and comparing the relative efficacy of the two approaches. Both the group and individual treatments are

abstinence based and include motivational enhancement, coping skills training, management of negative affect, skills to manage heavy drinkers in the social network, relapse prevention, and discussions of personal autonomy. In addition to determining their relative efficacy, investigators are examining hypothesized mechanisms of change in drinking that are common to both the group and individual treatments. The study is also examining the relative cost-effectiveness of the individual and group treatments in an effort to inform decision making by health service policy makers and administrators. Consistent with a growing trend in alcohol treatment research, the research team has developed a plan for transdisciplinary collaboration to explore genetic and environmental interactions that may influence the course of alcohol dependence among women as well as women's response to treatment.

Twin Study of Female Alcoholism and Other Disorders (Objective: 3.1). Adolescent substance abuse is a powerful predictor of adult adjustment and mental health problems. And yet the mechanisms linking early abuse to later maladjustment are not well understood. Using a unique sample of female twins studied prospectively from age 11 to 29, this project will examine how adolescent-onset substance abuse affects mental health and social and neurocognitive functioning in early adulthood. Specifically, a wave of data will be collected from subjects in the Minnesota Twin Family Study (MTFS) as they reach age 29. The resulting data will allow the investigators to study the developmental processes that link adolescent substance abuse with diverse adult outcomes and explore the mechanisms of substance abuse desistance in early adulthood. The female portion of the MTFS is based on 717 pairs of twins and their parents drawn from 2 population-based cohorts. The older twin cohort, originally seen at age 17 and followed up at ages 20 and 24, has completed the age-29 assessment. The younger cohort, originally recruited at age 11, before the initiation of significant substance use, has completed follow-ups at ages 14, 17, 20, and 24 and will be followed through age 29. The age-29 assessment is focused on outcomes potentially associated with adolescent substance use and risk and protective factors that might influence desistance from substance abuse. Data from both cohorts will be combined to examine the developmental trajectories leading to differences in mental health, social, and neurocognitive outcomes at age 29.

Cumulative Stress and Hazardous Drinking in a Community Sample of Adult Lesbians (Objective: 3.1). This study will examine how the accumulation of life stressors such as childhood sexual abuse, adult sexual assault, and discrimination based on race/ethnicity or sexual orientation is related to psychological distress and hazardous drinking in adult women. Understanding how different groups of women respond to and cope with multiple life stressors will aid the development of more effective alcohol abuse prevention and intervention strategies for understudied groups of women. In particular, very little is known about the factors that increase lesbians' risk for hazardous drinking. This project builds on and extends previous work by using cross-sectional and longitudinal data to model effects of cumulative stress on hazardous drinking among lesbians. Lesbians report high rates of traumatic events. Added to these acute stressors are chronic stressors unique to sexual minorities, creating cumulative stress that may be compounded in lesbians of color. The sample of respondents to be studied comes from a large, diverse sample of 384 adult lesbians (50 percent racial/ethnic minority) interviewed in 2000 and 2004 and from a new panel (n=250) recruited by respondent-driven sampling, with oversampling of young (age 18–25), Black, and Latina lesbians.

Neighborhoods, Alcohol Outlets, and Intimate Partner Violence (Objective: 3.9). The overall goal of this study is to gain a deeper understanding of how environmental factors, such as the density of alcohol outlets and neighborhood social disorganization, along with individual- and couple-level characteristics, increase risk for intimate partner violence (IPV). Using a multimethod approach, including geostatistical analyses of archival (e.g., U.S. Census and alcohol outlet) data from 50 California cities with populations between 50,000 and 500,000 and multilevel analysis of survey data from

2,000 married/cohabiting couples, the researchers will:

(1) Estimate the prevalence of self-reported IPV and problem drinking among married/cohabiting couples in relation to the density of alcohol outlets and neighborhood social disorganization;

(2) Investigate constituent couple characteristics that mediate relationships between neighborhood social disorganization and self-reported IPV and determine whether alcohol outlet density affects these relationships;

(3) Identify whether greater availability of alcohol is associated with patterns of venue use related to heavier drinking that affect increased self-reported IPV; and

(4) Determine whether the relationships between other important couple- and individual-level risk factors for IPV (e.g., non-White race/ethnicity, younger age, lower household socioeconomic status) are differentially affected by the level of neighborhood social disorganization.

Alcohol-Related HIV Risks Among South African Women (Objective: 3.9). Research consistently shows that alcohol is closely related to HIV transmission risks in southern Africa, although most research in drinking establishments there has focused on men. This project will conduct a multilevel prospective analysis of alcohol-related HIV/AIDS risks among women who drink in alcohol-serving establishments (shebeens, taverns, and bottle stores) in Cape Town, South Africa. The investigators are collecting environmental-level data from informal drinking places (shebeens), larger drinking places (taverns), and businesses that sell and do not serve alcohol (bottle stores) in two racial/cultural communities (Black Africans of Xhosa heritage and adults of mixed racial background). These locals will be studied by collecting data from key informants (n=20); alcohol-serving business owners, managers, and servers (n=60); interviews (n=240); cross-sectional surveys (n=900) of men and women drinkers; and a prospective cohort of women (n=300). The analyses will focus on the associations between establishment characteristics, socioeconomic conditions, gender dynamics, social norms and collective efficacy, and individual risk characteristics. This last variable will include alcohol expectancies and risk reduction self-efficacy of women who drink in the target settings.

Alcohol and Violence

Brief Intervention for Problem Drinking and Partner Violence. IPV remains a major source of morbidity and mortality in the United States, with women suffering the majority of adverse long-term consequences. While men and women perpetrate IPV at similar rates, an ongoing randomized clinical trial (RCT) will focus on IPV-involved women drinkers (victims, perpetrators, or both). IPV and heavy drinking (four or more drinks/day for women) are commonly seen as cooccurring conditions in emergency department (ED) settings, but these two conditions are rarely addressed together. Interventions that take a collaborative treatment approach to IPV and substance abuse have focused almost exclusively on male perpetrators, even though heavy drinking is also associated with IPV victimization and perpetration in women. Advised by international experts on gender and alcohol use and motivational enhancement therapy, a multidisciplinary group of investigators is conducting an RCT with 600 women ED patients who self-disclose cooccurring problem drinking and intimate partner violence. The project will assess whether a brief motivational intervention can decrease episodes of heavy drinking and incidents of IPV, the occurrence of which will be assessed weekly for 12 weeks. The 25-minute manual-guided motivational intervention will be delivered by trained social workers at the time of the ED visit, which will be followed by a 15-minute phone booster at 10 days. Both the intervention and control group will be contacted at 3, 6, and 12 months following the ED visit. Secondary outcomes include IPV severity, quantity or frequency of alcohol consumption, self-rated health, health behaviors, quality of life, and relationship satisfaction. This model could be generalizable to other acute health care settings.

Longitudinal Study of Social Support, PTSD, and Drinking in Rape Victims (Objective: 3.9). Research shows that posttraumatic stress

disorder (PTSD) and problem drinking are common sequelae experienced by women victims of adult sexual assault, and yet the role of social support in understanding these outcomes is unclear. An ongoing study is testing a theoretical model of relations between social support received by sexual assault victims and their post-assault adjustment, including PTSD, problem drinking, and positive adaptation. The plan is to recruit 1,832 women who (a) experienced either attempted or completed rape, and (b) disclosed their experience to at least 1 informal support provider. They will be selected from the local community, universities, and victim service agencies and will complete a series of 4 mail surveys, distributed at 6-month intervals over the course of 2 years. The researchers are investigating how women's experiences of general and assault-specific social support relate to their coping and behavioral responses and post-assault adjustment over time. Also to be explored is the prospective influence of women's experiences of social support on risk for sexual and nonsexual revictimization and whether such effects are mediated by women's coping and behavioral responses and post-assault adjustment. The research team is also examining how revictimization influences women's subsequent coping and behavioral responses and post-assault adjustment. These processes will be compared in victims of alcohol-related as well as non-alcohol-related sexual assaults. Finally, qualitative data gleaned from interviews with victims and informal support providers will yield a new understanding of how social support influences victims' post-assault adjustment and whether any differences are a function of whether the victim is a problem drinker and whether alcohol was involved in the assault.

Alcohol Use, Relationship Conflict, and Intimate Partner Violence. Although alcohol consumption has long been recognized as a risk factor in IPV, few studies have addressed whether acute alcohol consumption is a causal factor in episodes of relationship conflict or aggression. An ongoing study is addressing the proximal relationship between alcohol consumption and relationship aggression among a community sample of young married and cohabiting couples. There are several unique aspects to the research. First, although the majority of research to date has focused on the role of men's drinking in their perpetration of aggression, women's drinking also may contribute to relationship conflict and aggression. Thus, the role of women's drinking in relationship conflict and aggression—both within the laboratory and in naturally occurring conflict episodes—will be explicitly considered. Secondly, the study is the first to examine the daily relationship between alcohol use and episodes of relationship conflict in a nonclinical sample, and it is expected to address the relative importance of alcohol in naturally occurring relationship conflict. Thirdly, recognizing that alcohol may not facilitate conflict or aggression for all couples, the research will consider the role of potential moderating variables, including propensity toward aggression, behavioral self-control, and alcohol expectancies. The research is expected to provide important insight into the causal mechanisms underlying the alcohol-IPV relationship.

Alcohol and Aggression in Women. Aggression is a major public health concern, with devastating effects to perpetrators, victims, and society, and with associated annual costs of over $100 billion in the United States alone. Alcohol is most commonly linked to violent behavior, with the majority of serious violent acts across the nation occurring under the influence of alcohol. Although the effect of alcohol on aggression has been studied in men, there has been little research on women. This controlled laboratory study is the first to examine the effects of alcohol intoxication on physically aggressive behavior in women with intermittent explosive disorder (IED) and women without IED. In addition, the study is examining cognitive executive functioning as a moderator of alcohol-facilitated aggression in women. With the significant economic and social costs that result from aggression, much of which occurs under the influence of alcohol, furthering our understanding of the inter-relationship between physical aggression, executive functioning, and alcohol-facilitated aggression in women would help identify alcohol as a risk factor for female aggression. Furthermore, this will open up a new avenue of research into other possible risk factors for alcohol-facilitated aggression in women and guide the

development of treatment and intervention programs among women in much the same way that such research in men has done.

Brief Intervention to Reduce Drinking and Intimate Partner Violence in Women. This research project is evaluating the effects of adding a brief intervention that combines alcohol intervention with a standard batterer intervention in a comparison with individual interventions provided singly. Specifically, it is examining the effects of the intervention on alcohol use and the perpetration of violence and victimization among these women. In addition, the study aims to evaluate the relationship between women's alcohol use and IPV by examining the relationship between use and violence on women's drinking versus nondrinking days. The study fits under the NIAAA strategic plan goal to elucidate the relationships between alcohol and violence.

Reducing Violence Against Women with Alcoholic Partners. An ongoing research project is developing a training program in coping skills for women with an alcoholic partner. The study is comparing this program with a standard 12-step facilitation treatment. The project will evaluate and compare outcomes of the treatments, including levels of interpartner violence, negative affect, and negative marital behaviors among the partners. The study will also evaluate the women's coping-skill levels and drinking patterns and their relationships to the behavioral outcomes.

Developing Web-Delivered Coping Skills Training for Women with Alcoholic Partners. Nearly 1 in 20 adult women in the United States live with an alcoholic or problem-drinking partner. To address this issue, this project will develop and test an empirically supported, clinic-based coping skills training (CST) program for women with alcoholic/problem-drinking partners. The CST will be developed in a Web-accessible version. The aim is to develop an easily accessible, confidential, low-cost, evidence-based treatment for a large segment of the population that otherwise would not or could not receive or seek care for this widespread problem.

Mechanisms of Alcohol-Facilitated Intimate Partner Violence. IPV is a critical public health problem that requires clear and testable etiological models that may translate into effective interventions. Given that acute alcohol intoxication and a pattern of heavy alcohol consumption are among the most robust correlates of IPV perpetration, etiological models of how alcohol facilitates aggression are critical to the development of interventions. However, while an abundance of research has focused on moderators of the alcohol-IPV link, much less attention has been paid to conducting empirical studies on the specific affective and cognitive mediators of this relation. This limitation prevents research from developing and testing theoretically based interventions designed to reduce alcohol-facilitated IPV. The goals of this project are to:

(1) Test a mediation model of alcohol-facilitated IPV etiology; and

(2) Evaluate mechanisms of change via a theory-based manipulation that will inform IPV interventions for at-risk men and women.

Minority Stress, Alcohol Use, and Intimate Partner Violence Among Lesbians. Alcohol abuse and dependence, and the constellation of problems associated with these disorders, including IPV, are a serious health concern for sexual minority women, their partners, their families, and society as a whole. Despite documentation of important health disparities, a significant gap still exists regarding our understanding of why sexual minority women are more likely to experience alcohol-use disorders and IPV. This project tests a model of alcohol misuse and IPV among lesbians that was developed by integrating existing lines of research in the areas of clinical, social, and health psychology. Grounded in the minority stress model and mediation model of sexual minority stigma, the conceptual framework guiding this research focuses on sexual minority stressors, stigma-related processes, coping, emotional regulation, psychological and relationship distress, and drinking coping motives as potential predictors of alcohol misuse and IPV in lesbians. The specific aims are as follows:

(1) To examine the longitudinal relationship between sexual minority stressors and subsequent alcohol use (i.e., in terms of quantity, frequency, and binge drinking) and IPV; and

(2) To examine potential mediators of the relationship between sexual minority stressors and alcohol misuse and IPV.

A Randomized Controlled Trial of a Brief Intervention for Problem Drinking and Partner Violence. IPV remains a major source of morbidity and mortality in the United States, with women suffering the majority of its adverse long-term consequences. IPV and heavy drinking (four or more drinks/day for women) are commonly seen as cooccurring conditions in the emergency department (ED) setting, both acutely and chronically, with apparent bidirectional causation, but these two conditions are rarely addressed together. There is evidence that brief opportunistic interventions in the ED setting are effective in reducing subsequent hazardous drinking and alcohol-related injuries, but results have been less clear in women specifically. This project, which brings together a multidisciplinary group of investigators with experience in IPV, emergency medicine, brief ED interventions, motivational interviewing, psychotherapy efficacy research, and the modeling of complex psychosocial data, proposes a randomized controlled trial with 600 women ED patients who self-disclose cooccurring problem drinking and IPV to assess whether a brief motivational intervention can decrease primary outcomes of episodes of heavy drinking and incidents of IPV.

Initiatives

Request for Applications (RFAs)

Collaborative Initiative on FASD (CIFASD). These announcements solicited cooperative agreement applications from current awardees and new applicants to continue the previously funded "Collaborative Initiative on Fetal Alcohol Spectrum Disorders" (CIFASD), a multidisciplinary consortium of domestic and international projects. The CIFASD aims to accelerate specific areas of research related to the translation of new or improved capabilities in FASD clinical case recognition (through improved diagnosis and enhanced understanding of the domains of neurobehavioral impairment), interventions (behavior based, nutritional, or pharmacological) and prevention by fostering collaboration and coordinating basic, clinical, and translational research. (RFA-AA-12-004 and RFA-AA-12-005)

Building Interdisciplinary Research Careers in Women's Health (BIRWCH). ORWH and cosponsors, which include NIAAA, issued this RFA to support junior faculty members, known as BIRCWH scholars, by helping them to receive mentored research career development in interdisciplinary research on women's health or on sex/gender differences related to biology, health, or disease. NIAAA provides cofunding for one grant that focuses on understanding the interplay between women's health and addictive behaviors, specifically involving tobacco, alcohol, overeating, or illicit drugs. (RFA-OD-11-002)

Program Announcements (PAs)

Effects of In Utero Alcohol Exposure on Adult Health and Disease. The purpose of this funding opportunity announcement (FOA) is to support novel research on how prenatal alcohol exposure may contribute to the etiology of chronic diseases and health conditions later in life.

Central to this theme is the developmental origins of health and disease concept, which suggests that fetal adaptations in response to adverse intrauterine conditions may increase the risk for childhood and adulthood disease (e.g., cardiovascular disease, type 2 diabetes, obesity, select cancers, asthma, and behavioral disorders). Studies supported by this FOA will provide fundamental insights into a possible fetal basis to adult disease that may be influenced by maternal alcohol use. (PA-12-291 and PA-12-292)

Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence. NIAAA is continuing to participate with NIDA (National Institute on Drug Abuse) in an initiative to promote research on women and sex/gender differences in drug/alcohol abuse and dependence. This initiative encourages research from basic studies of

molecular genetics and neurotransmitters to studies of epidemiology, etiology, and prevention/treatment interventions that focus on sex/gender differences. Studies on sex/gender-based interventions related to HIV/AIDS and crosscutting issues related to stages of the life cycle, health disparities, methodological approaches, and gender-specific recruitment issues are also encouraged. (PA-11-047, PA-11-048, and PA-11-049)

Genetic Susceptibility and Variability of Human Structural Birth Defects. NIAAA participated with several ICs in this FOA, which invites R01 applications for research designed to study fundamental developmental processes using animal models in conjunction with translational/clinical approaches, with the goal of advancing understanding of the etiology of structural birth defects. Alcohol is a known teratogen, capable of causing FASD, a collection of birth defects and developmental disabilities that occur in individuals whose mothers drank alcohol during pregnancy. (PA-11-085)

Chronic Fatigue Syndrome: Pathophysiology and Treatment. NIAAA has a shared interest in two ORWH initiatives on pathophysiology and treatment of chronic fatigue syndrome (CFS) that extend until October 2014. The objective of these FOAs is to encourage research into the etiology, diagnosis, pathophysiology, and treatment of CFS in diverse groups and across the lifespan, and also into the environmental and biological risk factors, the determinants of heterogeneity among patient populations, and the common mechanisms influencing the multiple body systems that are affected in CFS. Interdisciplinary research is highly encouraged. (PAR-12-032 and PAR-12-033)

Publications: Brochures and Fact Sheets

- U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism. (2011). *Women and alcohol* [Electronic factsheet]. Retrieved from *http://pubs.niaaa.nih.gov/publications/womensfact/womensfact.htm*
- U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism. (2012). *Fetal alcohol exposure* [Electronic factsheet]. Retrieved from *http://pubs.niaaa.nih.gov/publications/FASDFactsheet/FASD.pdf*
- U.S. Department of Health and Human Services, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism. (2012). *Older adults and alcohol: You can get help* (NIH Publication No. 11-7350). Retrieved from *http://pubs.niaaa.nih.gov/publications/olderAdults/olderAdults.htm*

National Institute of Allergy and Infectious Diseases

Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to prevent, diagnose, and treat infectious and immune-mediated diseases, including diseases that affect the health of women and girls. NIAID involves women in many of its clinical studies on treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and other infectious diseases. NIAID also collaborates with other organizations on research initiatives within NIAID's mission areas that aim to improve women's health.

This biennial report provides an overview of selected NIAID-sponsored women's health activities. The first section describes scientific accomplishments in research on HIV/AIDS, non-HIV infectious diseases including sexually transmitted infections (STIs), and immunology and immune-mediated diseases. The accomplishments include (1) supporting clinical trials that test antiretroviral (ARV) drugs and topical microbicides to prevent the transmission of HIV to women or their partners as well as a new ARV drug regimen to minimize the risk of mother-to-child

transmission (MTCT) of HIV during breastfeeding; (2) epidemiologic studies on the effect of HIV infection on women's risk of cervical cancer or precancer; (3) development of a novel silicone-based microbicide gel formulation that women could use to protect against sexually transmitted HIV infection; (4) basic research to understand how foodborne infections can damage a pregnant woman's unborn child; (5) clinical studies of vaccines against human papillomavirus infection in HIV-infected women and girls; and (6) basic research that could lead to new treatment approaches to minimize the impact of estrogen on lupus and other autoimmune diseases, improve understanding of how genetic factors increase the risk of developing multiple sclerosis, and provide insights into immune-mediated complications of human pregnancy. The sections on related accomplishments in women's health research include career development and describe activities of NIAID's Women's Health Research Work Group. Additional sections address studies on sex/gender differences in disease outcomes and responses to therapy; research initiatives for HIV/AIDS, STIs and other infections, and autoimmune diseases; conferences and publications; and research on health disparities in special populations.

Accomplishments

Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS)

The United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that 34 million people worldwide are infected with HIV. Women face the greatest risk of acquiring HIV because of substantial mucosal exposure to seminal fluids, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners. Most women are infected with HIV through sex with men or injection drug use.

According to UNAIDS, in 2011, women accounted for more than half of all adults living with HIV worldwide and for 58 percent in sub-Saharan Africa. The Centers for Disease Control and Prevention (CDC) reported that the rate of new HIV diagnoses in women in the United States leveled off from 2006 to 2009, after increasing in previous years. This trend was accompanied by a slight decline in the rate of new AIDS diagnoses in women in the United States. However, HIV/AIDS and associated diseases and co-infections continue to cause substantial illness and death in the United States and worldwide. In 2011, WHO reported that HIV/AIDS is the leading cause of death globally for women of reproductive age.

In addition to facing complications associated with HIV/AIDS similar to those that also affect men, infected women also suffer gender-specific manifestations of HIV disease, including human papillomavirus (HPV)–related cervical dysplasia (abnormal, precancerous cell growth) and cervical cancer. HIV-infected women have a higher prevalence of HPV infection, a higher risk of progression from infection to disease, and an increased risk of invasive cervical cancer and other HPV-related cancers. Anal cancer is emerging as an important clinical entity in HIV-infected individuals. In women, an important risk factor for anal cancer is advanced cervical dysplasia, while sexual practices and behaviors have not been shown to be associated with anal cancer. (Note: For more information on HPV infection, please see Infectious Diseases Other than HIV/AIDS.)

Combination ARV therapy for HIV has not significantly decreased the incidence of HPV-related cancers. Other complications of HIV infection in women, such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, and severe herpes infections are reduced in the setting of successful combination ARV therapy. Drug metabolism differs in women compared with men, potentially resulting in differential responses to ARV therapy and an increased incidence of drug toxicities in women.

In many parts of the world, death and illness due to pregnancy and childbirth are a frequent occurrence. Thus, use of contraceptives is the most successful intervention to prevent maternal illness and death, and, by preventing pregnancy, to prevent MTCT of HIV. Hormonal methods of birth control are most

effective but may interact with antiretroviral drugs, which could lead to additional toxicities or treatment failures. Also, and perhaps more important, several recent studies have shown an increased risk of HIV transmission to an uninfected male partner if the woman is using hormonal contraceptives. Forms of contraception that are effective, safe, and do not increase the risk of transmitting HIV to an uninfected partner are urgently needed, as are safe and effective methods to prevent MTCT of the virus.

Achieving effective treatment of HIV infection may be more problematic for women than for men because women may have difficulty accessing health care and carry a large burden of caring for children and other family members, including those who also may be HIV-infected. They often lack social and financial resources to cope with HIV and other challenges.

NIAID is supporting investigations of the course of HIV/AIDS in women through multiple initiatives, including intramural studies; investigator-initiated research; the Women's Interagency HIV Study (WIHS), a long-term cohort study; and clinical trials to investigate gender-specific differences in HIV disease progression, complications, and/or treatment. These clinical trials are being conducted by the Microbicide Trials Network (MTN), the AIDS Clinical Trials Group (ACTG), the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), the HIV Interdisciplinary Network for Pathogenesis Research in Women, the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). The research described in this section supports ORWH strategic goal 1.6.

Epidemiologic Research

NIAID supports epidemiologic research in the following areas:

- The long-term natural history of HIV infection in women—In particular, research that evaluates the impact of ARV therapy on the clinical course of HIV disease throughout a woman's life span;
- The effect of hormonal, endocrine, bacterial, and local factors on the levels of HIV in the plasma and genital tract and on sexual transmission of the virus;
- Studies of older populations of HIV-infected women to investigate what pathogenic processes are related to HIV, ARV therapy, and/or the aging process;
- Characterization of acute clinical events and co-infections and their impact on HIV disease progression; and
- Studies of the female genital tract compartment, including the microenvironment, HIV virology, and immunology of the female genital tract compared with blood.

Women's Interagency HIV Study (WIHS)

WIHS is the largest observational study of HIV-infected women and includes participants living in eight U.S. metropolitan areas (in FY 2012, WIHS was expanded to include four new research consortia and to make it more representative of the U.S. epidemic). The majority of the more than 3,500 women enrolled in the study are African-American and Latina women living in urban areas. The size of the study, the number of recently diagnosed patients, and the availability of stored biospecimens allow the evaluation of clinical outcomes in the era of highly active antiretroviral therapy (HAART). Researchers are investigating factors such as the development of AIDS, drug resistance, co-infections, therapy use and treatment effects, metabolic abnormalities and toxicities, hormonal factors, aging, neurocognitive functioning, and physical impairment. This study has yielded discoveries that have led to a better understanding of how HIV is spread, how HIV disease progresses, and how it can best be treated. More information is available at *http://statepiaps.jhsph.edu/wihs*.

Scientific Advances

Risk of Cervical Precancer and Cancer Among HIV-Infected Women with Normal Cervical Cytology and No Evidence of Oncogenic HPV Infection. This NIAID-funded study showed that, through 5 years of follow-up, the risk of cervical precancer and

cancer was similar in HIV-infected women and HIV-uninfected women who had a normal Pap test result and who tested negative for cancer-causing forms of HPV. Additional studies may be necessary before considering whether to expand current recommendations to HIV-infected women regarding HPV cotesting and the suggested interval between Pap tests.

Keller, M. J., Burk, R. D., Xie, X., Anastos, K., Massad, L. S., Minkoff, H., … Strickler, H. D. (2012). Risk of cervical precancer and cancer among HIV-infected women with normal cervical cytology and no evidence of oncogenic HPV infection. *Journal of the American Medical Association, 308*(4), 362–369.

T-Cell Activation Predicts Carotid Artery Stiffness Among HIV-Infected Women. HIV disease is associated with increased arterial stiffness, which may be related to inflammation provoked by HIV-related immune perturbation. NIAID-supported investigators found that, among HIV-infected women, certain cellular markers of immune activation were associated with increased carotid artery stiffness. The findings suggest that proinflammatory populations of T cells, a type of immune cell, may produce functional or structural changes in blood vessels in HIV-infected women who have relatively severe damage to the immune system caused by the HIV.

Kaplan, R. C., Sinclair, E., Landay, A. L., Lurain, N., Sharrett, A. R., Gange, S. J., … Hodis, H. N. (2011). T cell activation predicts carotid artery stiffness among HIV-infected women. *Atherosclerosis, 217*(1), 207–213.

International Epidemiologic Databases to Evaluate AIDS (IeDEA)

The IeDEA consortium brings together clinical data collected as part of research initiatives and diverse care programs. Each of the seven global regions enrolls patients who are representative of the HIV epidemic within the region. In the United States, the North American AIDS Collaboration of Observational Research Databases includes data from more than 18,000 women living in the United States or Canada. The consortium's size allows for in-depth assessment of clinical outcomes, including rare events and their predictors. Globally, IeDEA represents the severity of the epidemic among women, with more than half of the data coming from women. More information is available at *http://www.iedea.org*.

Scientific Advance

Estimated Mortality of Adult HIV-Infected Patients Starting Treatment with Combination Antiretroviral Therapy. This study, supported in part by NIAID, found that many patients with HIV start treatment when their immune systems are already significantly suppressed by the disease and experience high levels of mortality during the first 6 months after treatment initiation—despite worldwide advances in the number of HIV/AIDS patients receiving antiretroviral therapy (ART). Maintaining contact with patients and using vital registries to determine death are critical for deriving accurate estimates of mortality, particularly in low- and middle-income settings. Along with the youngest patients, older patients with HIV have high death rates. With extended survival due to the expansion of ART coverage and the resulting aging of the HIV/AIDS population, the impact of age on mortality should be considered in decision making and policy making.

Yiannoutsos, C. T., Johnson, L. F., Boulle, A., Musick, B. S., Gsponer, T., Balestre, E., … Egger, M.; International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration. (2012). Estimated mortality of adult HIV-infected patients starting treatment with combination antiretroviral therapy. *Sexually Transmitted Infections, 88*(Suppl 2), i33–i43.

Prevention Research—Topical Microbicides

There is an urgent need to develop a safe, effective, and acceptable topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection. NIAID-sponsored research focuses on the development of topical microbicides that (1) prevent HIV infection and/or viral replication; (2) are safe and do not irritate vaginal, cervical, urethral, or rectal tissues; and (3) reduce HIV transmission and acquisition, even in the presence of other STIs, which increase the risk of acquiring HIV.

Microbicide Trials Network (MTN)

In 2006, MTN was formed to develop and evaluate microbicide products aimed at reducing the sexual transmission of HIV. MTN consists of a strong network of expert scientists and investigators from U.S. and international sites. The network uses a focused research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. More information is available at *http://www.mtnstopshiv.org*.

Scientific Advances

Potential for Rectal Use of OTC Lubricants to Increase Risk of STIs: Implications for Safety of Over-the-Counter (OTC) Lubricants and HIV/STI Prevention. NIAID-supported research has shown that use of OTC lubricants was associated with an increased incidence of rectal STIs in men and women practicing anal intercourse. This has significant prevention and public health implications in that OTC products could promote STIs. In other ongoing NIAID-funded work, researchers are examining the effects of a range of OTC lubricants on vaginal and rectal safety in a standardized animal safety model and studying their effects on tissue integrity and virus replication in a cervical tissue-derived organ culture model.

Gorbach, P. M., Weiss, R. E., Fuchs, E., Jeffries, R. A., Hezerah, M., Brown, S., … Cranston, R. D. (2012). The slippery slope: Lubricant use and rectal sexually transmitted infections: A newly identified risk. *Sexually Transmitted Diseases, 39*(1), 59–64.

Determining the Relationship Between Rectal Tissue Concentration of UC781 Microbicide and Biopsy Infectability: A First Step Toward Defining a Surrogate Marker for Efficacy. In trials conducted under NIAID's Integrated Preclinical/Clinical Program for HIV Topical Microbicides, researchers created a new statistical model that has allowed further analysis of data from an early-phase safety study (RMP-01) of the vaginally formulated UC781 gel as a rectal microbicide. This new statistical method allowed researchers to determine specific relationships between tissue drug concentrations and the effectiveness of UC781 in a biopsy challenge model, which tests the ability of HIV to infect small samples (biopsies) of rectal tissue from patients. This work provided the first estimate of the concentration of drug in gel that might be required to prevent HIV transmission, and identified the biopsy challenge model as a potential bridge to link drug concentration in tissues with possible efficacy of the drug.

Richardson-Harman, N., Mauck, C., McGowan, I., & Anton, P. (2012). Dose-response relationship between tissue concentrations of UC781 and explant infectability with HIV type 1 in the RMP-01 rectal safety study. *AIDS Research and Human Retroviruses, 28*(11), 1422–1433.

Developing Novel Gel Microbicide Delivery Systems: Coitally Independent Microbicide Gels. Researchers funded by the Integrated Preclinical/Clinical Program for HIV Topical Microbicides have developed a silicone-based gel to deliver the microbicide maraviroc. Through studies in nonhuman primates they showed that the silicone gel provides sustained delivery of maraviroc, opening the door to a gel-based vaginal microbicide that women could apply once daily, independent of sexual intercourse. In addition to providing higher and longer sustained release of maraviroc than a comparable water-based gel, the silicone gel offers better formulation for poorly water-soluble microbicides and could potentially be less messy than standard water-based gels.

Forbes, C. J., Lowry, D., Geer, L., Veazey, R. S., Shattock, R. J., Klasse, P. J., … Malcolm, R. K. (2011). Non-aqueous silicone elastomer gels as a vaginal microbicide delivery system for the HIV-1 entry inhibitor maraviroc. *Journal of Controlled Release, 156*(2), 161–169.

Clinical Trials

Vaginal and Oral Interventions to Control the Epidemic (VOICE) Trial (MTN-003). This large, randomized Phase IIb clinical trial—conducted at multiple sites in South Africa, Uganda, and Zimbabwe—was designed to evaluate the safety and effectiveness of two approaches to HIV prevention: oral tablets containing either the antiretroviral drug tenofovir or a combination of tenofovir and emtricitabine (known as

Truvada®), and tenofovir 1% vaginal gel. VOICE substudies examined the potential for developing drug resistance in women who acquire HIV while participating in the study, the impact of the oral tablet regimen on bone mineral density, the impact of individual and community factors on continued trial participation and adherence to treatment, and potential sources of efficacy dilution. In late 2011, the data and safety monitoring board recommended to discontinue first the oral tenofovir part of the study and then the gel part of the study, due to lack of efficacy. There was no evidence of major safety issues at either review. Follow-up of all 5,029 participants is complete. Primary study results released in March 2013 indicated that the three antiretroviral-based strategies intended to prevent HIV infection did not prove effective among study participants, who were predominantly young and unmarried. For reasons that are currently unclear, a majority of study participants were unable to use their assigned approaches daily as directed. VOICE C and VOICE D substudies are exploring women's motivations for adherence or nonadherence, and aim to further elucidate the issues that influenced their decisions. More information is available at *http://www.nih.gov/news/health/mar2013/niaid-04a.htm*.

MTN-001 was conducted in support of VOICE and was designed to examine differences in the pharmacokinetics (that is, bodily absorption, distribution, metabolism, and excretion) of oral and gel forms of tenofovir. The study showed that vaginal use of tenofovir gel resulted in higher concentrations of active drug in vaginal tissue than did the oral tablet.

Safety and Pharmacokinetic Study of a Single Dose of Vaginal Tenofovir 1% Gel (MTN-002). MTN has initiated a unique effort to examine microbicide use during pregnancy. This study examined the effects of applying tenofovir 1% gel as a one-time, single dose in 16 healthy HIV-negative women prior to giving birth by scheduled Caesarean delivery. The study demonstrated that tenofovir gel was safe, with lower concentrations of tenofovir detected in maternal serum and fetal cord blood than after oral tenofovir use.

A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) (MTN-020). This Phase III trial to evaluate the safety and effectiveness of an intravaginal ring (VR) containing the antiretroviral drug dapivirine has been initiated at multiple sites in sub-Saharan Africa. Approximately 25 percent of the estimated 3,500 women have been enrolled since the study was initiated in August 2012. This two-arm study comparing the monthly use of a dapivirine-containing VR to a matched placebo VR is being conducted in parallel with the Ring Study, a smaller safety and effectiveness study in southern Africa supported by the International Partnership for Microbicides, the sponsor of the dapivirine VR. These trials are the first to evaluate long-term, sustained delivery of an ARV from a VR for HIV prevention.

Rectal Microbicide Safety and Acceptability Studies. Researchers have completed two NIAID-supported studies evaluating tenofovir-containing microbicides for rectal use. RMP02/MTN-006 was a Phase I pharmacokinetic and safety study of the vaginal formulation of tenofovir 1% gel conducted in men and women in Los Angeles and Pittsburgh. Tolerability issues observed during this study led to reformulation of the tenofovir gel. The reformulated reduced glycerin (RG) tenofovir 1% gel was evaluated in U.S. men and women in MTN-007. Results demonstrated that RG tenofovir 1% gel was safe and well-tolerated. A multisite domestic and international Phase II expanded safety and acceptability study of the RG tenofovir 1% gel (MTN-017) in men who have sex with men (MSM) and transgender women is planned to start in 2013.

Evaluating Outcomes of Women Enrolled in Microbicide Trials. NIAID is supporting two studies (MTN-015 and EMBRACE/MTN-016) to better understand the impact of using microbicides prior to exposure to HIV, in an attempt to reduce the risk of infection (an approach known as pre-exposure prophylaxis, or PrEP) for women who either become infected with HIV or become pregnant while participating in a clinical trial. These studies are currently enrolling participants.

Integrated Preclinical/Clinical Program HIV Topical Microbicides Awards. Several studies

funded through this program were developed, initiated, and/or completed in 2012. They include the following: completion of a trial of rectal health, behaviors, and microbicide acceptability; a safety and acceptability study of UC781 vaginal microbicide gel for rectal application in individuals not infected with HIV (described above); a study of the pharmacokinetics and bodily distribution of oral tenofovir and vaginally formulated tenofovir gel used rectally; and studies to explore the sensory perceptions of vaginal product users and relate them to the physical properties of vaginal gels, films, and intravaginal rings. One ongoing study is the first clinical testing of a vaginal film containing tenofovir. This study includes dose-ranging to test the hypothesis that a vaginal film could be a more efficient drug delivery system than a hydrogel, due to decreased leakage. Studies planned to start soon include the first testing of a plant-produced antibody for vaginal prevention of HIV, use of optical imaging to determine drug pharmacokinetics in the body, development and clinical testing of rectal-specific microbicide gel formulations containing tenofovir and dapivirine, and the delivery of tenofovir using a novel polyurethane salt core intravaginal ring. More information is available at *http://www.niaid.nih.gov/topics/hivaids/research/prevention/pages/topicalmicrobicides.aspx*.

Prevention of Mother-to-Child Transmission (MTCT) of HIV

According to WHO, the vast majority of all HIV-infected infants and children acquire the virus from their mothers before or during birth or through breastfeeding. Most MTCT occurs late in pregnancy or during birth. Currently, the United Nations Children's Fund (UNICEF) and WHO recommend that infants born to HIV-infected mothers who do not have access to acceptable, feasible, affordable, sustainable, and safe replacement feeding should be exclusively breast-fed for at least 6 months. NIAID is conducting studies for prevention of mother-to-child transmission (PMTCT) in HIV-infected pregnant women. NIAID-sponsored PMTCT research focuses on the following goals:

- To define the mechanisms and risk factors for HIV transmission to children and adolescents and from mother to infant as well as risks for disease progression within the framework of clinical studies and trials;
- To develop and test additional ARV strategies for PMTCT of HIV infection through clinical trials in the United States and international settings; and
- To develop interventions for PMTCT of HIV via breast milk in settings where breastfeeding is the best assurance for infant nutrition.

International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

IMPAACT, sponsored by NIAID and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), is a network dedicated to significantly decreasing the mortality and illness associated with HIV disease in children, adolescents, and pregnant women. IMPAACT develops and evaluates safe and cost-effective approaches for the interruption of mother-to-infant HIV transmission; evaluates treatments for HIV-infected children, adolescents, and pregnant women; investigates strategies for treatment and prevention of co-infections and illnesses associated with HIV; and evaluates vaccines for preventing the sexual transmission of HIV among adolescents. More information is available at *https://impaactgroup.org/*.

Scientific Advances

The Effects of Single-Dose Nevirapine (SD NVP) on Future Treatment Options for Women and Children. NIAID-supported investigators published results from two major studies: OCTANE/A5208 and P1060. Both studies demonstrated that SD NVP (an antiretroviral drug) used for PMTCT can hamper the drug's future effectiveness as part of an HIV treatment regimen for either the mother or the child. More information is available at *http://www.niaid.nih.gov/news/newsreleases/2010/Pages/P1060OCTANE.aspx.*

Lockman, S., Hughes, M. D., McIntyre, J., Zheng, Y., Chipato, T., Conradie, F., …

Currier, J. S.; OCTANE A5208 Study Team. (2010). Antiretroviral therapies in women after single-dose nevirapine exposure. *New England Journal of Medicine, 363*(16), 1499–1509; Palumbo, P., Lindsey, J. C., Hughes, M. D., Cotton, M. F., Bobat, R., Meyers, T., … Violari, A. (2010). Antiretroviral treatment for children with peripartum nevirapine exposure. *New England Journal of Medicine, 363*(16), 1510–1520.

Efficacy and Safety of an Extended Nevirapine Regimen in Infant Children of Breastfeeding Mothers with HIV-1 Infection for Prevention of Postnatal HIV-1 Transmission (HPTN 046). This advanced-stage clinical trial, cofunded by NIAID, NICHD, the National Institute on Drug Abuse, and the National Institute of Mental Health, showed that an extended regimen of nevirapine (NVP) can safely be used to provide protection from MTCT of HIV via breastfeeding for infants up to 6 months of age. Extended breastfeeding reduces infant mortality in places that lack safe, clean water by protecting babies from common childhood diseases because breast milk contains protective antibodies from the mother that are not provided by formula feeding. The study found that giving the infants of HIV-infected mothers an antiretroviral drug daily for the full duration of breastfeeding safely minimizes the threat of HIV transmission through breast milk while preserving the health benefits of extended breastfeeding.

Coovadia, H. M., Brown, E. R., Fowler, M. G., Chipato, T., Moodley, D., Manji, K., … Maldonado, Y.; HPTN 046 Protocol Team. (2012). Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): A randomised, double-blind, placebo-controlled trial. *Lancet, 379*(9812), 221–228.

Three Postpartum Antiretroviral Regimens to Prevent Intrapartum HIV Infection. This HPTN study compared three ART regimens to prevent infection of HIV-uninfected infants born to HIV-infected women. In newborns whose mothers did not receive ART during pregnancy, a two- or three-drug ART regimen was found to be more effective than the drug zidovudine alone for preventing MTCT. The study also found that the two-drug regimen was less toxic and easier to use than the three-drug regimen. This study was funded primarily by NICHD with cofunding from NIAID.

Nielsen-Saines, K., Watts, D. H., Veloso, V. G., Bryson, Y. J., Joao, E. C., Pilotto, J. H., … Mofenson, L. M.; NICHD HPTN 040/PACTG 1043 Protocol Team. (2012). Three post-partum antiretroviral regimens to prevent intrapartum HIV infection. *New England Journal of Medicine, 366*(25), 2368–2379.

Clinical Trials

Promoting Maternal and Infant Survival Everywhere (PROMISE) Study. This large, multinational clinical trial, which began in 2010, is designed to determine how best to reduce the risk of HIV transmission from infected pregnant women to their babies during pregnancy and breastfeeding and the best strategies to preserve maternal health during and after pregnancy and breastfeeding. The study aims to enroll about 8,000 HIV-infected women who are pregnant or have recently given birth and about 6,000 HIV-exposed infants of these women. Study participants are being recruited from as many as 18 high- to low-resource countries. More information is available at *http://www.niaid.nih.gov/news/newsreleases/2010/pages/promise.aspx*.

Additional Studies on the Effects of SD NVP on Future Treatment Options for Women and Children. Two studies—ACTG 5207 in Africa, India, and Haiti and PACTG 1032 in Thailand—explored strategies to minimize viral resistance to ARV therapy and assess the impact of viral resistance in women or children receiving SD NVP to prevent MTCT of HIV.

HIV Treatment Reinitiation in Women Who Received Anti-HIV Drugs to Prevent Mother-to-Child Transmission of HIV (ACTG 5227). This study examined whether the impact of HAART in women for treatment of HIV is affected by prior exposure to HAART for PMTCT.

Studies to Evaluate Approaches for PMTCT. Several trials are investigating the use of ARVs in infants and mothers to prevent MTCT.

HPTN 040 assessed two different combinations of anti-HIV medications compared with a one-drug standard regimen given at birth. HPTN 046 assessed daily use of NVP for 6 months in infants to prevent HIV transmission in breastfeeding women. An investigator-initiated clinical trial assessed the impact of maternal HAART on transmission of HIV resistance to the infant during breastfeeding. P1025 is monitoring the health of HIV-infected pregnant women and their children who receive ART.

Vaccine Research

Vaccines serve as the foundation of preventive measures to curtail infectious disease epidemics. NIAID conducts and supports basic research in areas such as infectious diseases, microbiology, and immunology to generate the knowledge essential for developing safe and effective vaccines to prevent HIV infection. The recent positive findings from the RV144 HIV vaccine efficacy trial in Thailand, which showed that a candidate vaccine was partially effective at preventing HIV infection, have provided renewed energy in the field. NIAID is building on this achievement through a sustained commitment to pursuing both basic and vaccine discovery research while continuing to advance the most promising HIV vaccine candidates into testing. Even a partially effective HIV vaccine could have a significant positive impact on the health of women, particularly in resource-limited settings.

HIV Vaccine Trials Network (HVTN)

The HVTN is an international collaboration of scientists searching for an effective and safe HIV vaccine. HVTN's mission is to facilitate the process of testing preventive vaccines against HIV/AIDS. HVTN conducts all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses to testing vaccine efficacy. More information is available at *http://www.hvtn.org.*

Clinical Trial

Longitudinal Studies of Women at High Risk for HIV-1 Infection to Inform HIV Vaccine Trial Participation (HVTN 906; HVTN 907). HVTN completed two studies on the feasibility of identifying, recruiting, and retaining women at high risk for HIV infection for participation in vaccine trials. These studies will also estimate HIV incidence in study participants over an 18-month period. HVTN 906 enrolled 800 women with multiple risk behaviors living in New York City, Philadelphia, and Chicago. HVTN 907 also enrolled 800 women with high-risk behaviors in the Caribbean (Haiti, Dominican Republic, and Puerto Rico). Women in both studies received HIV counseling and testing, behavioral risk assessment, and pregnancy testing. They were also periodically asked to complete a vaccine trial participation questionnaire. Study investigators are analyzing the data and preparing their results for publication. The publications will examine the success of enrollment strategies, discuss factors that predict HIV prevalence, and identify factors that predict willingness to participate in future HIV vaccine trials.

Other Prevention Research—HIV Prevention Trials Network (HPTN)

Established in 2000, HPTN is a worldwide collaborative clinical trials network that develops and tests the safety and efficacy primarily of nonvaccine interventions designed to prevent the transmission of HIV. The HPTN research agenda focuses on the use of ARV therapy; treatment and prevention of sexually transmitted infections; treatment of substance abuse, particularly injection drug use; behavioral risk reduction interventions; and integrated combination strategies to reduce HIV transmission and acquisition. HPTN studies are conducted in various populations, including women, and in geographical regions that bear a disproportionate burden of HIV infection. More information on HPTN is available at *http://www.hptn.org*.

Clinical Trials

Women's HIV Seroincidence Study (ISIS) (HPTN 064). This multisite observational study was designed to estimate the overall HIV incidence in 2,099 women at high risk for HIV acquisition in the United States and to evaluate the feasibility of implementing an HIV prevention intervention trial in this population. Investigators also evaluated

laboratory tests for HIV; estimated study recruitment and retention rates; described sexual behaviors, alcohol and drug use, prevalence of domestic violence, and mental health indicators of women at risk for HIV; assessed women's preferred recruitment and retention strategies for future studies; described social, structural, and contextual factors to inform future intervention studies; and explored facilitators and barriers to HIV testing among men residing in the same high-risk areas. In January 2013, the investigators reported an estimated annual HIV incidence of 0.32 percent in the study population, indicating that the HIV incidence rate for women in the United States living in areas hardest hit by the epidemic is much higher than the overall estimated incidence rate in the United States for Black adolescent and adult women.

HPTN 069: Novel Exploration of Therapeutics for PrEP (NEXT PrEP). NEXT PrEP is a multisite, randomized, double-blind clinical trial of the safety and tolerability of four ARV drug regimens that could be used for PrEP: Maraviroc (MVC) alone, MVC and emtricitabine, MVC and tenofovir, and tenofovir and emtricitabine. This study will include 400 HIV-uninfected MSM and 200 HIV-uninfected women who engage in high-risk sexual behaviors. Objectives of the study, which is cofunded by the ACTG and includes some ACTG sites, include assessing the pharmacokinetics and tissue penetration of the drugs into rectal, vaginal, and cervical tissues.

Therapeutics Research

AIDS Clinical Trials Group (ACTG)

Established in 1987, ACTG is a multicenter clinical trials network that conducts translational and therapeutics research in the United States and internationally. Research priorities include translational research and optimizing the clinical management of HIV/AIDS, including HIV-related co-infections and diseases. In collaboration with other clinical trials networks, ACTG also pursues research and development of therapeutic vaccines and research on HIV treatment in pregnant women. More information is available at *http://actgnetwork.org*.

Scientific Advances

Once-Daily Antiretroviral Therapy Combinations for Treatment-Naïve, HIV-Infected Patients in Resource-Limited Conditions. This study, completed in 2010, compared the effectiveness of three different drug combinations in HIV-infected individuals starting their first HIV treatment regimens. Participants, 47 percent of whom were women, were recruited from the United States, South Africa, Malawi, Zimbabwe, India, and Thailand. The investigators found that two ART regimens demonstrated high efficacy and another ART regimen had inferior efficacy and should not be recommended for initial treatment of HIV in resource-limited settings.

Campbell, T. B., Smeaton, L. M., Kumarasamy, N., Flanigan, T., Klingman, K. L., Firnhaber, C., … Hakim, J. G.; PEARLS study team of the ACTG. (2012). Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: A randomized clinical trial in diverse multinational settings. *PLoS Medicine, 9*(8), e1001290.

Sex-Associated Differences in Pre-Antiretroviral Therapy Plasma HIV-1 RNA in Diverse Areas of the World Vary by CD4 T Cell Count. This baseline analysis of ACTG 5175 participants showed that being female was independently associated with lower plasma HIV-1 RNA levels in resource-limited settings and found a greater difference in blood levels of HIV between men and women as their levels of immune cells (known as CD4 T cells) increased. Additionally, women had higher CD4 counts than men at the time of enrollment in the study, suggesting that women had less-advanced HIV disease than men before the start of treatment in this study. The association between baseline HIV levels, sex, and response to ART will be further investigated in participant follow-up.

Grinsztejn, B., Smeaton, L., Barnett, R., Klingman, K., Hakim, J., Flanigan, T., … Currier, J.; PEARLS study team of the ACTG. (2011). Sex-associated differences in pre-antiretroviral therapy plasma HIV-1 RNA in diverse areas of the world vary by CD4(+) T-cell count. *Antiviral Therapy, 16*(7), 1057–1062.

HIV Levels in HIV-Infected Women During Pregnancy and After Childbirth (A5150). This observational study, completed in 2012, was designed to determine whether HIV-infected pregnant women taking anti-HIV drugs have increased amounts of HIV in their blood after delivery. The researchers found that in the early postpartum period, HIV-infected women commonly have increased amounts of virus in the blood. Unplanned changes in ARV regimens and discontinuations of treatment were frequent, suggesting that future efforts should find ways to improve the maintenance of ART in the postpartum period.

Sha, B. E., Tierney, C., Cohn, S. E., Sun, X., Coombs, R. W., Frenkel, L. M., … Stek, A.; ACTG A5150 Team. (2011). Postpartum viral load rebound in HIV-1-infected women treated with highly active antiretroviral therapy: AIDS Clinical Trials Group Protocol A5150. *HIV Clinical Trials, 12*(1), 9–23.

Use of a Transdermal Hormonal Contraceptive Patch in HIV-1 Infected Women Treated With Protease Inhibitors (PIs). An ACTG trial (A5188) studied the use of an estrogen/progesterone–containing hormonal contraceptive patch in HIV-infected women who were taking the PI lopinavir-ritonavir as part of an ART regimen. Among women using the patch, estrogen levels were higher and progesterone levels were lower in women on the PI-containing ART compared with levels in women who were not on ARV therapy. Nevertheless, the concentrations of contraceptive drugs in the women taking PIs suggest that the contraceptive patch is likely to remain effective. The investigators also noted a trend for the concentration of lopinavir-ritonavir to be decreased slightly in women using the contraceptive patch, and concluded that larger studies are needed to fully assess contraceptive efficacy versus risks of the contraceptive patch when it is used along with protease inhibitors.

Vogler, M. A., Patterson, K., Kamemoto, L., Park, J. G., Watts, H., Aweeka, F., … Cohn, S. E. (2010). Contraceptive efficacy of oral and transdermal hormones when co-administered with protease inhibitors in HIV-1-infected women: Pharmacokinetic results of ACTG trial A5188. *Journal of Acquired Immune Deficiency Syndromes (1999), 55*(4), 473–482.

Clinical Trials

Optimizing Treatment for Treatment-Experienced HIV-Infected People (A5241). This Phase IV study is designed to determine whether there is a benefit of adding a type of drug known as a nucleoside reverse transcriptase inhibitor to a new anti-HIV drug regimen. Twenty-two percent of study participants are women, which will allow investigators to analyze outcomes specifically in women.

Osteoporosis in HIV-Infected Postmenopausal Women. This ongoing clinical trial is examining the impact of HIV infection, ARV therapy, and traditional risk factors for osteoporosis on the prevalence of osteoporosis and the rate of bone loss in HIV-infected postmenopausal African-American and Hispanic women.

Depo-Provera in HIV-Infected Women (A5283). This study is evaluating the interaction between an injectable form of birth control, depo-medroxyprogesterone acetate (Depo-Provera), and an ARV known as Kaletra (lopinavir/ritonavir) in HIV-infected women. In addition, study investigators will explore the effects of Depo-Provera on the immune system.

PROMISE Study. (See listing in Prevention of Mother-to-Child Transmission of HIV section.) Some of the maternal health components of this study are being conducted in settings where HAART is the standard of care during pregnancy and women do not typically breastfeed. This maternal health component is seeking to determine the best strategy for treating pregnant women who have CD4 T cell counts greater than 400 (that is, those who have not progressed to AIDS) after delivering their baby.

The Effect of Vitamin D Repletion on Postmenopausal Women with HIV. This study, which is currently enrolling patients, will examine the effects of vitamin D supplementation on bone turnover, rates of bone loss, and indices of immune function in HIV-infected postmenopausal women. Prior research revealed that low vitamin D levels

are common in this population. One hundred women will be followed to determine the change in bone mineral density over 1 year. Because other research has suggested that HIV-positive women have higher rates of bone loss than HIV-negative women, successful therapy with vitamin D may help prevent complications of this bone loss, particularly bone fractures.

Centers for AIDS Research (CFAR)

The CFAR is a unique trans-NIH program that provides infrastructure to support interdisciplinary, peer-reviewed HIV/AIDS research in an environment that coordinates studies, promotes communication, provides shared services/expertise, and funds short-term feasibility studies that cannot be funded easily by other mechanisms. There are currently 21 CFARs (18 standard and 3 developmental) located at academic and research institutions throughout the United States. Several CFARs are actively supporting research activities in women. In 2011 and 2012, 9 CFARs supported 15 pilot projects through the CFAR Developmental Cores in the area of HIV research in women.

In addition, the Inter-CFAR Collaboration on HIV Research in Women is a network of CFAR investigators dedicated to promoting cutting-edge HIV research in women. The collaboration develops new strategies for future research to address HIV-related issues unique to women and promotes career development and professional growth among junior investigators interested in this field. The overall goal of the program is to identify gaps in knowledge in research on HIV in women and generate collaborative activity between CFARs and other research networks.

The Lifespan/Tufts/Brown CFAR has an HIV in Women & Underserved Populations Core that encourages and assists CFAR investigators to develop studies related to HIV and women covering a broad range of areas; assists in the submission of developmental grant applications and independent grant applications related to HIV and women; provides resources instrumental in the collection, cataloging, and maintenance of a repository of blood and genital tract secretions; provides training in genital tract collection for virologic and immunologic studies; and assists in the recruitment of women researchers in the area of HIV/AIDS research. More information on the HIV in Women & Underserved Populations Core is available at *http://192.138.176.29/cfar/core-svc-women.html.* More information on CFAR research is available at *http://www3.niaid.nih.gov/research/cfar*.

Infectious Diseases Other than HIV/AIDS

Many infectious diseases, including STIs such as HPV, are critical global and national health priorities. These diseases can have a devastating impact on women, with the potential for causing long-term health problems. For example, many diseases can cause pregnancy loss at any stage, problems with the development of the fetus, or complications for the newborn. The research described in this section supports ORWH strategic goal 1.6.

Malaria

Pregnancy malaria (PM) is associated with low birthweight, maternal anemia, and gestational hypertension and is a major cause of death and disease for women and their children in sub-Saharan Africa. Both inflammation and the fetal response to malaria parasite infection may contribute to these poor outcomes. PM is caused by infected red blood cells that stick to a type of sugar molecule (chondroitin sulfate A or CSA) in the placenta, leading to sometimes heavy accumulations of parasites in the placenta. Because women have no immunity to CSA-binding parasites before their first pregnancy, first-time mothers are most susceptible. Although the fetus is not usually infected by the parasite, exposure to PM in the uterus can increase a child's susceptibility to malaria during early life for reasons that are not yet clear.

Clinical Study

Pregnancy Malaria Immunology, Pathogenesis, and Vaccine Development Initiative. Clinical and laboratory investigations for this project, which was initiated by NIAID intramural scientists, aim to determine factors associated with malaria in

pregnant women and young children. These studies are informing intramural scientists' efforts to develop a PM vaccine.

Schistosomiasis

Schistosomiasis, also known as bilharzia, is a disease caused by the parasitic worms *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. Although schistosomiasis is not found in the United States, more than 200 million people are infected worldwide. Observational studies suggest that pregnant women infected with schistosomiasis deliver babies with lower birthweight than uninfected women and tend to have poorer pregnancy outcomes.

Clinical Trial

A Randomized Clinical Trial to Evaluate Treatment of Schistosomiasis During Pregnancy. This clinical trial in the Philippines will assess whether treating women with schistosomiasis in the second trimester of pregnancy is safe and whether it improves the birthweight of the newborn.

Chagas Disease

Chagas disease is caused by infection with *Trypanosoma cruzi*, a parasite prevalent in Latin America. CDC estimates that more than 300,000 people with T. cruzi infection, mainly immigrants, live in the United States. About one-third of people infected by the parasite, which is transmitted by the bite of an insect, develop serious cardiac or intestinal complications, often decades after the initial infection. Some pregnant women infected with *T. cruzi* transmit the infection to the fetus during pregnancy.

Clinical Trial

Congenital Transmission of *T. cruzi*. An NIAID-supported project is enrolling *T. cruzi*-infected pregnant women in Mexico, Honduras, and Argentina to evaluate whether congenital transmission from mother to fetus is influenced by the evolutionary lineage of the infecting parasite. A better understanding of the epidemiology of *T. cruzi* congenital infection is a crucial step toward the potential development of screening and early treatment programs for use in Mexico and Central America, as well as in the United States.

Foodborne Pathogens

Infectious diseases spread through food or beverages are a common, distressing, and sometimes life-threatening problem for millions of people in the United States and around the world. The CDC estimates that each year in the United States, 1 in 6 Americans (or 48 million people) gets sick, 128,000 are hospitalized, and 3,000 die of foodborne diseases. Pregnant women are at high risk for foodborne infections such as those caused by *Salmonella* or *Listeria* bacteria. These infections can lead to miscarriage, stillbirth, premature delivery, or infection in newborns.

Scientific Advance

The Immune Pathogenesis of Prenatal *Listeria monocytogenes* Infection. During pregnancy, a woman's immune system must maintain its defenses against infection by bacteria and other pathogens while at the same time tolerating foreign, or "nonself," molecules in the developing fetus. NIAID-supported researchers investigated the specific interaction between *Listeria monocytogenes*, which lives inside infected cells, and a subset of immune-suppressive cells in the mother known as regulatory T cells (Tregs), which create and maintain a hospitable environment for the fetus. They found that although *Listeria* can invade the fetus, especially with high-dosage infection, damage can also occur by infection-induced changes in maternal immune cells that make them markedly less hospitable to the fetus. Under these circumstances, maternal immune-mediated rejection causes fetal injury without direct bacterial invasion of the fetus or placenta. This occurred with infection by reduced dosages of virulent *Listeria* or by weakened *Listeria*. The researchers further demonstrated that *Listeria*'s entry into cells is the critical factor for immune-3mediated fetal injury. These results have important implications for designing new ways to prevent and treat prenatal infections and improve the outcomes of pregnancy.

Rowe, J. H., Ertelt, J. M., Xin, L., & Way, S. S. (2012). *Listeria monocytogenes* cytoplasmic

entry induces fetal wastage by disrupting maternal Foxp3+ regulatory T cell–sustained fetal tolerance. *PLoS Pathogens, 8*(8), e1002873.

Toxoplasmosis

Pregnant women can become infected with *Toxoplasma gondii,* the parasite that causes toxoplasmosis, through contact with cat feces that contains infectious forms of the parasite or by eating undercooked meat. Women who become infected while pregnant may miscarry, give birth prematurely, or have babies with eye or brain damage.

Scientific Advance

Currently available blood tests can determine whether a person has ever been infected with any strain of *Toxoplasma* parasite. An experimental test developed at NIAID improves upon older tests because it can detect the presence of strain-specific antibodies that distinguish infecting strains from one another. This test revealed which strains of the *T. gondii* parasite are most strongly associated with premature births and severe birth defects in the United States. The findings from this study support the value of screening for toxoplasmosis to identify patients who could benefit from treatment.

McLeod, R., Boyer, K. M., Lee, D., Mui, E., Wroblewski, K., Karrison, T., … Grigg, M. E.; Toxoplasmosis Study Group. (2012). Prematurity and severity are associated with *Toxoplasma gondii* alleles (NCCCTS, 1981–2009). *Clinical Infectious Diseases, 54*(11), 1595–1605.

Influenza

Each year, seasonal influenza is estimated to kill more than 36,000 Americans and hospitalize as many as 200,000 people in this country. Pandemic influenza can produce even greater devastation. NIAID funds a Maternal Immunization Program to support studies and clinical trials that evaluate the safety and efficacy of vaccines to prevent or treat infectious diseases in women and their babies. Two influenza vaccine studies are ongoing (see below).

Clinical Trials

Post-Partum Immunization with Live Attenuated Influenza Vaccine (LAIV) or Trivalent Influenza Vaccine (TIV) in Postpartum Breastfeeding Women (09-0007). This study is evaluating the safety of two different influenza vaccines in breastfeeding mothers and their infants. The study will also investigate differences in breast milk antibody immune responses against influenza between the two different vaccines. The study was successfully completed during two influenza seasons (2011–2012 and 2012–2013), enrolling 248 pairs of postpartum women and their babies. Data analyses are ongoing. Further outcome information is available at *http://www.clinicaltrials.gov/ct2/show/NCT01181323?term= maternal+immunization+with+vaccines&rank=6.*

Randomized, Double-Blind Trial on the Safety and Immunogenicity of Seasonal 2010–2011 Inactivated TIV in Pregnant Women (09-0005). This study evaluated safety and antibody production that results from a single intramuscular injection of the 2010–2011 inactivated TIV in women during the second or third trimester of pregnancy. The study was successfully completed, having enrolled 139 pregnant women and 44 nonpregnant women during the 2010–2011 influenza season. Preliminary safety data suggest that the vaccine is safe to be administered to pregnant women. Study investigators are analyzing the data on antibody responses, which are expected to be released soon. Further outcome information is available at *http://www.clinicaltrials.gov/ct2/show/NCT01173211?term=maternal+immunization+with+vaccines&rank=17*.

Human Papillomavirus (HPV)

HPV is the most common STI. Persistent infection with certain strains of HPV can lead to cervical cancer, which is one of the most common cancers in women worldwide. Other strains of HPV cause genital warts, benign tumors of the respiratory tract, and cutaneous warts. These lesions can be especially problematic in individuals whose immune systems are compromised by HIV infection or drugs given after organ transplantation. Two vaccines, Gardasil and

Cervarix, are licensed for the prevention of genital warts and cervical cancer due to HPV.

Clinical Trials

Clinical Studies of HPV in HIV-Infected Females. The A5240 study is evaluating the toxicities and complications of an HPV vaccine in HIV-infected women. Researchers are also evaluating the safety and efficacy of the HPV vaccine to prevent anal HPV infection in HIV-infected women (A5298). NIAID is supporting a similar study for HIV-infected girls (PACTG 1047). In addition, the A5282 study is comparing two different methods to prevent cancer of the cervix in women infected with HIV.

Hepatitis E Virus (HEV)

HEV is a major cause of hepatitis in much of the developing world and is increasingly identified as a cause of hepatitis in industrialized countries. Though most infections go undiagnosed and are self-limited, 10–25 percent fatality rates have been reported among HEV-infected pregnant women, as well as an increased risk of stillbirth and other adverse pregnancy outcomes.

Clinical Trial

Incidence and Natural History of Hepatitis E Virus in Pregnant Bangladeshi Women. This prospective, population-based study aims to determine the disease burden and consequences of infection and study the immunopathogenesis of HEV in 10,000 pregnant women and their newborn infants in South Asia. This research will establish the foundation for population-level interventions (for example, vaccines) to improve maternal and infant survival in resource-poor settings.

Microbiome

Microbes inhabit just about every part of the human body. Sometimes they cause sickness, but most of the time, microorganisms live in harmony with their human hosts, providing vital functions essential for human survival. NIAID participates in the NIH Human Microbiome Project, which is mapping the microbial makeup, or microbiome, of humans to better understand the role of microbes in health and disease. Some of these projects are examining how the vaginal microbiome helps maintain health and prevent infection in women.

Scientific Advance

Characterizing the Vaginal Microbiome. One NIAID-funded project characterized the vaginal bacterial communities of healthy women from four racial/ethnic groups (White, Black, Hispanic, and Asian). The results showed inherent differences between groups as well as among women within each group. The variety in bacterial communities in healthy women should be taken into account in risk assessment and disease diagnosis.

Ravel, J., Gajer, P., Abdo, Z., Schneider, G. M., Koenig, S. S., McCulle, S. L., … Forney, L. J. (2011). Vaginal microbiome of reproductive-age women. *Proceedings of the National Academy of Sciences of the United States of America, 108*(Suppl 1), 4680–4687.

Immunology and Immune-Mediated Diseases

NIAID supports investigations of immunology and immune-mediated diseases and their effects on women's health. The goal of this research is to increase the health and well being of women by developing new methods to prevent and treat autoimmune diseases, prevent rejection of the transplanted organ in women, and prevent the immunologic causes of infertility. The research described in this section supports ORWH strategic goal 1.2.

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own ("self") organs, tissues, and cells. Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis (MS), celiac disease, and inflammatory bowel disease. Many autoimmune diseases disproportionately affect women, and this group of diseases is among the leading causes of death for young and middle-aged women. NIAID supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs.

Autoimmunity

Scientific Advance

Tregs suppress other, self-reactive immune cells that can cause autoimmune disease. Tregs are a promising experimental treatment for autoimmune diseases, but the cells may lose some or all of their suppressor function while being grown and processed for therapeutic use. NIAID scientists developed an improved method for preparing clinical-grade Tregs that largely overcomes this problem.

Kim, Y. C., Bhairavabhotla, R., Yoon, J., Golding, A., Thornton, A. M., Tran, D. Q., & Shevach, E. M. (2012). Oligodeoxynucleotides stabilize Helios-expressing Foxp3+ human T regulatory cells during in vitro expansion. *Blood, 119*(12), 2810–2818.

Lupus

Systemic lupus erythematosus, more commonly known as lupus, is a chronic autoimmune disease. Inflammation caused by lupus can affect many body systems, including the central nervous system, joints, skin, kidneys, blood cells, heart, and lungs. Approximately 322,000 Americans are diagnosed with, or suspected of having, lupus. Ninety percent of the people with lupus are women, and generally the age of onset is between 15 and 45 years. Lupus is more common in Black, Hispanic, Native American, and Asian women than in White women.

Scientific Advances

Estrogen Influences Antibody Production. Women have a stronger antibody response to vaccines and infections than men do. Estrogen enhances not only the helpful antibody response against microbes but also the production of disease-causing autoantibodies that react against "self" molecules. In lupus patients, increased estrogen levels underlie increased autoantibody levels and severity of disease. NIAID-supported scientists discovered that estrogen affects the blood cells that make antibodies by strongly increasing the level of a trigger protein called HOXC4. This protein stimulates the production of a diverse array of antibodies and then refines the specificity of each antibody produced. These two steps of antibody maturation are important for producing strong immunity against microbes. In lupus patients, however, this effect of estrogen contributes to disease severity. This research may lead to new therapeutic approaches to minimize the impact of estrogen on lupus and other autoimmune diseases.

Mai, T., Zan, H., Zhang, J., Hawkins, J. S., Xu, Z., & Casali, P. (2010). Estrogen receptors bind to and activate the HOXC4/HoxC4 promoter to potentiate HoxC4-mediated activation-induced cytosine deaminase induction, immunoglobulin class switch DNA recombination, and somatic hypermutation. *Journal of Biological Chemistry, 285*(48), 37797–37810.

Neutrophil Death Linked to Lupus Pathogenesis. NIAID-supported scientists previously reported that patients with lupus, especially children, have increased activity of interferon-alpha, a protein released by immune cells in response to infection. They also found that lupus patients have increased numbers of persistently activated plasmacytoid dendritic cells, a type of immune cell that produces interferon-alpha and is usually activated only transiently by infection. In this study, they show that neutrophils, an abundant but short-lived type of white blood cell, are sensitized by exposure to elevated interferon in lupus patients and are killed by antibodies against nucleic acids (including DNA), another hallmark of lupus serum. DNA from dead neutrophils activates plasmacytoid dendritic cells to secrete more interferon-alpha. These new findings describe a pathway that might be specifically targeted for treating lupus.

Garcia-Romo, G. S., Caielli, S., Vega, B., Connolly, J., Allantaz, F., Xu, Z., … Pascual, V. (2011). Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Science Translational Medicine, 3*(73), 73ra20.

Multiple Sclerosis (MS)

MS, an inflammatory disease of the central nervous system, is the leading cause of neurologic disability among young adults. MS is thought by many researchers to arise when the immune system attacks the myelin sheath that insulates nerve fibers within

the brain and spinal cord. MS affects about 400,000 Americans, and women are affected about two times more frequently than men. MS commonly results in visual disturbances, muscle weakness, and loss of coordination; in severe progressive cases, it can result in partial or complete paralysis.

Scientific Advances

Improved Genetic Analyses Identify Additional MS Susceptibility Genes. A genetic contribution to MS has long been suspected due to the increased incidence of the disease in family members of patients diagnosed with MS. The International Multiple Sclerosis Genetics Consortium, which includes investigators funded by NIAID, has conducted the most comprehensive search to date for genes that confer susceptibility to MS. This study of nearly 10,000 individuals confirmed most of the previously identified susceptibility genes and identified an additional 29 genes that may also play a role in the disease. Many of the genes implicated in this study influence the development and function of immune cells called helper T cells, which are a major focus of NIAID-funded MS research.

International Multiple Sclerosis Genetics Consortium; Wellcome Trust Case Control Consortium 2, Sawcer, S., Hellenthal, G., Pirinen, M., Spencer, C. C., Patsopoulos, N. A., … Compston, A. (2011). Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature, 476*(7359), 214–219.

Genes and the Environment Combine to Influence Susceptibility to MS. Numerous studies have indicated that altered immune function plays a role in the development of MS. In this study, NIAID-supported researchers demonstrated that genetically determined variations in the sugar molecules attached to proteins on the surface of immune cells can alter their function in ways that confer susceptibility or resistance to MS. Furthermore, the study showed that vitamin D, long suspected to influence the development of MS, can increase the attachment of sugars to T cell surface proteins and thereby decrease their potential to cause disease in a mouse model of MS. These findings bring together two previously unrelated research areas that provide potential for simple interventions to treat or reduce the risk of MS.

Mkhikian, H., Grigorian, A., Li, C. F., Chen, H. L., Newton, B., Zhou, R. W., … Demetriou, M. (2011). Genetics and the environment converge to dysregulate N-glycosylation in multiple sclerosis. *Nature Communications, 2*, 334.

Systemic Sclerosis

Systemic sclerosis (or scleroderma) is a group of autoimmune diseases in which the immune system is thought to stimulate cells called fibroblasts, which then produce too much of the fibrous protein collagen. Systemic scleroderma is the form of the disease that not only includes the skin but also involves the tissues beneath the skin, the blood vessels, and the major organs. The excess collagen forms thick connective tissue that can interfere with the function of affected organs. An estimated 40,000 to 165,000 people in the United States have this disease, and women—especially middle-aged women and African-American women—are more likely than men to have it.

Clinical Trial

The **Scleroderma Cyclophosphamide or Transplantation (SCOT)** study is assessing the safety and potential usefulness of (1) high doses of drugs to suppress the immune system followed by transplantation of immune system stem cells compared with (2) monthly high doses of the immunosuppressive drug cyclophosphamide for systemic sclerosis. The hypothesis is that high-dose immunosuppressive therapy will destroy the malfunctioning immune system and replacement with immature immune cells will permit the development of a healthy immune system, inducing a long-term remission or even eradication of the disease. The high doses of cyclophosphamide may reduce symptoms more effectively than the standard low-dose therapy. The enrollment and treatment phases of the trial are complete and follow-up is ongoing. More information is available at *http://www.sclerodermatrial.org/*.

Understanding the Maternal-Fetal Interface

A fundamental question in the immunology of pregnancy is how a fetus develops within the mother without being recognized as foreign by the mother's immune system, a phenomenon known as tolerance. A combination of signals and responses modulates the milieu in which the fetus and the maternal immune system coexist. Discerning the immune mechanisms that are involved during pregnancy can provide insights into immune regulation and reproductive success.

Scientific Advances

Inhibition of T Cells During Pregnancy Protects the Fetus. NIAID-supported researchers examined the decidua (the structure that encases the fetus and the placenta) from pregnant mice to understand the mechanisms that were involved in protecting the fetus from attack by the mother's immune system. They found that genes that produce proteins responsible for attracting immune cells to sites of inflammation (chemokines) were silenced. This inhibited access of T cells to the fetal–maternal interface, thereby preventing rejection of the fetus. These findings provide insight into a mechanism of immune tolerance between the mother and the fetus, and may have further implications for understanding conditions such as transplant rejection and the survival of cancer cells within a host.

Nancy, P., Tagliani, E., Tay, C. S., Asp, P., Levy, D. E., & Erlebacher, A. (2012). Chemokine gene silencing in decidual stromal cells limits t cell access to the maternal-fetal interface. *Science, 336*(6086), 1317–1321.

Pregnancy-Induced Peripheral Tregs Protect Against Pregnancy Loss. NIAID-funded researchers identified a mechanism that controls peripheral Tregs or pTregs. These cells develop outside of the thymus (a glandular organ) and generally limit inappropriate immune responses to foreign substances such as those from the diet and non-harmful bacteria. Investigators identified a noncoding DNA sequence, found only in placental mammals (such as human and mice), that increases the levels of Foxp3, a protein needed for activation of pTregs in pregnant mice. Mice that are deficient in this noncoding sequence have fewer pTregs and are at increased risk of embryo loss during pregnancy. These finding suggest that pTregs may have developed in placental mammals to protect the fetus from rejection by the maternal immune system, and may provide insight into complications of human pregnancies.

Samstein, R. M., Josefowicz, S. Z., Arvey, A., Treuting, P. M., & Rudensky, A. Y. (2012). Extrathymic generation of regulatory T cells in placental mammals mitigates maternal-fetal conflict. *Cell, 150*(1), 29–38.

Protein Secreted by the Fetus During Pregnancy May Reprogram Immune Cells. Results from NIAID investigators suggest that natural killer (NK) cells, immune cells usually dedicated to killing virus-infected cells and tumor cells, acquire new functions to help expand blood vessels in the uterus during pregnancy. This reprogramming of the mother's NK immune cells occurs in response to a signal sent by the fetus. Understanding how these cells are regulated could provide new insights into pregnancy complications due to poor fetal blood supply.

Rajagopalan, S., & Long, E. O. (2012). Cellular senescence induced by CD158d reprograms natural killer cells to promote vascular remodeling. *Proceedings of the National Academy of Sciences of the United States of America, 109*(50), 20596–20601.

Related Accomplishments in Women's Health Research

Career Development

NIAID continues to cosponsor the Building Interdisciplinary Research Careers in Women's Health mentored career development awards, which support the development of women's health researchers. This activity supports NIH ORWH strategic goal 6.2.

NIAID also convened a half-day research training symposium, Lessons in Leadership: Honoring NIAID's Women in Science, on May 4, 2011. The symposium brought together leading intramural and extramural NIAID women scientists with intramural postdoctoral researchers, research fellows, and junior investigators to share critical career

strategies in biomedical research. This activity supports NIH ORWH strategic goal 6.1.

Trans-NIAID Women's Health Research Work Group

The Trans-NIAID Women's Health Research Work Group focuses on women's health and gender-based research activities that advance the mission and research priorities of NIAID and provides recommendations for future women's health research opportunities. The work group performs the following functions:

- Heightens awareness across NIAID of the importance and substance of women's health and gender-based research across the Institute;
- Develops a common framework for identifying and assessing women- and gender-based research;
- Encourages trans-NIAID and trans-NIH collaborations on women's health and gender-based research activities; and
- Coordinates a seminar series highlighting issues and advances in women's health research.

The Work Group convened four Women's Health Seminars in 2011–2012. The goal of this seminar series is to highlight infectious and immune-mediated disease research that advances women's health. Presentation topics included prevention of infections in pregnant women and their children, HIV transmission and therapy in a cohort of Kenyan women, interactions between pathogens and the placenta during pregnancy, and HIV prevention and treatment in U.S. women. NIAID, in partnership with the Fogarty International Center and the NIH Office of Research on Women's Health, also convened two NIAID International Women's Health Day Lectures, which focused on malaria and neglected tropical diseases in women.

Significant Plans for Sex/Gender Analysis or Sex and Gender Studies

The **Multicenter AIDS Cohort Study,** a study of MSM, and **WIHS** are closely linked to ensure that data collected in the two studies can be combined and compared whenever appropriate. Studies that compare outcomes for men and women in pharmacology, cardiovascular disease, aging, sleep patterns, metabolic disorders, mental health, and neurologic diseases are ongoing. These projects have demonstrated differences in the pharmacology of antiretroviral drugs and differences in the clinical outcomes between men and women with HIV in the United States.

The **IeDEA** program (see HIV/AIDS Accomplishments, above) combines data from nearly one million people with HIV globally. With these data, researchers are able to evaluate gender differences in disease outcomes and therapy response. A recent study by the Southern Africa IeDEA consortium, exploring gender differences in survival between HIV-infected men and women, found that men had a higher mortality rate than women.

Cornell, M., Schomaker, M., Garone, D. B., Giddy, J., Hoffmann, C. J., Lessells, R., … Myer, L.; International Epidemiologic Databases to Evaluate AIDS Southern Africa Collaboration. (2012). Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: A multicentre cohort study. *PLoS Medicine, 9*(9), e1001304.

ACTG has evaluated the differences in response to therapy between the sexes in the context of large randomized clinical trials in clinical trials networks. They found that women metabolize some antiretroviral drugs differently than men, leading to differences in the way the drugs are tolerated and differences in treatment outcomes. This difference has been observed in several clinical trials, and research is ongoing to determine the mechanism.

Umeh, O. C., Currier, J. S., Park, J. G., Cramer, Y., Hermes, A. E., & Fletcher, C. V. (2011). Sex differences in lopinavir and ritonavir pharmacokinetics among HIV-infected women and men. *Journal of Clinical Pharmacology, 51*(12), 1665–1673.

Smith, K., Tierney, C., Daar, E., Mollan, K., Budhathoki, C., Sax, P., … Collier, A.; ACTG A5202 Study Team. (2011, March). Association of race/ethnicity and sex on outcomes in ACTG Study A5202. Paper

presented at the 18th Conference on Retroviruses and Opportunistic Infections. Abstract retrieved from *http://www.retroconference.org/2011/Abstracts/41176.htm*.

Sex-associated differences appear even before treatment, as described above (ACTG 5175 baseline analysis). Other studies, such as the **NEXT PrEP** study, which explores the safety and tolerability of new potential PrEP regimens, and the **Optimizing Treatment for Treatment-Experienced HIV-Infected People** (A5241) study will also examine sex differences.

NIAID also supports several research studies that focus on better understanding gender differences in disease outcomes. The **Toll-like Receptor-Mediated Gender Differences in HIV-1 Pathogenesis** project investigates possible mechanisms for higher immune activation in women compared to men infected with HIV and the faster disease progression in women compared to men. The results from these studies will guide future studies in humans and may provide supporting data for the use of molecules that block the Toll-like receptor to reduce HIV-1–induced immune activation and pathology.

Other NIAID studies can also provide insights on sex-based differences. For instance, NIAID-funded researchers have discovered greater mortality in female compared with male mice during systemic viral infections with three viruses: murine cytomegalovirus, vaccinia virus, and—even more so—herpes simplex virus type I. These sex differences were independent of androgens (male sex hormones) and only partially attributable to estrogens. Enhanced male survival was mediated by sex differences in signaling through type I interferon and the transmembrane molecule DAP12. These findings will contribute to the development of a robust model of sex-specific differences in innate immune responses.

Geurs, T. L., Hill, E. B., Lippold, D. M., & French, A. R. (2012). Sex differences in murine susceptibility to systemic viral infections. *Journal of Autoimmunity, 38*(2–3), J245–J253.

Research Initiatives and Conferences

Requests for Applications (RFAs)

NIAID supports a number of initiatives on research related to women's health, including the following:

Integrated Preclinical/Clinical Program for HIV Topical Microbicides. This RFA, sponsored by NIAID and the National Institute of Mental Health, was reissued in 2012 to stimulate iterative preclinical and clinical research on novel microbicide strategies for HIV infection. The goal is to advance the field of microbicides and facilitate the transition of microbicide candidates from preclinical development to clinical evaluation (*http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-12-003.html*).

Combined Multipurpose Prevention Strategies for Sexual and Reproductive Health. The goal of this 2011 RFA is to stimulate the development of interventions that women could use to prevent STIs, reproductive tract infections, HIV, or unintended pregnancies. The strategies could include microbicides, devices, vaccines, and/or contraceptives, but must target at least two indications (*http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-11-016.html*).

Cooperative Study Group for Autoimmune Disease Prevention (CSGADP). CSGADP was established in 2001 as a collaborative network of investigators with a focus on prevention of autoimmune disease. The group defines "prevention" as halting the development of autoimmune disease prior to clinical onset by means other than global immunosuppression. The mission of CSGADP, which is cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, is to engage in scientific discovery that significantly advances knowledge towards the prevention and regulation of autoimmune disease. The 2011 RFA resulted in seven cooperative agreements, with goals that include identifying common and disease-specific mechanisms of autoimmunity, linking markers of risk for autoimmune disease to alterations in immune function, and advancing our understanding of genetic and

environmental risk factors for autoimmune disease (*http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-11-034.html*).

Conferences and Publications

The Lifespan/Tufts/Brown CFAR hosted the CFAR Joint Symposium on HIV Research in Women in September 2012. The objectives of the meeting were (1) to identify gaps in knowledge in research related to HIV and women and develop strategies that will move the field forward; (2) to generate collaborative activity between the different CFARs and with other research networks highlighting cutting-edge science; and (3) to promote and emphasize opportunities for young investigators.

NIAID cosponsored a supplement to "Women's Health Issues," the journal of the Jacobs Institute of Women's Health, entitled "Bringing Gender Home: Implementing Gender-Responsive HIV/AIDS Programming for U.S. Women and Girls" [2011. "Women's Health Issues," 21(6 Suppl)]. This supplement highlighted selected scientific articles on women's health and HIV research. Several of the HIV researchers who submitted articles have NIAID funding. The dissemination of gender-specific scientific findings in the field of HIV research supports NIH ORWH strategic goal 4.1.

Research on Health Disparities Among Special Populations

NIAID supports research to understand and eliminate health disparities among special populations, including minorities, rural women, lesbians, women of lower socioeconomic status, and women with disabilities. The following scientific advances and ongoing and planned activities are highlighted in this report:

- WIHS;
- VOICE Trial;
- ASPIRE;
- MTN-015 and EMBRACE/MTN-016;
- The Effects of SD NVP on Future Treatment Options for Women and Children;
- Additional Studies on the Effects of SD NVP on Future Treatment Options for Women and Children;
- Efficacy and Safety of an Extended Nevirapine Regimen in Infant Children of Breastfeeding Mothers with HIV-1 Infection for Prevention of Postnatal HIV-1 Transmission (HPTN 046);
- Three Postpartum Antiretroviral Regimens to Prevent Intrapartum HIV Infection;
- PROMISE Study;
- HIV Treatment Reinitiation in Women Who Received Anti-HIV Drugs to Prevent Mother-to-Child Transmission of HIV (ACTG 5227);
- Studies to Evaluate Approaches for PMTCT;
- Longitudinal Studies of Women at High Risk for HIV-1 Infection to Inform HIV Vaccine Trial Participation;
- ISIS;
- Once-Daily Antiretroviral Therapy Combinations for Treatment-Naïve HIV-Infected Patients in Resource-Limited Conditions;
- Sex-Associated Differences in Pre-Antiretroviral Therapy Plasma HIV-1 RNA in Diverse Areas of the World Vary by CD4 T-Cell Count;
- Osteoporosis in HIV-Infected Postmenopausal Women;
- A Randomized Clinical Trial to Evaluate Treatment of Schistosomiasis During Pregnancy; and
- Congenital Transmission of *T. cruzi*.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Executive Summary

Overview

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic, translational, and clinical research; research training; and information programs on many of the more debilitating diseases affecting Americans. NIAMS funds studies on a number of diseases that affect women disproportionately, including osteoporosis, osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus (lupus), scleroderma, and fibromyalgia. NIAMS is committed to uncovering the bases of these sex differences and devising effective strategies to treat or prevent them.

Program Highlights

The anticipated increase in the U.S. elderly population will be accompanied by a larger group of women who are at risk of fragility fractures. New diagnostic methods are being developed to assess bone quality and predict its impact on individuals' health status in order to prevent morbidity from osteoporosis. These approaches include monitoring bone mineral density and bone microstructure. NIAMS also supports an active basic biology portfolio that could inform the development and use of drugs that improve bone quality.

NIAMS oversees research into the causes and treatment of acute and chronic joint injuries, including repetitive stress and sports injuries. Studies on the prevention and healing of anterior cruciate ligament (ACL) injuries—and efforts to understand how these injuries increase the risk of osteoarthritis (OA)—are a key component of the NIAMS women's health portfolio; young women who play sports such as soccer and basketball are more likely to suffer these injuries than male athletes who participate in the same sports.

The ORWH has been a longstanding contributor to the Osteoarthritis Initiative, a trans-NIH public–private partnership to facilitate development of treatments for people who have knee OA. The Osteoarthritis Initiative is the basis for a new project of the Foundation for the National Institutes of Health Biomarkers Consortium to evaluate biochemical and imaging biomarkers for more precise ways of measuring OA progression and to provide tools to assess the effectiveness of new treatments.

Much of the NIAMS budget supports basic research into the biological processes underlying health and disease. Over time, discoveries have led to new treatments for people with a range of debilitating conditions. For example, NIAMS-funded basic research during the 1990s improved the understanding of the molecular mechanisms of inflammation and immune system dysfunction that causes rheumatoid arthritis (RA). The laboratory results were translated to biologics—drugs in the form of biological molecules that are widely prescribed for millions of patients who have RA. Ongoing NIAMS-funded studies are identifying the factors that contribute to differences in symptoms and severity of chronic pain conditions. These findings are helping to personalize treatments for individual patients.

With support from ORWH and other NIH components, NIAMS supports a robust information dissemination and outreach program to distribute research-based information to the public, patients, and health care providers. For example, NIAMS oversees the NIH Osteoporosis and Related Bone Diseases National Resource Center (NRC), which is cofunded by the National Institute on Aging, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Dental and Craniofacial Research, National Institute of Diabetes and Digestive and Kidney Diseases, ORWH, and the HHS Office on Women's Health.

Report of NIAMS

Accomplishments

Osteoporosis

Osteoporosis, or porous bone, is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures of the hip, spine, and wrist. In the United States, more than 40 million people either already have osteoporosis or are at high risk due to low bone mass. Osteoporosis can occur in both men and women and at any age, but it is most common in older women.

Hip fracture is the most devastating consequence of osteoporosis. It leads to short- and long-term functional impairment, loss of independent living ability, and even death. According to the National Center for Health Statistics, there were 281,000 hospital admissions for hip fractures among people aged 65 and older in 2007; three-quarters of these fractures occurred in women. The incidence of hip fracture increases with age. Therefore, hip fracture will most likely become an even larger public health problem as the U.S. population ages.

The next three advances relate to NIH Strategic Plan for Women's Health Research Objective 3.8: Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

Baseline Bone Mineral Density Measurements Are Key to Future Testing Intervals. The U.S. Preventive Services Task Force recommends bone mineral density testing for women aged 65 years and older. Although Medicare pays for a dual-energy x ray absorptiometry (DXA) test every 2 years, the appropriate interval between tests is unclear. In early 2012, the longstanding NIH-supported Study of Osteoporotic Fractures demonstrated that many women may not need to be tested as often, particularly if they have a healthy bone mineral density when they are first tested and do not have medical conditions that increase their risk of losing bone. The data suggest that while some women at the highest risk of osteoporosis may benefit from annual exams, women with the lowest risk could be tested much less frequently unless other aspects of their health change.

Study Further Elucidates Role of Arthritis in Fracture Risk.[1] Using data from the Women's Health Initiative (WHI), NIAMS-funded researchers have learned more about the association between arthritis and the risk of fractures. Their findings underscore the need for bone health strategies in people who have different types of arthritis, including OA—a condition that was once considered to "protect" against fractures. The WHI afforded the researchers an opportunity to study a large number of women: Of the women who reported a history of arthritis, 63,402 met the criteria for the OA group, and 960 met the criteria for the RA group. The control group comprised a total of 83,295 women who did not have arthritis. These women were followed for nearly 8 years, and the occurrence of clinical fractures in the OA, RA, and non-arthritis control groups was recorded. When compared with WHI participants who did not have arthritis, women in the RA or OA group had significantly more fractures. The increased risk in the RA group was highly significant and pertained to all types of fractures studied. Consistent with earlier studies that focused only on hip fractures, the OA group did not experience more hip fractures than the control group, but women with OA had a modest but significant increase in spine fractures. The investigators concluded that the increase in fracture risk observed in both groups confirms the need for fracture prevention among people who have OA and people who have RA.

Hip Fractures Increase Short-Term Risk of Death in Healthy Older Women. Data from the longstanding NIH-funded Study of Osteoporotic Fractures show that the first year (especially the first 3 months) after a hip fracture is a critical period of time for women 65 years and older, during which they face an increased risk of death. Although the reasons for this increased mortality are unclear,

[1] Support for this project includes NIAMS grant R21 AR060811, which was cofunded by ORWH.

the study emphasizes the importance of preventing hip fractures, understanding the factors that contribute to the increased risk of death, and developing interventions that can decrease mortality rates immediately following fractures. This is especially important for women younger than 70 years of age, who have the most potential for additional healthy, active years.

Bone Quality

As described above, bone mineral density, as measured by DXA, is an important risk factor for osteoporotic fracture. However, neither bone mineral density data alone, nor when combined with medical and family history, can fully predict who will break a bone. An imaging method known as high-resolution peripheral quantitative computed tomography (HR-pQCT) provides information about the fine details of the interior structures and outer surfaces of bones. Analysis of HR-pQCT data by a mathematical technique called finite element analysis (FEA) has been proposed as a surrogate measure of bone strength.

The next advance relates to NIH Strategic Plan for Women's Health Research Objective 2.5: Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.

Vertebral Fractures Are Sentinels for Structurally Abnormal Bone Elsewhere in the Body. Vertebral fractures are common, particularly in women after menopause, and may indicate structural abnormalities in the skeleton overall. Researchers analyzed HR-pQCT data from more than 200 women and found structural differences in the distal tibia (i.e., lower shin bone) in women who had vertebral fractures when compared with women who had broken a nonvertebral bone (e.g., wrist, ankle, or hip), even though DXA scans showed nearly equivalent densities in the lower leg bones. The structural changes detected by HR-pQCT and FEA indicate differences in bone stiffness and strength, which relate to fracture risk. The differences observed in microscopic bone structure of women with vertebral fractures, compared with women who had nonvertebral fractures, indicate that vertebral fractures are associated with significant deterioration of bone architecture and stiffness at some regions, such as the weight-bearing distal tibia, which are far removed from the site of the fracture. Although these single time point measures need to be confirmed in a larger, longitudinal study, they imply that vertebral fragility fractures depend less on bone mineral density than fractures at other sites do.

Bone Biology

Bone health depends on the balance between two tightly coupled, opposing processes that constitute the bones' constant remodeling activities: Bone resorption, in which bone cells called osteoclasts remove old damaged bone, and bone formation, in which bone cells called osteoblasts lay down new bone. Basic NIH-funded research into the mechanisms underlying bone buildup and breakdown—and how drugs influence these processes—could lead to new treatments for people who are at risk of osteoporotic fractures.

The next three advances relate to NIH Strategic Plan for Women's Health Research Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. The third advance also addresses Objective 3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan; and Objective 3.6: Study sex/gender differences in the aging processes.

Researchers Explain Why Combined Osteoporosis Regimen Falls Short. Current therapies for osteoporosis aim either (1) to inhibit the bone resorption process using a class of drugs called bisphosphonates (e.g., alendronate), or (2) to stimulate bone formation by parathyroid hormone (PTH). Although logic predicted that the combination of bisphosphonates and PTH should be more effective for treating osteoporosis than either drug alone, clinical trials using both drugs at the same time showed that the effects of PTH were impaired by the use of alendronate. Subsequent research demonstrated that alendronate blunts PTH's bone-building activity by inhibiting the release of a bone-building protein, which,

in turn, decreases recruitment of bone precursor cells to the bone remodeling site. The improved understanding of the mechanisms underlying bone turnover may help to provide a rationale for future osteoporosis therapies. The results also show that the timing and sequence of antiresorptive and bone-building therapies could be important for optimal outcome: The use of PTH before bisphosphonates would likely be more effective than the reverse.

Treatment-Related Bone Changes and Fractures in Osteoporosis Explain Rare but Devastating Side Effect. Many women with osteoporosis are treated with bisphosphonates. While large clinical trials have shown that the drugs are safe over the short term (about 3 years), recent reports have emerged of rare but serious adverse events suspected to be associated with long-term use. One of the most troubling is the occurrence of atypical femoral fractures. While these events are highly infrequent and most treated individuals benefit from the use of bisphosphonates, it is important to examine bone from these fractures to determine precisely which changes account for them. One study analyzed bone obtained from postmenopausal women who had experienced fractures attributed to osteoporosis or bisphosphonate use. It revealed that bisphosphonate treatment resulted in a more uniform distribution of both the mineral and organic substances in bone when compared with untreated samples. Within the bisphosphonate-treated group, samples from patients with atypical fractures showed increased mineralization and mineral crystallinity compared with samples from patients who had typical fragility fractures. These structural differences could result in bone that is weaker and more brittle, which could lead to unexpected fractures with long-term use of bisphosphonates. This paper and related papers from other groups show that long-term use of these agents may have detrimental effects on the material properties of bone in some patients and actually decrease the bones' intrinsic resistance to fracture. Understanding these changes and finding ways to monitor and reverse them will lead to more appropriate use of bisphosphonates and reduced rates of osteoporotic and atypical fractures.

Predictors of Low-Trauma Fractures in Younger Women Differ from Those of Men. Although most fragility fractures occur in older adults, younger women can also be at risk. NIH-funded researchers are searching for methods to identify premenopausal women with very low bone mineral density who are at greatest risk for fracture. Identifying such a method would have considerable cost savings, as well as a profound effect on patients' lives. Recent findings in men have shown that idiopathic osteoporosis is often associated with a low level of serum insulin-like growth factor, a hormone that has been shown to regulate normal bone formation. The marker and other bone metabolism markers could not distinguish between premenopausal women with fractures and those who had very low bone mineral density but no fractures. Both groups of women with very low bone mineral density had higher-than-normal levels of bone breakdown products and PTH in their blood. Therefore, despite the promising results in men, these biochemical markers would not be useful in predicting a woman's fracture risk.

Osteoarthritis

OA is the most common form of arthritis. Nearly 27 million Americans, age 25 and older, have osteoarthritis. Before age 45, more men than women have osteoarthritis; after age 45, it is more common in women. Healthy cartilage allows bones to glide over one another, and it absorbs energy from the shock of physical movement. In osteoarthritis, the surface layer of cartilage breaks down and wears away. This allows bones under the cartilage to rub together, causing pain, swelling, and stiffness. Bone spurs develop, permanently changing the joint's shape.

The next two advances relate to NIH Strategic Plan for Women's Health Research Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. The third relates to Objective 2.5: Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.

Bone Drug Holds Promise as Therapy for People with Osteoarthritis. Researchers recently demonstrated that a PTH-based drug that has already been approved for older women with osteoporosis can restore cartilage in a mouse model of injury-induced knee OA. The osteoporosis drug teriparatide restores bone strength by targeting bone-building cells. Scientists knew that cartilage in arthritic joints—but not in healthy joints—expresses receptors for PTH. Combined with knowledge about the hormone's effects on cartilage cells in the growth plate areas of bone, researchers speculated that teriparatide might also target cartilage in arthritic joints. This finding is an example of how clinical observations can inform basic research questions: The investigators designed their animal experiments after colleagues noted that people with OA who were taking PTH for osteoporosis had less arthritis pain. If subsequent studies show that teriparatide has a favorable risk-benefit profile and stimulates cartilage regeneration in patients, it would be the first disease-reversing drug available for the millions of Americans who are plagued by OA.

Researchers Uncover Clues Related to Metal-on-Metal Hip Implants. With support from an ARRA-funded RC2 (Grand Opportunity) grant, scientists made a surprising discovery about the lubricating layer that forms in the joints of metal-on-metal hip implants. Although the all-metal joints are not designed with lubrication, a thin layer develops between the metal ball and socket once implanted in the body. Investigators thought that the layer must be made of proteins, like the fluid in normal joints. Instead, this solid layer, made mostly of carbon, is more like an industrial lubricant than joint fluid. This raises the possibility that researchers can create safer, longer-lasting implants which, in turn, could have a profound impact on the long-term success and societal costs of total joint replacements (the only treatment for end-stage OA).

Can X Ray Changes Predict Functional Outcomes in Knee Osteoarthritis? Although past research has failed to find a connection between gradual x ray changes and minor changes in physical function in people who have knee OA, logic suggests that structural and functional deterioration should be correlated at a gross level. Researchers analyzed data from the Multicenter Osteoarthritis Study (MOST) and compared the rate of disease-related changes in knee structure with the development of functional limitations, as assessed through performance-based measures such as walking speed. Compared with people whose joints did not change, patients whose knees deteriorated the most dramatically over 2.5 years were twice as likely to develop the functional limitations that rendered them eligible for a knee replacement. This was true regardless of whether a person had knee OA when they joined the study or whether the person developed knee OA after the study began. The investigators hypothesized that there might be an increased risk of disability with rapid knee deterioration because the people who had the more rapid structural changes had less time to develop compensatory behaviors than those who experienced a more gradual decline or those whose disease had stabilized. Of note, the structural changes described in this study can be easily monitored with x ray exams. If clinicians could predict which patients would develop severe disability, these patients could then receive rehabilitative therapy to retain their mobility or get surgery before end-stage OA caused their overall health to deteriorate.

Anterior Cruciate Ligament Injuries and Posttraumatic Knee Osteoarthritis

According to the American Academy of Orthopaedic Surgeons, female athletes who participate in jumping and pivoting sports, such as basketball and soccer, are between 2 and 10 times more likely to injure the ACL of the knee than male athletes who participate in the same sports. These types of injuries make it increasingly likely that a person will develop knee OA within one or two decades after the injury.

The next three advances relate to NIH Strategic Plan for Women's Health Research Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

Researchers Identify Factors that May Predict Long-Term Outcomes Following Reconstruction of the Anterior Cruciate Ligament of the Knee. Surgeons use a variety of techniques to repair damaged ACLs, and it is possible that some procedures stabilize the damaged knee better than others. Using an existing cohort of ACL-injured patients from the Multicenter Orthopaedic Outcomes Network (MOON), researchers demonstrated that the surgical techniques in use today restore knee stability for at least 6 years. Of the almost 400 participants, those who did not smoke and were of healthy body weight at the time of injury had a more successful recovery and continued to be more active than their smoking or overweight counterparts. Meniscal tears that did not require surgery and tears in other ligaments did not hinder a person's recovery. The people who had reinjured a previously repaired knee and needed a second (revision) surgery did not recover as well as those who were undergoing surgery for the first time, underscoring the need for researchers to develop strategies to prevent re-injuries. Moreover, patients who received their own tissue improved more than those who received donor implants. Although most participants returned to sports, many did not return to their pre-injury levels. The young women in the study were significantly less active 6 years after the procedure than the men were. The authors did not discuss the reasons for the decline, except to note that the reduced activity levels may adversely affect the patients' knee health as they age.

Post-Injury Response Could Be Key Step in Osteoarthritis Development. Scientists long considered OA a disease of wear and tear. Use the joints long enough, people reasoned, and they are bound to wear out. But research in recent years suggests that inflammation plays a role in OA. A new study helps confirm inflammation's contribution and points to new targets for treatment, and perhaps prevention, of this common joint disease. The new results show that initial joint damage triggers a chain of molecular events that escalates into an attack on the joints by the "complement system"—a process by which the body fights infection. The complement system has been a pharmaceutical target for some time, due to its role in other diseases. While the side effects associated with current strategies overwhelm the potential benefits for OA patients, an appreciation for the complement system's role in OA development offers hope that joint deterioration, and the associated pain and functional limitations, might someday be preventable.

Early Data from Animal Models Show Bioengineered Anterior Cruciate Ligaments Performing As Well As Tissue Grafts. Finding an effective ACL repair strategy to reduce the development of posttraumatic OA remains a health care challenge. Researchers are testing a bioenhanced ACL repair technique that may provide an alternative for people who have ACL injuries and reduce the need for tendon grafts. The new, supplemental ACL tissue consists of a collagen scaffold enriched with platelet plasma, which is attached directly into the injured joint without replacing the torn ligament with a tendon. After 15 weeks of healing, the joints of the animals with the bioenhanced ACL repair behaved similarly to those that received a tendon graft; both surgical strategies outperformed the untreated joints. The researchers are completing a follow-up study, supported by an ARRA supplement, to determine whether the bioenhanced ACL construct reduces posttraumatic OA.

Rheumatoid Arthritis

RA affects an estimated 1.3 million Americans. It is a debilitating autoimmune disease, characterized by chronic joint inflammation, in which the body's natural defense system attacks its own tissues. RA occurs in all races and ethnic groups. Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults also develop it. Like some other forms of arthritis, RA occurs much more frequently in women than in men. About two to three times as many women as men have the disease.

The next advance relates to NIH Strategic Plan for Women's Health Research Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. The second and third RA advances are examples

of research related to Objective 2.5: Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.

New Rheumatoid Arthritis Drug Targets NIH-Discovered Protein. In early November 2012, the U.S. Food and Drug Administration approved the drug tofacitinib to treat adults with moderately to severely active RA who either do not respond adequately to methotrexate or who are intolerant of it. Tofacitinib is a member of a new class of drugs developed to target Janus kinases. One member of the Janus kinase family, JAK3, was discovered in the early 1990s by NIAMS researchers. Subsequent studies carried out at NHLBI, in collaboration with NIAMS, led to the idea that drugs to block Janus kinases might protect against the damaging inflammation associated with RA and other autoimmune diseases. The approval of tofacitinib represents the first time in a decade that the FDA has approved an oral disease-modifying antirheumatic drug (DMARD) for RA patients. This broad class of drugs slows or halts the progression of damage from the disease, rather than merely providing relief from symptoms. Unlike biologic treatments for RA—which are also DMARDs and target immune system proteins—tofacitinib is a pill, not an infusion or an injection.

New Genetic Risk Score Predicts Development of More Severe Rheumatoid Arthritis. Knowledge of genes associated with RA risk is allowing researchers to continue to refine algorithms for calculating a person's risk of developing the disease. A recent version of these algorithms, based on data from nearly 1,100 women who are participating in the long-standing, NIH-funded Nurses' Health Study, was found to predict severe forms of RA better than earlier tools. Severe forms of RA were characterized by joint damage, blood chemistry, and age at disease onset. The ability to distinguish between disease subtypes suggests that different genetic mechanisms are involved in what we now consider to be a single disease. Ultimately, a simple blood test could be developed to facilitate early diagnosis, personalized treatment, and prevention of RA.

Blood Lipid Profiles Predict Cardiovascular Disease in Patients with Rheumatoid Arthritis. The chronic inflammation that accompanies RA increases a person's risk of developing cardiovascular disease (CVD) and experiencing a heart attack or stroke (the leading causes of death for RA patients). Along with high blood pressure and smoking, cholesterol measures such as low-density and very low-density lipoproteins are CVD risk factors in the general population. Researchers measured different classes and subclasses of the protein component of lipoproteins in a cohort of RA patients. Their findings shed light on the extent to which these molecules contribute to the increased inflammation-associated CVD risk in people who have RA. Although this unique observation needs to be repeated, it offers potentially valuable markers for monitoring personalized treatments (e.g., combinations of statin drugs with other types of lipid-lowering agents) for RA patients to reduce their risk of cardiovascular complications that may affect both short- and long-term morbidity and mortality.

Juvenile Arthritis

The CDC estimates that 294,000 children under age 18 have some form of arthritis or rheumatic condition.

The next advance relates to NIH Strategic Plan for Women's Health Research Objective 2.5: Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.

Can Emotional Patterns Predict Changes in Pain and Function in Children with Arthritis? The well-documented relationship between pain and negative emotions in children who have chronic pain conditions such as juvenile arthritis prompted researchers to study how a child's emotional patterns might predict daily pain and functioning. Data collected from electronic diaries of 43 girls, with an average age of 13.2 years, showed that children who experienced a wider range of negative emotions over the course of a day experienced more pain and were less active than their counterparts who had more consistent emotions. Girls who experienced a wider range of positive emotions reported

higher overall pain, but the pain did not appear to limit their activities. This work in preteen and teenage girls provides a new glimpse into how regulating emotions predicts pain and function outcomes in juvenile arthritis and suggests that electronic diaries are a useful research tool.

Lupus

Lupus is a chronic autoimmune disease that, for unknown reasons, causes the immune system to mistakenly attack the body's own healthy cells and tissues. An estimated 90 percent of people diagnosed with lupus are women. Lupus is more prevalent in African-Americans, Hispanics, and Asians. African-American women are three times more likely to get lupus than Caucasian women. African-Americans and Hispanics/Latinas tend to develop lupus at a younger age and have more symptoms at diagnosis (including kidney problems).

Immune Function and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE; a type of lupus) is a heterogeneous disease, meaning that symptoms and disease severity vary widely among patients and may come and go unpredictably. This highly variable clinical course makes it difficult to diagnose, treat, and monitor. The ability to easily and correctly classify subtypes of disease and measure disease activity would accelerate research in the field and greatly help with the diagnosis and treatment of patients. The clinical heterogeneity of SLE likely reflects its complex etiology, which is thought to involve the interaction of multiple genes and environmental factors.

The next advance relates to NIH Strategic Plan for Women's Health Research Objective 2.5: Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls. The other advances in this Immune Function and Systemic Lupus Erythematosus section relate to Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

Researchers Develop a Method to Detect and Classify Lupus Subtypes Using a Drop of Blood. Functional abnormalities in T cells—immune cells that are important in SLE pathogenesis—can be traced to aberrant T cell gene expression patterns. Using only a small amount of blood to measure expression levels of 30 genes associated with SLE, a group of researchers demonstrated that they could (1) distinguish SLE patients from healthy people and from patients who had RA, and (2) classify their disease subtypes. Although studies including larger numbers of patients will be needed to substantiate these results, the findings suggest an ability to establish a gene expression "signature" for subgroups of SLE patients, which may help to diagnose disease, predict disease severity, and target treatment.

Scientists Shed Light on Link Between Dead Cell Clearance and Lupus. Incomplete removal of cells that die during apoptosis—the biological process of programmed cell death—contributes to the development of autoimmune diseases, including SLE. In healthy individuals, immune cells called phagocytes envelop dead cells and remove them without triggering inflammation or other adverse immune responses. A protein called MFG-E8 signals phagocytes to surround and ingest apoptotic cells. In people with lupus, however, apoptotic cells are not properly cleared, causing the immune system to attack the body's own cells. NIAMS-funded researchers studying mice that lacked MFG-E8 found that the animals' phagocytes were slower to take up apoptotic cells and processed the dead cells differently after engulfing them. This activated immune cells and caused an autoimmune reaction. Although researchers do not yet know all the specifics of how apoptotic cells and their debris are processed in lupus, the work points investigators toward potential new treatment targets.

Unexpected Role of Immune Cells in Lupus Provides New Drug Target.[2] NIAMS-supported research is providing surprising insights into the immune process involved in

[2] Support for this project includes NIAMS grant R01 AR044077, which was cofunded by ORWH.

lupus. In infectious disease models, dendritic cells are important for activating two other types of immune system cells, T cells and B cells, as part of the response to invaders such as viruses and bacteria. But the role they play in autoimmune diseases like lupus is unclear. When researchers deleted dendritic cells from lupus-prone mice, disease activity was reduced significantly. While this finding confirmed that the cells play an important part in disease progression, the scientists were surprised that the removal of the dendritic cells did not block other immune system cells: Instead of initiating the immune response, the dendritic cells amplified it. While current lupus therapies are directed largely toward T cells and B cells, the new research suggests therapies targeted at blocking dendritic cells may reduce tissue damage without shutting down the entire immune response in lupus and other autoimmune diseases.

Cardiovascular Risk and Pediatric Lupus

Statins are used widely in adult populations for the control of atherosclerosis. Lupus in pediatric populations is generally more severe than in adults, with comorbidities such as CVD, which is related to premature atherosclerosis. Because of this increased risk of CVD, researchers investigated the potential benefits of statin treatment to slow the progression of atherosclerosis in children with lupus.

The advance below supports NIH Strategic Plan for Women's Health Research Objective 2.9: Encourage collaborative interactions among clinicians, bioethicists, and technologists regarding accessibility of new technologies, drugs, and other interventions relevant to women's health.

Study Shows Statins Fail to Slow Atherosclerosis Progression in Young Lupus Patients. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus study, known as APPLE, involved 20 sites across North America that participate in the Childhood Arthritis & Rheumatology Research Alliance, or CARRA. Over 200 pediatric lupus patients were enrolled in the double-blind, prospective, placebo-controlled trial of statins that evaluated the health of the patients' blood vessels over a 36-month trial period. The difference in the carotid intima-media thickness, a measure of atherosclerosis, was not significant between the statin-treated and placebo-treated groups. While the results do not support routine treatment with statins in pediatric lupus patients for the prevention of atherosclerosis, the study showed that 3 years of statin therapy was safe for these children. Because the study showed that the drug used in the study, atorvastatin, was safe and improved other markers of CVD (i.e., the drug lowered the children's total cholesterol, LDL cholesterol, and high-sensitivity C-reactive protein levels), researchers hypothesize that statins may benefit patient subgroups who have severe disease; these studies are ongoing.

Scleroderma

Scleroderma is a rare, severe, and heterogeneous autoimmune disease that involves progressive hardening of the skin and of internal organs. The characteristic hardening is due to fibrosis. Systemic sclerosis is one form of scleroderma and involves many parts of the body, such as skin, internal organs, and blood vessels. This form of the disease affects more women of African than European descent.

The next two advances relate to NIH Strategic Plan for Women's Health Research Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

Researchers Identify Possible Therapy for Fibrotic Lung Disease Due to Scleroderma. Fibrotic lung disease in systemic sclerosis was originally thought to be caused by overexpression of connective tissue proteins by local fibroblast cells. However, newer evidence suggests that fibrocytes, which arise from immune cells in the blood (monocytes), migrate from the bloodstream to the lungs, where they take on fibroblast-like characteristics and contribute to fibrosis. Recent research found fibrocytes in lung tissue samples from systemic sclerosis patients with interstitial lung disease but not in samples from healthy control subjects. Levels of caveolin-1, a cell membrane protein that appears to regulate fibrosis, were significantly reduced in the animals' and patients' damaged

lungs. When researchers treated the mice with a special protein fragment (the caveolin scaffolding domain, or CSD), levels of caveolin-1 increased, the fibrocytes produced fewer proteins associated with sclerotic lung disease, and fibrocyte migration and disease progression were curtailed. This knowledge may contribute to the development of more effective therapies to treat or prevent interstitial lung disease in systemic sclerosis patients.

Scientists Identify an Agent that Protects Against Fibrosis in Skin and Lungs. Researchers have identified an agent that—in lab tests—protected the skin and lungs from fibrosis. The agent, called E4, is a fragment of the protein endostatin, which is being studied as a cancer treatment. NIAMS-supported scientists identified endostatin as a possible therapy for fibrosis based on earlier observations that levels of the protein were elevated in fibrosis. At first, they were uncertain whether the protein worsened or improved fibrosis. After observing that it blocked fibrosis when added to cells grown in a laboratory dish, the researchers looked for the specific part of the endostatin fragment that was protective against fibrosis. When the scientists evaluated the peptide E4 in healthy human skin cells under conditions where they should have become fibrotic, the skin remained normal. E4 also protected the skin and lungs of mice from thickening. In addition, the researchers found the peptide could reverse existing damage. The eventual goal is the development of therapies that will prevent or reverse fibrosis and preserve organ function. While such a therapy is likely still years away, the identification of E4, and its effectiveness in laboratory studies using human skin, is an important start.

Fibromyalgia

Fibromyalgia syndrome is a chronic disorder, characterized by widespread pain and tenderness. It is frequently accompanied by other symptoms, such as fatigue, insomnia, depression, and anxiety. Researchers at the CDC estimate that fibromyalgia affects 5 million Americans ages 18 and older. Between 80 and 90 percent of those diagnosed with fibromyalgia are women, and the reason for this difference is unknown. The precise cause of fibromyalgia is also not known, but research suggests that it is related to a problem with the central nervous system's processing of pain. As with some other chronic pain conditions, people with fibromyalgia often develop a heightened response to stimuli, experiencing pain that would not cause problems in other people.

The next advance provides a basis for additional studies that will promote NIH Strategic Plan for Women's Health Research Objective 2.7: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. The second and third advances pertain to Objective 2.3: Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women and girls, and Objective 2.5: Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of disease and conditions of women and girls, respectively.

Stress Increases Transmission of Pain Signal. NIAMS-supported researchers have found that stress changes the activity of nerve cells present in muscle (nociceptors) that send pain messages to the brain and spinal cord. They found that nociceptors in leg muscles of stressed animals had a lower threshold for response. When the same amount of force was applied to the muscles of stressed and nonstressed animals, the nociceptors of stressed animals sent more signals from the muscle to the brain/spinal cord. In addition, the messages from nociceptors of stressed animals travelled faster along the nerve, and there was more variability in the duration between signals sent by the cells. This described difference in nociceptor function may contribute to the increase in pain that often occurs in times of stress. This work is a launching point for elucidating the molecular mechanisms through which stress leads to nociceptor changes. Identifying the mechanisms through which stress exacerbates the symptoms of fibromyalgia syndrome and other chronic, widespread pain conditions is important to further understanding and improved development of rationally designed treatments.

Improved Measurements for Treatment Response in Fibromyalgia Clinical Trials May Improve Research Efficiency and Patient Care. Because fibromyalgia is a multisymptom disease that affects multiple aspects of patients' lives, outcome measures to determine whether new or existing therapies actually work (in clinical trials or patient care) need to capture improvement in a variety of important concepts. However, it is not feasible to evaluate changes in each symptom in the course of routine clinical care. Researchers needed to develop an easy-to-use, reliable strategy to determine clinically meaningful improvement. After testing 24 alternatives, they concluded that the 2 best strategies captured improvements in pain, physical function, fatigue, sleep, depression, anxiety, and cognition. Such clinical outcome measures will allow a better understanding of how individual medications or nonpharmacologic approaches such as cognitive behavioral therapy (CBT), tai chi, or exercise work. Efficient, valid measures of fibromyalgia symptoms will also allow comparisons of different individual treatment strategies and their combinations.

Cognitive Behavioral Therapy Is an Effective Treatment for Patients with Juvenile Fibromyalgia. Recent research has shown that CBT can be effective in helping adults with fibromyalgia syndrome manage pain and functional disability, and improve their coping skills. To determine whether CBT could help teens who have juvenile fibromyalgia (JFM), NIAMS-supported researchers compared the efficacy and safety of a CBT intervention to improve coping skills for managing JFM with a program to educate teens about their disease. Most of the study participants were Caucasian girls. While both interventions were effective in reducing symptoms, those who received CBT showed a more pronounced and significant improvement in functional abilities and depressive symptoms. CBT also improved participants' total well-being, as measured through health-related quality-of-life measures. There was a small yet significant reduction in pain severity with CBT; however, there was not much difference in the reduction of pain severity based on the type of intervention used (CBT vs. fibromyalgia education). No study-related adverse events were reported.

Health Disparities

Several of the diseases mentioned above disproportionately affect women from underrepresented minority groups. NIAMS is committed to exploring genetic, biological, and environmental risk factors among different racial and ethnic populations; conducting behavioral research into cultural issues that can influence disease management and outcomes (e.g., risk behaviors and medical compliance); investigating problems concerning access to care and exploring the impact of language barriers and cultural health literacy on health care delivery; and incorporating findings from these efforts into patient education strategies to promote healthy behaviors and improve lives.

The next two advances relate to NIH Strategic Plan for Women's Health Research Objective 3.9: Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

Researchers Explore the Influence of Racial and Ethnic Disparities on Health Outcomes Among Persons with Rheumatoid Arthritis. A recent NIH-supported study is among the first to examine whether variations in RA symptoms and disease activity among diverse racial/ethnic groups in the United States are moderated by the setting in which patients receive care (private vs. public clinics). Researchers investigated associations of race/ethnicity with disease activity and physical function in a diverse RA cohort, which included many immigrants and people with limited English proficiency. Most of the participants were female (84 percent); only a third were non-Hispanic Caucasians. Patients attending a public county clinic were generally of lower socioeconomic status and had more severe disease activity than those who attended a private, university-affiliated clinic; no noteworthy differences in disease were found among people in the different racial, ethnic, and linguistic groups who were treated at the county clinic. At the university clinic, differences in disease among racial/ethnic groups were more pronounced: African-Americans had the most severe forms

of RA, followed by Hispanics and Asian/Pacific Islanders, compared with Caucasians. Disease activity was also increased among immigrants and non-English language groups in the university hospital setting. African-Americans, Hispanics, and immigrants receiving care at the university clinic also had more functional impairment than Caucasian university patients who were native English speakers. At present, researchers have several possible explanations for these health disparities—including the stage at which disease is diagnosed and treatment begins, health literacy, and patient behavior and support—and plan to explore the extent to which these or other factors contribute to differences in patients' health.

Predictors of Work Disability in Patients with Scleroderma. Researchers examined data from an ethnically diverse group of people who have scleroderma (84 percent of whom are female) to identify characteristics that predict whether the disease is likely to prevent an employed person from continuing to work. Of the 131 patients who were working full time at the start of the study, more than a quarter became disabled and stopped working over the next 4.5 years. The researchers found that higher education was correlated with the likelihood of working. Caucasians of any education level were more likely to still be employed when compared with non-Caucasians of similar education. Clinical and patient-reported predictors of disability included pulmonary involvement and fatigue. The extent to which people had social support (as measured by their interpersonal support evaluation list score) was correlated with their continued employment. While these results are consistent with other research, the diversity of this population contributes data that are more generalizable and descriptive than results from previous studies about the effects of scleroderma on the inability to work.

Information Dissemination

Disseminating information about research progress continues to be an essential component of the NIAMS mission. NIAMS is committed to communicating research advances to all segments of the public. The driving force behind NIAMS-funded research is the potential to improve the lives of those who are affected by bone, joint, muscle, or skin diseases. ORWH has a long history of supporting the NIAMS-led NRC and the NIAMS Information Clearinghouse. In FYs 2011 and 2012, NIAMS updated more than 100 of its publications, many of which are focused on diseases or conditions that disproportionately affect women. The Institute also adapted some publications for Spanish and Chinese speakers.

Examples of materials that would be appropriate for inclusion in a central portal of information for women's health research findings suitable for the specific needs of researchers, health care practitioners, patients, and their families (NIH Strategic Plan for Women's Health Research Objective 5.6) follow.

Bone Health

There are many ways women can slow or prevent bone loss. Eating enough bone-healthy nutrients, getting appropriate exercise, and being mindful of risk factors go a long way toward lifelong bone health. The following publications, available through the NRC at *http://www.niams.nih.gov/Health_Info/Bone/default.asp*, address issues related to women's bone health and were updated or published for the first time in FYs 2011 or 2012.

- "Bone Health and Osteoporosis: A Guide for Asian Women Aged 50 and Older" (in English and Chinese)
- "Fitness: Overtraining Risks"
- "Healthy Bones – Why They Matter for African Americans"
- "Healthy Bones – Why They Matter for American Indians and Alaska Natives"
- "Healthy Bones – Why They Matter for Asian Americans and Pacific Islanders"
- "Healthy Bones – Why They Matter for Chinese Americans" (in English and Chinese)
- "Healthy Bones – Why They Matter for Hispanics and Latinos" (in English and Spanish)

- "Isabel's Story (a Fotonovela): How She and Her Family Learned About Osteoporosis and Bone Health" (in English and Spanish)
- "Osteoporosis and African American Women"
- "Osteoporosis and Asian American Women" (in English and Chinese)
- "Osteoporosis and Hispanic Women"
- "Osteoporosis: Peak Bone Mass in Women"
- "Pregnancy, Breastfeeding, and Bone Health"
- "What Breast Cancer Survivors Need to Know About Osteoporosis"
- "What People With Anorexia Nervosa Need to Know About Osteoporosis"
- "What People With Lupus Need to Know About Osteoporosis" (in English and Spanish)

The following NIAMS bone health materials are written at a sixth- or seventh-grade reading level in a question-and-answer format. They are two to six pages long.

- "Bone Health for Life – Easy-to-Read Information for Patients and Families" (in English and Spanish)
- "What Is Osteoporosis?" (in English and Spanish)
- "What Are Ways to Prevent Falls and Related Fractures?" (in English and Spanish)
- "What is Bone?"

Joint Injuries

- "Ana's Story (a Fotonovela): How She and Her Family Learned About Sports Injuries." This bilingual booklet discusses sports injuries in young people. When a girl named Ana injures her knee playing soccer, she and her extended family learn about treating and preventing sports injuries.

  — *http://www.niams.nih.gov/Health_Info/Sports_Injuries/ana_story_english.asp* (English)

  — *http://www.niams.nih.gov/Portal_en_espanol/Informacion_de_salud/Lesiones_deportivas/ana_story_espanol.asp* (Spanish)

Autoimmune and Rheumatic Diseases

- "Questions and Answers about Juvenile Arthritis." This booklet describes the different types of juvenile arthritis and treatment options. Information is also provided about current research.

  — *http://www.niams.nih.gov/Health_Info/Juv_Arthritis/default.asp*

- "Handout on Health: Systemic Lupus Erythematosus." This booklet contains general information about systemic lupus erythematosus (SLE or "lupus"). It describes how lupus is diagnosed and treated, as well as considerations for women who have lupus and are pregnant or considering becoming pregnant. Highlights of current research are provided.

  — *http://www.niams.nih.gov/Health_Info/Lupus/default.asp*

- "Handout on Health: Scleroderma." This booklet describes what scleroderma is, its causes, and treatment options. It includes information on current research.

  — *http://www.niams.nih.gov/Health_Info/Scleroderma/default.asp*

- "What Is Fibromyalgia?" This easy-to-read fact sheet describes what fibromyalgia is, its causes, and treatment options. It highlights current research on fibromyalgia.

  — *http://www.niams.nih.gov/Health_Info/Fibromyalgia/fibromyalgia_ff.asp* (English)

  — *http://www.niams.nih.gov/Portal_en_espanol/Informacion_de_salud/Fibromialgia/default.asp* (Spanish)

- "Questions and Answers about Fibromyalgia." This booklet contains general information about fibromyalgia. It describes what fibromyalgia is, its causes, and treatment options. Highlights of current research on fibromyalgia are also included.

  — *http://www.niams.nih.gov/Health_Info/Fibromyalgia/default.asp*

Initiatives

In FYs 2011 and 2012, NIAMS participated in the following ORWH-led funding opportunity announcements:

- **PA-08-246 (*http://grants.nih.gov/grants/guide/pa-files/PA-08-246.html*), Chronic Fatigue Syndrome (CFS): Pathophysiology and Treatment (R01); PA-08-247 (*http://grants.nih.gov/grants/guide/pa-files/PA-08-247.html*), CFS: Pathophysiology and Treatment (R21).** This solicitation was created to stimulate research on the epidemiology, diagnosis, pathophysiology, and treatment of CFS. Applicants were encouraged to address age, environmental, and biological risk factors for CFS and the common mediators influencing multiple body systems affected by the disease.
- **PAS-07-381 (*http://grants.nih.gov/grants/guide/pa-files/pas-07-381.html*), Advancing Novel Science in Women's Health Research (ANSWHR) (R21); PAS-07-382, Advancing Novel Science in Women's Health Research (ANSWHR) (R03).** This funding announcement emphasized support of pilot projects or small, self-contained projects that promoted innovative, interdisciplinary research to advance new concepts in women's health research and research on sex/gender differences.

National Institute of Biomedical Imaging and Bioengineering

Executive Summary

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) was established by law in December 2000 and received its first appropriation and grant funding authority in fiscal year (FY) 2002. As NIBIB continues to mature and establish programs, funding opportunities have been developed to support a variety of scientific areas, including programs aimed at fostering women's health research.

NIBIB serves as the hub within NIH for coordination of biomedical imaging and bioengineering efforts. The Institute:

(1) Fosters, conducts, supports, and administers research and research training programs in biomedical imaging and bioengineering by means of grants, contracts, and cooperative agreements;

(2) Provides coordination, integration, and review of progress in and the planning of biomedical imaging and bioengineering research;

(3) Formulates research goals and long-range plans with the guidance of the National Advisory Council for Biomedical Imaging and Bioengineering; and

(4) Sponsors scientific meetings and symposia, collaborates with industry and academia, and fosters international cooperation regarding biomedical imaging and bioengineering.

NIBIB recognizes the significant potential of improved imaging technologies in the early detection of disease. During FY 2011 and FY 2012, NIBIB funded grants that were focused on women's health research or technologies aimed at improving devices for female populations. These projects ranged from advanced imaging methodologies to tissue engineering activities designed specifically for women's diseases such as breast cancer, diseases with profound consequences for women such as sexually transmitted diseases, and conditions that predominate in women such as temporomandibular joint (TMJ) disease.

Most NIBIB-funded projects in women's health align strongly with Goal 2 of the NIH Strategic Plan for Women's Health Research: Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs. In particular, many projects align with Objective 2.6 of that plan: Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery. An example of such a project is Development of Advanced Techniques for Magnetic

Resonance (MR) of the Newborn Brain, a study that is developing assessment techniques for neonates that are noninvasive and give a rapid characterization of brain maturation in premature and term newborns.

Many other projects funded by NIBIB align with Objective 2.7 of the plan: Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls. An example of a project that aligns with this objective is Multifunctional Protein Nanocapsules for Targeted Delivery, which incorporates several functionalities into 25-nm (nanometer) protein-based nanoparticles to deliver targeted cancer therapy for the treatment of breast cancer.

During FY 2011 and FY 2012, NIBIB supported research on women's health in the following areas: factors that influence careers of women in science and engineering, technologies to reduce health disparities, aging, breast cancer, solid tumors, sexually transmitted infections, reproduction and fetal health conditions, and TMJ disorder.

Dr. Roderic Pettigrew, the first director of NIBIB, began his tenure at the NIH in September 2002. Since his arrival, NIBIB has reorganized the Institute to facilitate the support of interdisciplinary research in areas of relevance to the missions of NIH and NIBIB.

In December 2004, Dr. Anthony Demsey joined NIBIB as the director of the Office of Extramural Policy and subsequently of the Office of Research Administration. Under his purview, Dr. Demsey has the overall responsibility for managing and monitoring all NIBIB activities that focus specifically on women's health research. Dr. Karen Peterson has direct day-to-day responsibility for overseeing women's health research. Drs. Demsey and Peterson serve as NIBIB's representatives on the Coordinating Committee on Research on Women's Health.

Accomplishments

Highlighted below are significant NIBIB research accomplishments and funding in FY 2011–FY 2012 related to women's health.

Breast Cancer

Validation of Sensorized Breast Models for High-Stakes Clinical Skills Assessment

The long-term goal of this project is to build valid and reliable technologies that can be used to ensure that minimum performance standards are met by all health care professionals who perform hands-on clinical examinations and procedures at the point of care. The immediate goal is to build and validate a set of sensor-enabled breast examination simulators that can be used to define performance standards for the clinical breast examination. The investigators hypothesize that palpation techniques used in the clinical breast examination can be quantified and that improper techniques that result in a missed diagnosis can be identified using sensor-enabled breast models.

Bioimaging with Nanopyramids

This project aims to apply nanopyramids, a new type of nanoparticle with unique and tunable optical properties, to the detection of breast cancer. Nanopyramids will be targeted to the epidermal growth factor receptor (EGFR) and the tyrosine kinase receptor (ErbB2, or HER2 in humans). Biofunctionalized nanopyramids will bind to EGFR and HER2 and will be bright and easily visible in dark-field microscopy. The targeted nanopyramids will also be conjugated to a contrast agent for magnetic resonance imaging (MRI), potentially enabling whole-body detection of breast cancers. Early detection of EGFR and HER2 in breast cancer cells facilitates targeted treatment and may increase survival rates.

Dedicated Breast Scanner for Monitoring Response to Early-Stage Breast Tumors

The objective of this project is to develop a positron-emission tomography (PET) scanner specifically designed to provide high-resolution, high-sensitivity reconstructed tomographic images to characterize and monitor the response to chemotherapy and radiotherapy of early-stage (stages I and II) breast tumors. This task is not performed adequately in multipurpose whole-body

clinical PET scanners, and current dedicated breast PET scanners force trade-offs between sensitivity and specificity and do not have full flexibility in imaging the whole breast (including the chest wall) and the axilla. This ongoing project, using a novel geometric design and time-of-flight information to attain high sensitivity and a high signal-to-noise (SNR) ratio, aims to produce an imager that removes prior limitations, thereby allowing for improved staging and evaluation of response to treatment of early-stage breast cancer.

Dual-Drug High-Dose PLGA-Lipid Hybrid Nanoparticles for Drug Delivery

The objective of this project is to develop a nanoparticle, using a unique and novel lipid-polymer hybrid nanoparticle platform, which can contain two chemotherapy drugs, doxorubicin and paclitaxel, with sufficiently high drug loading that a single or a few nanoparticles can kill a drug-resistant cancer cell. Concurrent delivery of the two clinically approved anticancer drugs at high dosage to the same breast cancer cells in a targeted manner is expected to overcome chemoresistance to cancer drugs.

Evaluation of Digital Breast Tomosynthesis as a Method for Routine Breast Cancer Screening

Digital breast tomosynthesis (DBT) is considered a very promising development in breast cancer imaging, as clinical pilot studies have demonstrated that DBT yields higher sensitivity and specificity than projection mammography, the current tool of choice for breast cancer screening. However, there is concern regarding the use of DBT for routine breast cancer screening because this technique generates approximately 50 times more images than projection mammography and thus requires extensive review time for the radiologist. One investigator funded by NIBIB is trying to gain insight into the likely success of DBT as the modality of choice for population breast cancer screening by comparing the performance of radiologists in detecting breast cancer when interpreting DBT cross-sectional images with their performance in interpreting digital mammography images, with the comparison done using time-controlled viewing experiments.

High-Resolution Whole-Breast MRI

The applicants proposed to develop, implement, and validate breast MRI methods with very high spatial resolution at 3 Tesla (3T). Although breast MRI has recently been shown to be cost-effective in screening high-risk patients or patients with a contralateral breast cancer, some limitations remain in accurately identifying small lesions and in false positives. Higher-resolution MRI can address all of these limitations, providing a more accurate tool for assessment of breast cancer. Improved specificity may reduce the rate of unnecessary biopsy while also making MRI effective for screening lower-risk patients. Increased sensitivity for small lesions will allow for earlier detection of cancer and result in increased survival rates and a reduced screening frequency.

Low-Dose Breast Computed Tomography with Photon-Counting Detector

This study focuses on a breast computed tomography (CT) system that has the capability of producing images of higher quality at a dose lower than that used in current breast CT systems. The key to the system involves a photon-counting and energy-resolving x-ray detector. Properties of low noise and high quantum efficiency translate to a higher-image SNR at a lower dose. The SNR of breast CT systems using a photon-counting detector can be improved by 30 percent versus those with a charge-integrating flat panel detector. An SNR improvement of 30 percent equals a dose reduction of 40 percent in breast CT. Thus, the project aims to provide clinicians with images of higher quality while exposing patients to lower dosages.

Parallel Detection and Computation for Diffuse Optical Tomography of Breast

The aim of this work was to develop and assess near-infrared diffuse light-imaging schemes for tumor detection and characterization. The researchers used a combination of experimental, theoretical,

and computational tools and techniques to develop computational schemes for improving the accuracy of three-dimensional (3D) reconstruction and recruiting more high-risk patients for in vivo measurements. Diffusion optical tomography (DOT) reconstruction images of total hemoglobin concentration and scattering have been correlated by radiologists specializing in MRI and categorized into well-correlated, intermediate, and poorly correlated cases in terms of tumor position. In optical contrast studies, DOT has successfully distinguished benign from malignant invasive carcinomas.

Development of Practical Mid-Infrared Spectroscopic Imaging Technology for Cancer

The project proposes to develop a new chemical imaging instrument to image biopsy tissues to achieve early decisions and accurate diagnoses. The goal is to develop techniques for processing breast and prostate cancer biopsy samples. Using imaging technology, the investigators propose to accomplish these goals without using dyes, stains, or human supervision, which could transform the standard practices used for histological assessment.

MRI Evaluation of Tumor Growth and Treatment Response

This project addresses the quantitative evaluation of tumor growth and treatment response using MRI by integrating dynamic contrast-enhanced MRI (DCE-MRI) measurements with quantitative metrics derived from other imaging modalities such as diffusion-weighted MRI (DW-MRI), fluorodeoxyglucose PET (FDG-PET), CT, and optical methods. The performance of these methods in serving as reporters on tumor growth and treatment response will be evaluated when used separately or in combination to evaluate the human response to breast cancer treatment.

Portable, Easy-to-Use Imaging System for Cervical Cancer Screening

This project is a collaboration between Rice University in Texas, and the University of Botswana (in sub-Saharan Africa) to carry out a pilot clinical study on the use of a high-resolution microendoscope for diagnosis of cervical cancer. Cervical cancer is the leading cause of cancer death among women in developing countries, and it imposes a particularly high burden in sub-Saharan Africa among HIV-positive women. The portable imaging system developed by the investigators has significantly better sensitivity and specificity than the visual inspection methods routinely used; the goal is to show that this battery-powered technology is a cost-effective solution for cervical cancer screening in low-resource environments.

Hot Flash Research Tool for Broad Population Research Studies

This work is focused on exploring the physiological processes and therapies associated with hot flashes. These studies require an objective measure of the hot flash phenomenon that optimally correlates with self-reported diary data, is specific to hot flashes, and is accurate under ambulatory conditions. The investigators propose to develop a small, inexpensive, lightweight, wearable ambulatory sternal skin conductance measurement and recording tool suitable for monitoring hot flashes in long-term studies in broad populations.

Nanocrystal Delivery of Hydrophobic Anticancer Drugs

Recent advances in nanotechnology have made it possible to design drug carriers with nanometer (nm)-scale features that have the potential to deliver insoluble or poorly soluble drugs to improve their pharmacokinetics. For example, the drug paclitaxel has a significant impact on solid tumors and is currently approved by the FDA for the treatment of breast and ovarian cancer. The clinical application of paclitaxel, however, is limited by its low solubility in water. The goal of this project is to develop safe and cost-effective nanocrystals for the delivery of poorly soluble anticancer drugs that can be effectively scaled up and commercialized to treat breast cancer. The project team has developed unique nanocrystals that encapsulate more than 99 percent of the paclitaxel drug and have shown antitumor activity and low toxicity in a murine breast cancer

model. Studies are also under way to scale up and commercialize this technology using a three-phase engineering method that results in significantly lower acute toxicity than do commercial paclitaxel formulations and lowers drug dosing with improved efficacy.

Nanodevice for the Clinical Breast Examination

NIBIB supported the development of an inexpensive, noninvasive, handheld screening tool for early detection of breast cancer. This nanodevice digitally images the palpability of a tumor and the nature of its attachment to surrounding tissue. This device would enable family physicians and other clinicians to screen patients who do not have access to the more expensive screening tools and avoid unnecessary exposure to radiation used in mammography. The quantitative image, including the size, hardness, and palpability of the mass, provides a set of orthogonal measurements that would significantly improve clinical breast examination and improve specificity, that is, a low rate of false positives, to help physicians make well-informed decisions about whether to perform further testing and promote the initiation of therapy at the earliest stages of breast cancer.

Reversing Electrostatic Interactions for Improved Gene Delivery

Improved or alternative treatment options are needed for breast cancer. Currently, there is no standard of care for metastatic breast cancer. All of the first-line combination therapies are regarded as equally efficacious and have a 60 percent response rate. A team of investigators is developing a new approach to deliver tumor suppressor genes by reversing electrostatic interaction in amphiphilic systems. In this approach, functional amphiphiles undergo transition from cationic to anionic in cells and release DNA from supramolecular assemblies. The overall goal of these studies is to design, synthesize, and evaluate new charge-reversal amphiphiles to enhance the efficiency of gene transfection. The results from delivering the p53 gene indicated a 50 percent knockdown of the gene and showed that endocytosis is the pathway responsible for transfection, unlike that used by conventional liposomal delivery systems.

Speckle-Free Transmission Ultrasound for Breast Imaging

This project has several goals: (1) Develop and implement a breast ultrasound fluoroscopy system (BUFS), which includes image acquisition and postprocessing for the C-scan ultrasound images; (2) generate preliminary tests with a laboratory prototype; (3) redesign and fabricate a premarket system suitable for imaging the human breast; and (4) develop an interface mechanism for the C-scan ultrasound camera and the breast. Scientists and engineers working on the project successfully built a higher-dynamic range CMOS (complementary metal-oxide-semiconductor) base ultrasound sensor. Two different C-scan systems were built: the first was a C-scan ultrasound attenuation system designed to examine breast phantoms and breast specimens (there are plans to begin small animal and ultrasound CT studies); the second system is a "dry" breast ultrasound fluoroscopy system prototype whose design was modified to enable better coupling of the transducers, and capabilities for sensing small image areas that are integrated into a larger breast image using a "stitching" algorithm. The stitching algorithms were developed as a set of Fourier composition techniques for the integration of C-scanned images. The investigators plan to perform a series of physical tests and imaging performance studies to evaluate the quality of the ultrasound images and to conduct a limited clinical trial (premarket testing) to compare conventional mammography and conventional ultrasound for imaging breast tissue. The investigators expect that a clinically viable system will soon be available for the diagnosis of breast cancer.

Time-Resolved Breast Imaging Using a Combined MRI and Optical Tomography Approach

A breast cancer patient's response to primary systemic therapy is important in deciding whether to switch to a different treatment regimen or to progress to surgery immediately. The overall goal of this proposal is to combine MRI and near-infrared spectroscopy and tomography (NIRS-DOT) to characterize the predictive value of compression-enabled measurements of tissue

hemodynamics, blood flow, and oxygen consumption as new biomarkers that would be sensitive to the progress of therapy and quantify the relationship of these biomarkers to the final pathological outcome. Fast optical tomography would be used during breast compression to investigate the biomechanical and metabolic characteristics of normal and lesion tissues, with the goal of improving specificity for cancer diagnosis and noninvasively monitoring the progress of chemotherapy.

Volumetric Mapping of Breast Cancer Biomarkers Using High-Speed Magnetic Resonance

This project is aimed at developing a novel ultra-high-speed 3D MR spectroscopic imaging (MRSI) exam to map total choline (tCho), a sensitive biomarker of breast tumor status. Although MRI plays an increasingly important role in the screening, clinical diagnostics, and treatment follow-up of breast cancer, its overall specificity is still low, resulting in a considerable number of benign biopsies. Recent studies have reported that adding quantitative MRS measurements of tCho to a dynamic contrast-enhanced (DCE) MRI exam produces improvements in the sensitivity, specificity, and accuracy for all readers, and it improves interobserver agreement between readers. A second promising application of breast MRS involves predicting response to treatment, possibly within 24 hours after the first dose of chemotherapy for locally advanced breast cancer. The much-higher spatial resolution and shorter measurement time of the technology compared to conventional MRS methods will enable clinically feasible mapping of tCho to enhance the limited specificity of routine DCE MRI.

Highly Fluorescent Magnetic Nanoprobes for Enhanced Cancer Imaging and Therapy

The broad objective of this proposal is to develop new multifunctional nanoprobes with superior optical and magnetic properties for enhanced molecular cancer imaging and therapy. An electromagnetic device for producing a controllable magnetic field gradient will be designed and used in the guiding of the nanoprobes to target cells. The targeting efficacy of the fluorescent nanoprobes (also incorporating drug load) will be evaluated in the imaging and treatment of breast cancer in model systems.

Breast CT Scanner for Earlier Cancer Detection

On the basis of initial tests, breast CT has demonstrated enormous potential to detect breast cancer early and lead to more timely treatments for breast cancer patients. While breast CT would probably improve cancer detection in all women, some women may have risk factors (dense breasts, genetic markers, etc.) that would require more than one screening session with breast CT. Investigators have designed and constructed the first dedicated breast CT scanner, using a breast CT table that eliminates the need for compression of the breast, is capable of 10-second breast imaging, and produces 3D images of the breast. The team also found that breast CT may be able to routinely detect breast tumors that are smaller than those that can be detected by mammography. More important, the radiation dose of breast CT studies was found to be comparable to that of mammography.

A high-quality prototype breast CT scanner was built in 2004 during the first period of funding from NIBIB. In addition, a phase II clinical trial evaluated the efficacy of breast CT for the early detection of breast cancer in a group of women likely to have breast cancer. A second, more sophisticated prototype breast CT scanner was fabricated in 2007, adding the capability of simultaneous PET imaging and other enhancements to the breast CT technology, and further clinical trials are being conducted in a second funding period. A third prototype with several improvements will be built in the current funding period.

Receiver Operating Characteristic (ROC) Analysis for Computer-Aided Breast Cancer Diagnosis

The NIBIB funds several projects on ROC analysis for computer-aided diagnosis of breast cancer. ROC analysis is used to evaluate a diagnostic method for sensitivity (the

fraction of positive cases that are properly identified) and specificity (the fraction of negative cases that are properly identified). Improving the sensitivity means fewer cases of cancer are missed during screening, whereas improved specificity means fewer false alarms that can cause undue stress and worry for women. One of these projects is working to improve the software that is used to analyze data from experiments that are conducted to evaluate the diagnostic performance of imaging modalities. The software will be improved to manage situations in which some of the radiologists read all of the clinical cases, while others read only a portion of the cases or situations where there are many more positive cases than negative cases in an experimental data set. Another project will develop free-response ROC (FROC) and clinically relevant, case-based figures-of-merit (FOM) to quantify performance in observer performance studies. This work is also developing realistic data simulators to validate various FROC and ROC methodologies that have been developed. To date, this project has developed case-based FOMs and is implemented in the publicly available JAFROC software package. Work on the data simulator is progressing, and the application of these techniques to mammography data is currently ongoing, with the acquisition and analysis of clinical data.

Magnetic Resonance Elastography

The goal of this research is to develop, validate, explore, and identify high-impact applications of a new diagnostic imaging technology for quantitatively assessing the mechanical properties of tissues: MR elastography (MRE). In this technology, mechanical waves are generated in tissue, and a remarkably sensitive phase-contrast MRI technique, using synchronous motion-sensitizing gradients, is employed to directly image the pattern of wave propagation. Specially developed mathematical algorithms are used to analyze the wave images and to generate quantitative images that depict the stiffness and other mechanical properties of tissue. Using MRE to palpate tissues will allow clinicians to identify breast lesions and will distinguish benign lesions from malignant ones.

Advanced High-Resolution Two-Dimensional X-Ray Detector for Mammography

The goal of this project is to improve the image quality and reduce the cost of digital mammography. The research team will develop a computed radiography system for mammography based on novel glass ceramic materials. These materials will be used to develop a transparent phosphor material that is less expensive and can attain better performance than existing phosphor materials. Because they are transparent, these materials do not suffer from loss of resolution and increase in noise due to light scattering from grain boundaries, as do polycrystalline materials. Specifically, the investigators plan (1) to perform structural investigations, (2) to optimize the transparent phosphor material for the application in computed radiography mammography, (3) to design and construct a readout system for transparent phosphor material, and (4) to characterize and benchmark the new computed radiography.

Near-Infrared Diffused-Light Imaging with Ultrasound Guidance

The goals of this project are to explore the utility of a novel hybrid ultrasound/optical imaging technique for (1) accurate diagnosis of breast lesions that could result in the reduction of benign biopsies and (2) assessing chemotherapy response and evaluating treatment efficacy. Investigators have developed a novel hybrid ultrasound/optical imaging system that uses simultaneous optical (infrared) and ultrasound sensors in a handheld probe. This method provides accurate detection of tumor angiogenesis (i.e., the formation of new blood vessels) and the distribution of these new blood vessels, which helps distinguish benign lesions from early-stage cancers. This method will be tested in a large number of patients who will also receive ultrasound-guided biopsy. Early results indicate that this may be a promising adjunct to mammography and may help to reduce the number of benign breast biopsies, as compared with methods that have been in use for more than 20 years.

Ultrasound Imaging of Breast by Use of a Hemispheric Array and Inverse Scattering

Investigators are developing a high-resolution, quantitative 3D ultrasound breast imaging method using a hemispheric transducer array. This system is designed to achieve high-resolution image reconstruction and quantitative measurements of normal versus malignant tissues. Successful completion will result in a screening method for breast cancer without the use of x-rays. In addition, this method will overcome limitations of x-ray mammography such as low resolution, low contrast in dense breasts, and poor imaging of breasts with implants, and it will eliminate the need for compressing the breast. This device may ultimately change the way screening for breast cancer is performed and significantly improve detection, diagnosis, and monitoring for cancer recurrence or response to treatment. The system may replace mammography and other radiation-based methods as the standard of care.

Robotic Haptic Feedback System for Breast Biopsy (Bx)/Radiofrequency Ablation (RFA) of Breast Tumor Under Continuous MRI

This project proposes to develop an image-guided robotic system that will be able to perform breast biopsy and deliver radiofrequency ablation (RFA) at the site of the breast tumor. The investigators will incorporate continuous MRI during the procedure so that sampling errors will be minimized during the biopsy. Furthermore, the haptics in the teleoperated robotic system will provide force feedback to the clinicians to guide the biopsy and RFA needle with wider areas of access to various regions of the breast.

Design Studies and Optimization of Phase-Contrast Mammography

A new form of x-ray imaging called phase-contrast imaging allows visualization and differentiation of soft tissues that is much greater than in conventional x-ray imaging while considerably reducing the radiation dose. Investigators plan to adapt this method to mammography and expect that it will improve the ability to image dense breasts, which are challenging to visualize using conventional mammography. This study is in a very early stage. Prototype imagers will be built by the end of the current funding period and will be evaluated objectively for improvements in image quality, improved detection capabilities, and reduction in radiation exposure. If successful, this new imaging modality will improve a radiologist's ability to detect subtle cancer features while allowing earlier treatments.

Decision Support System for Predicting the Outcome of ER+ Breast Cancers

Of the 120,000 women diagnosed annually with estrogen receptor-positive (ER+) breast cancer in the United States, the vast majority are considered to be at high risk for having a distant recurrence (metastasis) within 10 years. Under current National Comprehensive Cancer Network guidelines, these women are recommended to have adjuvant chemotherapy in addition to the standard hormonal treatment. However, almost 85 percent of these women do not benefit from chemotherapy and suffer its deleterious side effects. The investigators propose to use a computer vision and machine-learning technique to extract information from digitized histological sections and develop a low-cost approach using a continuous image-based risk score for predicting the risk of recurrence. This work is funded as an SBIR (Small Business Innovation Research) application and is currently in phase I.

Tumor-Specific Gene Vectors for Imaging and Therapy of Metastatic Disease

The long-term objective of this new grant is to facilitate the development of safe and efficient dual-function gene therapy and imaging viral vectors to treat disseminated cancers, including malignant breast neoplasms. The goal of this research is to develop improved targeted viral vectors for intratumoral expression of therapeutic and imaging reporter genes.

Tubulin-Binding Upconversion Nanoparticles for Breast Cancer Imaging and Therapy

This project intends to develop a targeted cancer diagnosis and treatment system via tubulin-binding nanoparticles that can be imaged with near-infrared light. Tubulin makes up the microtubules involved in chromosome segregation of dividing cells such as cancer cells, and targeting these nanoparticles to breast cancer cells could aid in destroying the cancer.

Drug-Based Polycations for Combination Drug-Gene Delivery

The long-term goal of this project is to establish a new class of biodegradable gene delivery vectors that can also function as active pharmacologic agents to attack human breast cancer. The project combines biodegradable dendritic prodrugs based on a cationic drug that will efficiently deliver tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene to triple-negative breast cancer cells and then decompose into the original drug BENSpm, thus augmenting the therapeutic effect of TRAIL.

Other Cancers

Multifunctional Protein Nanocapsules for Targeted Delivery

Recent advances have applied nanotechnology and nanoparticles as diagnostic and therapeutic agents for the treatment of cancer. The goal of this investigation is to incorporate multiple functionalities into 25-nm protein nanoparticles and to test their potential for the targeted delivery of doxorubicin in treating breast cancer cells. The synthesis involves the genetic engineering of chimeric proteins that encapsulate the drug molecule and dissociate at a specific pH to release the drug. The quaternary protein assembly comprises 60 subunits, and its modular structure enables the nanoscale architecture with cell-targeting peptides to be specifically tailored in a straightforward manner. Studies thus far have shown an increase in the effectiveness of this drug at a lower dose than that used in synthetic drug delivery systems and with a decrease in side effects. The interior surfaces of the 60-protein subunits of the nanoparticle are enriched in hydrophobic amino acids so that hydrophobic drugs can be maintained in the nanoparticles by hydrophobic interaction. At the pH of the tumor environment, the nanoparticles dissociate to release the drugs at the tumors.

Applications of Titanium Oxide Nanoconjugates

This project is developing TiO2-biopolymer nanoconjugates as new vehicles for biotechnology. Depending on the nanoparticle coating, these nanoconjugates cause either DNA scission or interact with cellular proteins. Both of these activities can be used to interfere with cancer maintenance and progression. In addition, novel nanocomposites and nanoconjugate formulations are being developed that provide increased photocatalytic activity and modulate contrast for MRI, improving therapeutic potential and allowing for monitoring of composite nanoconjugate delivery and retention. These nanoconjugates are being applied to a papillomavirus-induced rabbit liver carcinoma model. These experiments are models for cervical carcinoma and some head-and-neck tumors that are also induced by the papillomavirus.

Optical Coherence Tomography Image-Guided Surgical Resection of Solid Tumors

Image-guided surgical interventions have the potential to improve the outcomes of surgery by providing improved visualization and differentiation of normal and pathological tissue intraoperatively and in real time. A critical need exists for an image-guided interventional technology that is capable of real-time intraoperative imaging for the complete resection of a tumor mass, of detecting and removing individual tumor cells that have migrated across tumor margins, and of detecting cells that have metastasized to lymph nodes. Optical coherence tomography (OCT) is an emerging high-resolution, real-time biomedical imaging technology capable of intraoperative imaging for tumor detection and intervention. This project will use OCT for high-resolution image-guided surgical interventions for the identification and resection of solid tumors, suspicious regions around the

tumor, and lymph nodes that show evidence of metastatic cancer. To do this, the investigators are developing a high-speed surgical microscope-based OCT system with fast image-processing hardware that will be tested in an animal model of breast cancer. The use of OCT for image-guided surgical interventions has the long-term goal of improving surgical outcomes by enabling complete resection of tumor with real-time, high-resolution visualization of the surgical field.

Thermally Targeted Drug Delivery by Elastin Biopolymers

The term "cancer" describes a collection of diseases caused by multiple genetic mutations arising from environmental insults, somatic DNA replication errors, and inherited genetic defects. The modern treatment of cancer typically includes various combinations of radiation, chemotherapy, surgery, or drug-based therapies. A critical failure in such therapies/treatments, however, can ultimately lead to metastases. A team of investigators is developing a new combination strategy to treat ovarian cancer using a novel drug delivery approach. The dual-targeting delivery strategy described in this proposal attacks both the tumor vasculature and the cancer cells directly when a localized hyperthermia approach is applied. Here, scientists have developed elastin-like polypeptide nanoparticles (ELPs) that undergo a transition from a solid to a liquid when heated. This causes the delivery vehicles to aggregate in targeted regions of tumors. In the first stage of therapy, the tumor vasculature is ablated by irradiating the aggregated ELPs that are formed, and in the second stage, the drug doxorubicin is released to kill the remaining cancer cells. Studies thus far have shown that these thermally triggered ELPs result in increased tumor accumulation and better distribution in tumors to improve overall therapeutic efficacy compared with conventional therapeutic approaches such as a single-drug delivery modality or nonthermally targeted systems.

Joint Segmentation of MR and CT Scans for Gynecologic Cancer Brachytherapy

In gynecologic brachytherapy, radioactive isotopes are placed directly into a cancer of the uterine cervix or vagina in order to eradicate the cancer. This is usually done with the insertion of a hollow applicator into the tumor, with a 3D CT volume used to guide subsequent radiation planning. Because MRI provides a clearer delineation of the target volume that should receive the highest dose of radiation, current practice is for patients with large tumors to undergo both a CT scan and an MRI. Usually, these data sets are aligned, and treatment regions are outlined in a complex process requiring input from the radiation oncologist and physicist while the patient is under anesthesia and awaiting treatment. The funded project plans to improve the efficiency of this workflow by using advanced image analysis methods. In this process, using Bayesian segmentation techniques, the team plans to develop tools that can simultaneously register the MR and CT images for the planning of radiation treatment. In the first year, the team has developed a graph-based segmentation algorithm that implements within a few seconds, and the team has tested it for bladder segmentation. Some of these results were presented at the fourth NCIGT (National Center for Image Guided Therapy) and NIH workshop, and they have been submitted for publication to PLOS ONE.

Reproductive Health

Center for Point-of-Care Technologies Research for Sexually Transmitted Diseases

The goal of this project is to develop point-of-care tests for sexually transmitted diseases (STDs), with *Chlamydia trachomatis* being a main focus, as it is the most common bacterial STD. The STD area is optimal for the development of point-of-care tests, given the stigma, privacy, and confidentiality issues that limit the effectiveness of current approaches to testing and follow-up treatment. These infections have serious long-term consequences for women because many, if not most, STD infections are asymptomatic. The center is developing a range of technologies for detection of *Chlamydia trachomatis,* including immunoassays and molecular diagnostic approaches; center staff are assessing the acceptability

of sample collection by patients and the ability of patients to obtain accurate results compared with testing by trained health care professionals.

Development of Advanced Techniques for Magnetic Resonance of the Newborn Brain

This project is focused on developing both imaging and metabolic assessment techniques through MRI and MR spectroscopy in neonates. With the extraordinarily high number of premature births in the United States, more than 540,000 per year, and the extremely high human and economic costs associated with these events, neonatal MRI is a critically important advance in radiological care. The investigators on this project propose to develop and translate new specialized 3T MRI tools for the noninvasive characterization of brain maturation and injury in both premature and term newborns.

Fetal Functional Magnetic Resonance Imaging

Fetal functional MRI (f-fMRI) has immense potential to further the understanding of normal and pathological fetal neurofunction and development. Studies on the development and application of f-fMRI are motivated in part by the need to monitor fetuses at risk for intrauterine growth restriction. The purpose of this study is to design, to implement, and to optimize a technique for blood-oxygen-level-dependent f-fMRI. These techniques involve novel approaches for reducing the field of view of the MRI image, and they will substantially reduce major artifacts due to fetal or maternal motion. The imaging techniques will be used to compare normal fetuses and fetuses at risk for intrauterine growth restriction.

Molecular and Cellular Transport in Mucus

STDs and unwanted pregnancy create tremendous burdens on individuals, on U.S. society, and on national health care costs. The goal of this project is to understand the biological barriers to protein and DNA transport at mucosal surfaces and to produce new polymeric delivery systems to enhance immune protection within the female reproductive tract. The study team has designed and synthesized biodegradable nanoparticles that can cross the human cervical mucus layer, enter specific cells, and release complex agents such as siRNA and DNA to treat or protect against infectious diseases such as genital herpes and specific pathogens. The team is also expanding into investigating new delivery systems to treat SIV infection in rhesus macaques, which provide the premier model of HIV infection in humans.

MRI of Fetal Ventriculomegaly: Morphology and Outcome

Ultrasound is the imaging modality of choice for fetal evaluation. However, in many cases, ultrasound is nonspecific, and further development of ultrasound techniques is needed, especially for fetuses with ventriculomegaly. Fetuses with ventriculomegaly are a heterogeneous population, and it is likely that using additional MRI data will facilitate improved counseling and management of these patients. This research is based on the hypothesis that the additional use of MRI with ultrasound will improve the diagnostic utility of that modality for patients with ventriculomegaly and increase the ability to predict outcomes when compared with ultrasound alone.

Point-of-Care Ultrasound for Maternal Health

Ultrasound has become an integral part of prenatal care, and yet many patients in rural or underserved areas do not have access to this diagnostic equipment. System costs and the need for trained operators limit the use of ultrasound to hospitals, clinics, and doctor's offices. Researchers at General Electric's Global Research Center in Niskayuna, NY, are tackling both challenges. First, they developed a low-cost method to fabricate ultrasound transducers—the probes that generate and receive sound waves—and now they are developing software that automatically adjusts image quality, thereby reducing the need for specialized operator training.

Development of Spatial-Temporal Analysis Tools for Uterine Biomagnetic Signals

This study was designed to record the magnetic field corresponding to the electrical activity of uterine contractions and to provide requisite spatial-temporal information. To take advantage of the spatial-temporal resolution in uterine magnetomyographic signals, the study investigators further enhanced the computational and analysis tools and developed this system as a clinical device to predict the onset of labor for both term and preterm patients. The goal is to develop techniques to improve the extraction, recognition, and validation process of uterine magnetomyographic activity. This ability would be of great clinical benefit for the management of the term patient and especially for the management of patients at high risk for premature delivery.

Development of Analysis Tools to Enhance Fetal Neurological Assessment

The ultimate goal of this project is to develop a clinical neurological assessment tool for the developing fetus. The project investigators have shown that fetal spontaneous brain signals can be extracted from biomagnetic recordings with sufficient signal-to-noise ratio. Further, they have shown the applicability of using these signals to track the neurological activity of growth-restricted fetuses. The success of these studies was largely dependent on the development of appropriate analysis tools. The investigators have moved on to the next stage of the project to further improve the analysis methods to account for spontaneous fetal data that occur over long-duration data sets and to develop clinically relevant indices to track fetal neurological maturation. The investigators also plan to extend their studies to the other high-risk subgroups, such as chronically hypertensive and pregnancy-induced hypertensive mothers.

A Low-Cost Cardiac Annunciator to Reduce Stillbirths and Neonatal Deaths

Some of the 3.7 million neonatal and 2.6 million stillbirths that occur in the world each year could be avoided if birth attendants were made aware that some neonates who are unresponsive at birth are alive and can be resuscitated. The ultimate goal of this project (funded through an Indo-U.S. collaborative program for low-cost medical devices) is to develop and evaluate a simple cardiac annunciator that can be placed on the chest of the newborn infant to detect the electrocardiogram and produce a sound and a light flash for each detected heartbeat. The device will be developed in the United States and will be tested in clinical facilities both domestically and in India.

Cell-Phone-Based Protocols for Diagnosis and Management of Childhood Pneumonia

While pneumonia is the leading cause of death in children worldwide, the current approach, using paper-based protocols and relying on a clinician's ability to manually count the respiratory rate, has proved inadequate for diagnosing pneumonia in a timely manner and in implementing effective treatment options. The proposed work (funded through an Indo-U.S. collaborative program for low-cost medical devices) plans to develop, design, and test an Android smartphone-based device that incorporates a user-friendly digital version of local integrated management of neonatal and childhood illness (IMNCI) protocols and tools for assessing respiratory rate and oxygen saturation. This device will be used to provide appropriate treatment algorithms and instructions on managing childhood pneumonia. The project was recently funded and has completed initial field trials, and the data are being analyzed for future modifications.

National Physicians Cooperative to Preserve Fertility for Female Cancer Patients

This cooperative includes 5 core institutions and 15 allied centers throughout the United States. The primary goals are to (1) collect adult ovaries from women with cancer and distribute them for basic science research; (2) educate providers, patients, and the community through the allied centers about fertility options for women with cancer; and (3) disseminate the technical knowledge on follicle maturation and cryopreservation to

the allied centers. Active research into fertility preservation and germinal tissue preservation could provide opportunities for restoring fertility and other ovarian functions after cancer treatment to improve posttreatment quality of life. Subjects can enroll under one of two separate institutional review board (IRB)–approved protocols. In one protocol, ovarian tissue cryopreservation for fertility preservation, 80 percent of tissue is preserved for the woman's use and 20 percent is allotted for the research repository. In the second protocol, when ovaries are removed for medical indications and the women do not want fertility preservation, tissue is donated for research only. Virtual grand rounds are conducted quarterly and preserved on the Web site of the Oncofertility Consortium, which is a component of the National Physicians Cooperative. The Oncofertility Consortium operates the National Fertility Hotline, and providers and patients either approach the consortium's Web site or use its hotline approximately 10 times per week. The National Physicians Cooperative experienced a 220 percent increase in providing fresh tissue in the year reported in the latest progress report.

Biomaterials Core of the Oncofertility Consortium

The biomaterials core of the Oncofertility Consortium has two major missions: first, to develop enabling technologies for cryopreserving and maturing primate ovarian follicles and, second, to provide materials and training to satellite locations for the maturation procedures. The biomaterials core has successfully continued the development of advanced techniques in follicle cryopreservation and culture. Dissemination of its techniques has continued with the Oncofertility Saturday Academy and the training of more than 300 investigators in the year detailed in the progress report, as well as in the creation of a first- and second-generation DVD highlighting the first- and second-generation biomaterials developed for oncofertility research and cryopreservation of ovarian follicles. This project is also developing hydrogel matrices to assist in the transplantation process.

Temporomandibular Joint Disorder

Tissue Engineering TMJ Articular Fibrocartilage

Temporomandibular joint (TMJ) disorders are painful conditions that disproportionately affect women and for which there are few (if any) successful treatments. The TMJ is the small, complex joint that forms the articulation of the lower and upper jaws, and it is characterized by an unusual hybrid type of cartilage. Several major technical hurdles have prevented the development of clinically useful engineered cartilage, particularly the optimization of mechanical properties, and obtaining an appropriate cell source. Investigators in this project have been using several advances (cell sourcing, bioreactor growth systems, scaffolds with functional tensile strength) to generate TMJ articular cartilage appropriate for implantation and repair of the TMJ. These researchers have identified several scaffolds with high tensile strength that may support tissue engineering of TMJ cartilage. These studies are intended to lead to translational research, where these tissue-engineered constructs will be assessed in preclinical models.

Initiatives

In FY 2011–FY 2012, NIBIB led and participated in several initiatives that addressed areas relevant to women's health. These are described below.

NIBIB-Led Initiatives

RFA-EB-10-002—Development and Translation of Medical Technologies that Reduce Health Disparities (SBIR [R43/R44])

NIBIB sponsored a Funding Opportunity focused on reducing health disparities through the development and translation of appropriate medical technologies, new or existing, that can have a significant impact on health care access and health outcomes for health disparities in populations. The RFA (Request for Applications) supports a wide range of research aimed at the development of innovative diagnostics, treatments, and preventive strategies to reduce and, eventually eliminate, health disparities.

PAR-11-044—Indo-U.S. Collaborative Program on Low-Cost Medical Devices (R03)

NIBIB has initiated a funding program to encourage collaborative research and/or technology development between scientists and engineers in the United States and India to develop new, low-cost, appropriate diagnostic and therapeutic medical technologies for low-resource settings and underserved populations within the United States and/or India. The program announcement supports a wide range of research, including maternal/neonatal/infant health, cardiovascular diseases, cancer screening, and translational research, among others.

Joint Initiatives

RFA-GM-09-012—Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering (R01)

NIBIB participated in a trans-NIH Funding Opportunity for research on (1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering and variation across different subgroups and (2) the efficacy of programs designed to eliminate sex/gender disparities and promote the careers of women in these enterprises. This program is designed to better understand the factors that influence existing outcomes, to promote the identification of new principles that would inform the development and adaptation of existing intervention strategies, to analyze differences in the career activities of men and women scientists and engineers that could inform the development of interventions for remediation, and to promote the analysis of career patterns to further support new programs.

PAS-10-226—Advancing Novel Science in Women's Health Research (ANSWHR) (R21)

With ORWH, NIBIB cosponsored a trans-NIH investigator-initiated exploratory developmental program designed to promote innovative, interdisciplinary research to advance new concepts in women's health research and the study of sex/gender differences. Published research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. The ANSWHR program is focused on stimulating and supporting innovative research that will advance new concepts in women's health research and the study of sex/gender differences.

Health Disparities Among Special Populations of Women

The NIBIB is continuing to develop and support a research portfolio that pursues cutting-edge science in the area of women's health research. The NIBIB increased its commitment to women's health research from $16 million in 2011 to $17.3 million in 2012.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Executive Summary

The mission of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is to ensure that every child is born healthy and wanted; that women suffer no harmful effects from reproductive processes; and that all children can achieve their full potential for healthy and productive lives, free from disease or disability; and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation. Within this mission, NICHD supports essential research that plays a unique role in women's health, aiming to overcome many of the complex challenges that women encounter over their lifetimes. NICHD is home to much of the nation's leading science related to women's overall health, gynecological health, pregnancy, and childbirth, as well as studies of diseases and conditions related to these topics.

NICHD supports a wide-ranging research portfolio in women's health, including research on preconception care, fertility preservation, maternal obesity, oogenesis, ovarian failure, uterine fibroids, pelvic floor disorders, endometriosis, vulvodynia, infertility, contraception, HIV, menopause, violence, obstetrical pharmacology, preterm birth, stillbirth, assistive reproductive technologies, and many other aspects of women's health to improve the lives of women around the world. Not only does the Institute support research on women's health, but it also conducts outreach and dissemination activities and develops press releases and publications to share research results and health information with the general public. Because women's health issues are related to a variety of other research areas, the Institute partners with many NIH Institutes, Centers, and Offices, as well as other federal agencies, to support its women's health research, training, and outreach activities.

NICHD's accomplishments in women's health research are wide-ranging and address conditions across the life stages. Highlighted in this report are just some of NICHD's recent activities related to women's health. The report is organized to briefly summarize the NICHD organizations that focus on women's health; highlight some of the Institute's recent accomplishments and activities across categories affecting women's health, such as training and special populations; and list and briefly describe initiatives and conferences related to women's health, again across categories. Outreach and dissemination activities are also included throughout the report. When available, hyperlinks are included for more information about specific activities. Additional information about the Institute's research on women's health is available on the NICHD Web site: *http://www.nichd.nih.gov/news/resources/spotlight/Pages/052312-womens-health.aspx*

NICHD Organizational Health Components

NICHD supports research and activities that promote women's health through the Office of the Director (OD) and across seven major research components.

The OD provides overall leadership, planning, direction, coordination, and evaluation of the Institute's research programs and activities. The NICHD leadership is committed to supporting research initiatives that will improve the health of women. In 2012, the Institute released *Scientific Vision: The Next Decade,* a statement outlining an ambitious but achievable scientific vision for NICHD and its research communities. NICHD worked with its external partners to identify the next decade's most promising scientific opportunities. Themes in the statement that address women's health issues include promoting innovative research in reproduction and pregnancy and pregnancy outcomes. Expanded research aims to improve the reproductive health of women and provide novel diagnostic and therapeutic targets for conditions affecting fertility. Novel approaches to prevent, diagnose, and manage gynecologic disorders, including endometriosis, pelvic floor disorders, and fibroids, could greatly improve the quality of life for women. To advance the health of women, future research will study pregnancy as both a biomarker and a cause of later disease in the mother (*http://www.nichd.nih.gov/publications/pubs/Documents/NICHD_scientific_vision120412.pdf*).

In 2012, NICHD underwent a reorganization of its extramural program in an effort to capitalize on emerging scientific opportunities and to reduce barriers to scientific and interdisciplinary collaboration. From this reorganization emerged a new branch supporting research in women's gynecologic health:

The Gynecologic Health and Disease Branch (GHDB) supports and promotes basic science, translational and clinical research, and research training programs related to gynecologic health in women and adolescent girls. The GHDB portfolio emphasizes studies of the menstrual cycle, uterine fibroids, endometriosis, polycystic ovary syndrome, pelvic floor disorders, and menopause transition/perimenopause, as well as studies of the mechanisms underlying chronic pelvic pain, vulvodynia, and dysmenorrhea. The Branch also supports research training and career development programs of investigators interested in women's

reproductive health. Within this program area, a focus of the GHDB is to advance research into selected gynecologic health concerns by sponsoring research efforts in areas that have been either overlooked or underfunded, including reproductive health outcomes in minority women (*http://www.nichd.nih.gov/about/org/der/branches/ghdb/Pages/overview.aspx*).

Of the 13 remaining branches, the 5 described below lead and support a wide range of women's reproductive health issues.

The Contraceptive Discovery and Development Branch (CDDB), formerly the Contraception and Reproductive Health Branch, develops and supports research and research training programs in contraceptive development, pelvic floors disorders, and other areas of reproductive health. Major research areas include studies of new contraceptive methods; mechanisms of action and effects of contraceptive and reproductive hormones, drugs, devices, and procedures; and optimal formulations and dosages of contraceptive agents and spermicidal microbicides (*http://www.nichd.nih.gov/about/org/der/branches/cddb/Pages/overview.aspx*).

The Fertility and Infertility Branch, formerly the Reproductive Sciences Branch, supports scientific research aimed at alleviating human infertility, uncovering possible new pathways to control fertility, and expanding fundamental knowledge of processes that underlie human reproduction. To this end, the Fertility and Infertility Branch provides funds for basic, clinical, and translational studies that will enhance our understanding of normal reproduction and reproductive pathophysiology, as well as enable the development of more effective strategies for the diagnosis, management, and prevention of conditions that compromise fertility, with the ultimate goal of promoting a better quality of life for all individuals. In 2012, the Branch cosponsored the annual meeting of the American Society for Reproductive Medicine on Ovarian Reserve: Regulation and Implications for Women's Health. The purpose of the meeting was to address current questions surrounding ovarian reserve and its implications for women's fertility and overall health (*http://www.nichd.nih.gov/about/org/der/branches/fi/Pages/overview.aspx*).

The Maternal and Pediatric Infectious Disease Branch (MPIDB) supports and conducts a wide range of domestic and international research related to the epidemiology, diagnosis, clinical manifestations, pathogenesis, transmission, treatment, and prevention of HIV infection and its associated infections (such as tuberculosis [TB], malaria, and hepatitis), as well as noninfectious complications in pregnant and non-pregnant women, infants, children, adolescents, and the family unit as a whole. As the HIV epidemic has evolved in the United States and globally, the MPIDB has ensured that research funded by the Branch reflects these changes and addresses important research opportunities and gaps as they arise. The research gaps in children and pregnant women related to many HIV-associated coinfections, such as TB, hepatitis, and malaria, have become evident as HIV research has become increasingly global in nature. The MPIDB has responded accordingly by promoting and funding new research related to these infectious pathogens, as well as the investigation of vaccines to prevent HIV-related or other high-priority infectious diseases in children, adolescents, and pregnant women (*http://www.nichd.nih.gov/about/org/der/branches/mpidb/Pages/overview.aspx*).

The Obstetric and Pediatric Pharmacology and Therapeutics Branch, formerly the Obstetric and Pediatric Pharmacology Branch, promotes basic, translational, and clinical research to improve the safety and efficacy of pharmaceuticals and to ensure centralization and coordination of research, clinical trials, and drug development activities for obstetric and pediatric populations. The Branch is responsible for developing and supporting a comprehensive national effort to increase the knowledge base for understanding how to appropriately treat disease during pregnancy, infancy, and childhood, using pharmaceuticals that are appropriately tested within their target populations (*http://www.nichd.nih.gov/about/org/der/branches/opptb/Pages/overview.aspx*).

The Pregnancy and Perinatology Branch seeks to improve the health of mothers and children by supporting research in maternal health, pregnancy, fetal well-being, labor and delivery, neonatal and infant health and well-being, and the long-term health outcomes associated with pregnancy and with fetal and infant development (*http://www.nichd.nih.gov/about/org/der/branches/ppb/Pages/overview.aspx*).

Additionally, NICHD has a robust intramural research division that spans 11 research programs focused on ensuring the health of humans from birth into adulthood. *The NICHD Division of Intramural Research* conducts interdisciplinary research in both basic and translational science to enhance the understanding of the biology of development and reproduction, to ensure the health of infants who develop into adulthood and to optimize the health of women. The Division strives to understand the basics of science through research in cell biology and metabolism, molecular medicine, genomics, and developmental endocrinology. For example, the intramural Program in Perinatal Research and Obstetrics (PPRO) studies pregnancy and pregnancy complications. PPRO provides state-of-the-art prenatal care to women enrolled in NICHD protocols and has made major contributions to understanding the mechanisms of disease in premature labor/delivery and preeclampsia (*http://www.nichd.nih.gov/about/org/dir/Pages/index.aspx*).

Accomplishments

Contraception

Increase in Use of Long-Term Contraceptives and Disparities in Access to Sterilization. The development of safe and effective contraceptives is essential for reducing unintended pregnancies and allowing women to control their own fertility. A study funded by NICHD took a retrospective look at women's use of birth control and found a significant increase in the use of long-acting reversible contraceptives, such as injectables and intrauterine devices. These methods require less effort to use, and public education about their efficacy and safety may increase use and decrease the number of unintended pregnancies. Alternatively, many women choose to undergo female sterilization as a permanent form of birth control. However, a survey of over 800 low-income Latina women in Texas found that these women face difficulties in obtaining sterilization. Problems included the 30-day waiting period required by the state Medicaid program and being told that there were no Medicaid funds available. Many women reported that they were counseled by their health care providers that they were "too young," although all were over 21, and some were in their late 30s.

Fertility

Researchers Identify Protein Essential for Embryo Implantation. Researchers identified a key step in the establishment of pregnancy; their discovery shows how the hormone progesterone suppresses the growth of the uterus's lining so that a fertilized egg can implant in the uterus. This key step, the researchers discovered, occurs when a protein called Hand2 suppresses the chemical activity that stimulates growth of the uterine lining, also known as the uterine epithelium. Hand2, previously found to increase in uterine cells as progesterone levels rise, is the switch that turns off estrogen's stimulating effect on the epithelium. The finding may contribute to understanding some forms of unexplained female infertility. The finding also has implications for understanding disorders in which growth of the uterine epithelium surges out of control, such as endometrial cancer or endometriosis, the latter a disease in which endometrial tissue appears on the ovaries, bowel, or other tissues outside the uterus.

PCBs, Other Pollutants May Play Role in Pregnancy Delay. A recent study revealed that couples with high blood levels of polychlorinated biphenyls (PCBs) and similar environmental pollutants take longer to achieve pregnancy than do couples with lower levels of the pollutants. The couples were part of the Longitudinal Investigation of Fertility and the Environment (LIFE) study, established to examine the relationship between fertility and exposure to environmental chemicals and lifestyle. Other analysis

from the LIFE study found that high blood levels of lead and cadmium also were linked to pregnancy delay. These studies suggest that men and women planning to have children should limit their exposure to these environmental chemicals.

Polycystic Ovary Syndrome

Research Reveals Links Between Genetics/Race and Fertility Treatments and PCOS. Polycystic ovary syndrome (PCOS) is a condition in which a woman's body produces more androgens (a type of hormone) than normal. High levels of these hormones interfere with the development and release of eggs as part of ovulation. As a result, fluid-filled sacs or cysts can develop on the ovaries. Because women with PCOS do not release eggs during ovulation, this condition is the most common cause of female infertility. Researchers found that there are two genes, *DENND1A* and *THADA*, connected with PCOS risk in non-Hispanic White women. Other research revealed that women who skipped progestin treatment, a common first step in infertility treatment for PCOS, were actually four times as likely to conceive as were women given progestin. In addition to infertility, women with PCOS may have hirsutism, which is excessive hair growth on the face, chest, stomach, thumbs, or toes. Treating both infertility and hirsutism can be difficult. For example, drugs used to treat hirsutism should not be used for women who want to become pregnant because they can interfere with fertility or even cause birth defects. Researchers conducted a study and found that hirsutism did not worsen when women were given medication to stimulate ovulation.

Gynecologic Health

Genetic Variations May Predispose Some Women to Stress-Induced Amenorrhea. Amenorrhea is the absence of menstrual bleeding, or menses. Functional hypothalamic amenorrhea is a reversible form of this condition and is due to deficiency in a key hormone, GnRH (gonadotropin-releasing hormone). The absence of menses because of GnRH deficiency is commonly caused by stressors like excessive exercise, poor nutrition, and psychological distress. However, women vary widely in their susceptibility to developing amenorrhea in response to stress. Researchers found 6 genetic mutations in 7 of 55 patients with stress-related amenorrhea but found no mutations in 422 women with normal menstrual cycles. The mutations found in patients were in the same genes found in women who are born with the congenital form of the condition. The results strongly suggest that genetic variations may explain why some women are more likely to suffer from stress-induced amenorrhea. This work adds important information to the study of how the complex interaction of genes, environment, and hormones can affect fertility in women.

Many Women Experience Vulvodynia, but Few Receive Diagnosis and Treatment. Vulvodynia is a chronic pain condition that affects women and girls of all ages. A population-based survey of women in the Detroit region estimated that over 100,000 women have vulvodynia. An additional 218,000 women had symptoms of the disorder in the past, but those symptoms had resolved. Symptoms were reported to last over 12 years on average; however, most women never went to a physician about their condition. Of the women who did seek medical attention, only a small percentage was actually diagnosed with vulvodynia. Instead, these women were most often diagnosed as having estrogen deficiency or yeast infections. The results of the survey indicate that improved diagnosis and treatment methods for vulvodynia are urgently needed.

Primary Ovarian Insufficiency

Researchers Slow Immune Attack on Ovaries in Mice. In a study of mice, researchers have slowed an immune system attack on the rodents' ovaries. The mice developed a disorder resembling primary ovarian insufficiency (POI), a menopause-like condition that affects women under the age of 40, usually years and sometimes even decades before normal menopause. Some cases of POI appear to result from an autoimmune response, an immune system attack on the body's own tissues. In their mouse study, the researchers nearly halted the immune assault. They believe they were able to do this

by teaching the animals' immune systems to recognize that the ovarian protein is a part of the body's own tissues. The study results may one day lead to a way to identify women with a high probability of developing autoimmune POI early, perhaps in time to explore fertility-sparing options such as frozen embryo storage or freezing unfertilized eggs. POI affects about 1 percent of women under the age of 40 in the United States, according to the authors.

Endometriosis

Studies Link Genes with Endometriosis and Identify Possible Mechanism of Infertility. Understanding the specific genes and mechanisms associated with endometriosis is a critical step toward the development of therapeutics for this common condition that affects millions of women. Studies linked genetic regions on chromosome 7 with increased risk of endometriosis in women of European ancestry. Another genetic region on chromosome 10 was linked with endometriosis-related fertility. Researchers elsewhere showed that the interactions between progesterone and a gene known to be important to the normal reproductive process are interrupted in women with endometriosis. These disruptions are thought to contribute to the infertility often associated with endometriosis.

Drug Treatments Show Promise of Inhibiting or Suppressing Growth of Endometriosis. Researchers examined potential treatment options for endometriosis. Resveratrol, which possesses anti-inflammatory properties and is known to inhibit the growth of some cancer cells, was found to significantly reduce the invasiveness of human endometrial cells and inhibit endometriosis in mice. Mice treated with another anti-inflammatory compound, retinoic acid, had significantly fewer endometrial lesions, significantly fewer lesions that had developed blood vessels, and significantly less lesion volume than the placebo-treated mice. In addition, the amounts of two proteins associated with inflammation were significantly lower in the treated mice. These results suggest that resveratrol and retinoic acid may hold treatment value for women with endometriosis.

Uterine Fibroids

The High Cost of Uterine Fibroids. A study funded by NICHD estimated that uterine fibroids cost the U.S. between $5.9 and $34.4 billion annually, including direct costs (surgery, hospital admissions, outpatient visits, and medications), indirect costs (lost work time because of absenteeism and short-term disability), and pregnancy and obstetric-related costs associated with fibroid tumors. These large figures emphasize the importance of developing new, effective treatments and earlier diagnosis for uterine fibroids.

Genetic Cause of Infertility Associated with Uterine Fibroids. Uterine fibroids are often associated with reduced fertility in women. Scientists found that the tuberous sclerosis complex (TSC), which is associated with the growth of noncancerous tumors, was involved in several parts of different reproductive processes. For example, in mice without the TSC genes, many egg cells did not mature properly. Egg cells that did mature correctly were able to be fertilized, but they could not exit the fallopian tube to enter the uterus for implantation. Any disruptions to the TSC by fibroids could lead to infertility.

Testing a New, Noninvasive Technique for Diagnosing and Predicting Treatment Outcomes for Uterine Fibroids. A new, noninvasive diagnostic technique known as magnetic resonance elastography (MRE) may provide a feasible method for studying uterine fibroids ranging widely in size and weight, without harmful effects to patients. MRE found wide variations in fibroid stiffness, which may be useful in differentiating fibroids from other, less common types of uterine masses and also for predicting outcomes of minimally invasive procedures to shrink or eliminate fibroids.

Development of Nonsurgical Treatment Options for Uterine Fibroids. Although surgery remains the main treatment option for fibroids, recent studies have shown promise for drug treatment. In a small-scale randomized clinical trial, scientists administered a drug to 42 women suffering from fibroids. These investigators found that women who received the drug treatment

had reduced fibroid size, decreased bleeding, and improved quality of life. Research found that treatment of fibroid cells with another drug decreased the function of important structural genes and, when the drug was administered at high concentrations, decreased the ability of fibroid cells to multiply. Lastly, treatment with vitamin D reduced the size of uterine fibroids in laboratory rats predisposed to developing benign tumors.

Race and Postpartum Birth Control Method Are Associated with Natural Shrinking of Uterine Fibroids. In many women, fibroids may be eliminated altogether or decrease in size during pregnancy or in the postpartum period. To analyze the factors that might help fibroids shrink during pregnancy, researchers studied over 200 women with fibroids who became pregnant. The study found that in 72 percent of the women, fibroids shrank between the early pregnancy and postpartum periods. Black, non-Hispanic women were less likely to have fibroid regression. Participants using progestin-only birth control methods postpartum had significantly less fibroid regression than those using a combined estrogen-progestin contraceptive or a nonhormonal contraceptive method. These results may help scientists develop new treatments for fibroids in women who are not pregnant.

Pelvic Floor Disorders

Researchers Predict Many More Women to Undergo Surgery for Pelvic Floor Disorders in Coming Years. Pelvic floor disorders, including those resulting in stress urinary incontinence or pelvic organ prolapse, are common conditions in older women. These conditions are often expensive to manage, and surgery is a frequently used intervention. Researchers estimated that the number of surgical patients for pelvic floor disorders can be expected to increase by 47 percent by 2050. These data demonstrate an urgent need to develop effective, low-cost interventions for pelvic floor disorders to minimize the public health burden.

Extra Treatment During Prolapse Repair Reduces Incontinence Rate. Surgery is commonly used to repair pelvic organ prolapse, a condition that occurs when the pelvic muscles weaken and can no longer provide support to the pelvic organs. Postsurgery complications include urinary incontinence, which may be corrected by a second surgical procedure in which a sling is inserted to support the bladder in its normal position. This second surgery can result in complications such as incomplete bladder emptying, bladder perforation, bleeding complications, and urinary tract infections. However, placement of a sling in the pelvis was found by researchers to reduce women's chances of incontinence. These findings provide useful information to patients and clinicians when considering the risks and benefits of inserting a sling during prolapse repair surgery.

Study Shows Benefits, Drawbacks for Women's Incontinence Treatments. Scientists compared two commonly used treatments for female urinary incontinence, prescription anticholinergic medications and a form of Botox® taken by injection. The study showed that over 6 months the two treatments were about equally effective in decreasing episodes of urinary incontinence. The treatments had different side effects, however. The oral medication was more likely to be associated with dry mouth, while women who received the Botox were more likely to have urinary tract infections and to experience incomplete bladder emptying.

Anal Lacerations During Childbirth Linked to Fecal Incontinence Years Later. Women who have experienced vaginal childbirth are more likely to develop fecal incontinence, although researchers do not fully understand the reasons why. To better understand the relationship between childbirth and anal incontinence, researchers compared the risks of developing anal incontinence in three groups of women: 90 women who experienced an anal sphincter laceration (a tear in the anal canal) during vaginal childbirth, 320 women who delivered vaginally without an anal laceration, and 527 women who delivered by cesarean section. The scientists discovered that women who sustained an anal sphincter laceration were the most likely to experience anal incontinence 5 to 10 years after childbirth.

Assessing Complications of Pelvic Floor Disorder Reconstructive Surgery. Researchers found that a new Pelvic Floor Complication Scale more accurately classifies

complications specific to pelvic surgeries. This scale will allow surgeons and patients to more easily compare the benefits and risks of various surgical procedures than was possible using another scale designed to measure general surgical complications.

Pregnancy

A Prospective Cohort Study of Physical Activity and Time to Pregnancy. Researchers conducted a study to examine how physical activity affects the time it takes a woman to become pregnant. Scientists reviewed reports of physical activity among over 700 women in Denmark who were attempting to become pregnant. Moderate physical activity was associated with a slight reduction in the time to become pregnant in all women, regardless of weight. However, scientists discovered that more vigorous physical activity was associated with a longer time to become pregnant in women who had normal or a low weight. For overweight and obese women, physical activity of any type either slightly shortened the time to become pregnant or had little to no effect. These findings indicate that physical activity of any type might improve fertility among overweight and obese women. Thin women who choose moderate physical activity instead of more vigorous physical activity may also improve their fertility.

Experiments Evaluate Risks, Benefits of Taking Medications During Pregnancy. The decision to take medication while pregnant can be difficult and requires evaluating possible health risks and benefits associated with taking or not taking medication. Recent research efforts evaluated how pregnancy outcomes may be affected when pregnant women take certain drugs. For example, a pregnant woman's exposure to the active agent in the drug Tamiflu was 30 percent lower than in nonpregnant women. This suggests that moderately high doses of the drug may be needed to prevent or treat influenza in pregnant women. In another example, scientists assessed whether women who took topiramate, a prescription drug used to prevent seizures, were at increased risk of having babies with cleft lip. They found that women who took topiramate during the first trimester of pregnancy were more likely to have babies with cleft lip, with or without cleft palate. However, the risk of cleft lip remained low, at an estimated 1 in 200 babies, for women who took topiramate. Lastly, researchers confirmed that nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common type of drug taken by women in the earliest stage of pregnancy. However, there was no association between use of over-the-counter NSAIDs in the first trimester and increased risk of miscarriage.

Ectopic Pregnancies Do Not Show a Unique hCG Pattern. Scientists conducted a study to examine whether human chorionic gonadotropin (hCG) levels can become a diagnostic tool for ectopic pregnancies. Because ectopic pregnancies are more common among African-Americans, researchers assessed whether hCG levels or patterns differed among different racial and ethnic groups. Researchers analyzed hCG blood levels of women who experienced pelvic pain and/or bleeding in their first trimester. The hCG levels were then compared to hCG patterns of viable pregnancies and miscarriages to evaluate whether there was an hCG pattern that could predict ectopic pregnancy. No pattern in hCG levels was found in the 179 ectopic pregnancies in the study. For some women with ectopic pregnancy, hCG patterns were similar to miscarriage or viable pregnancy patterns. Finally, African-Americans were more likely to have changes in hCG levels, and ectopic pregnancies took longer to diagnose.

Women Spend Longer in Labor Than 50 Years Ago. To assess changes over time in obstetric practice and the patterns of labor and delivery, NICHD researchers analyzed data on more than 140,000 childbirths, comparing data from the 1960s with the 2000s. The results showed that women had significantly longer labor on average in the 2000s than in the 1960s. The researchers could not identify all of the factors that accounted for the longer labor in the 2000s group, but they concluded that the change was likely due to changes in obstetric practice. Compared with the 1960s group, women in the 2000s group were older and heavier. Women in the 2000s were more likely to be given epidural anesthesia (injections of painkillers into the spinal fluid), and they were also more likely

to be given oxytocin (a drug that may be used to speed up labor). The rate of cesarean births increased dramatically between the 1960s and the 2000s, from about 3 percent to about 12 percent. In the 1960s, use of a surgical incision and the employment of forceps were more common than in the 2000s.

Maternal Insulin Resistance and Preeclampsia. Preeclampsia is a potentially serious, complex disorder characterized by high blood pressure and protein in the urine during pregnancy. When preeclampsia is severe, it can affect many organs and can cause serious or even life-threatening problems for mother and baby, including premature birth, low birth weight, seizures, and kidney problems. To learn more about the causes of preeclampsia, researchers conducted a study to determine whether mothers with insulin resistance in their second trimester are more likely to develop preeclampsia later in their pregnancies. These scientists measured insulin resistance for a group of over 1,100 low-risk women having their first pregnancy. They discovered that women who had a higher elevated score on insulin resistance tests were more likely to develop preeclampsia later in their pregnancy, even after factors such as body mass index (BMI), race, ethnicity, blood pressure at enrollment, and gestational age were taken into account. In addition, Hispanic and African-American women had a higher percentage of elevated scores on these insulin resistance tests than did those of other races/ethnicities, as did obese women versus those of normal weight.

Comparison of Noninvasive Methods of Monitoring Contractions During Labor. Current methods of monitoring contractions during labor often fail or are invasive. These deficiencies pose an increased risk to the mother and the fetus for labor complications, and they are greater in women who are obese. The tocodynamometry (TOCO) method uses a monitor secured around the mother's abdomen with a belt to detect contractions. While TOCO is noninvasive, it has a high failure rate. An alternative to this method is an intrauterine pressure catheter (IUPC), but it is much more invasive and runs the risk of causing an infection. A third method, known as electrohysterography (EHG), measures contractions noninvasively by detecting the electrical activity of the uterine muscles through electrodes attached to the mother's abdomen. Results from a study showed that the EHG technique was more consistent than the IUPC at detecting contractions than the TOCO technique. In addition, the EHG technique was found to be more sensitive than the TOCO technique and was also better at detecting contractions accurately. The sensitivity of the EHG and TOCO techniques both got worse as the patient's BMI increased; however, it was significantly worse with TOCO than with the EHG. These results indicate that EHG is a more effective method for monitoring contractions in women, whether or not they are obese.

Depression During Pregnancy May Affect the Nutritional Quality of Breast Milk. Researchers surveyed 287 women to examine whether symptoms of depression during pregnancy affect the concentration of DHA (docosahexaenoic acid) in breast milk. Four months after childbirth, samples of breast milk were collected from these women to measure the concentration of DHA. The results showed that women who reported depressive symptoms in the first 20 weeks of pregnancy had lower concentrations of DHA in their breast milk. The same association was not found in women who reported depressive symptoms later in pregnancy. Because depression prior to pregnancy was not measured, it was unclear whether the women in this study were experiencing chronic depression or temporary depression due to stress or hormonal changes associated with pregnancy. However, because levels of DHA measured in breast milk are reflective of long-term influences on the body to store DHA over time, low levels of DHA in breast milk are likely associated with chronic depression.

Reported Miscarriage Rates Increase Over Time, Likely Due to Earlier Awareness of Pregnancy. Scientists analyzed how reported miscarriage rates from 1970 to 2000 may have been affected by the introduction of home pregnancy tests and women's earlier awareness of pregnancy. The researchers discovered that reported miscarriage rates increased by about 1 percent per year. The greatest increase occurred in the first 7 weeks

of pregnancy, and there was no increase in reported miscarriages after 12 weeks of pregnancy. Additionally, although highly educated women are typically more likely to have access to prenatal care, women at higher education levels were more likely to report miscarriages. Taken together, these two findings suggest that the use of home pregnancy tests may have increased women's awareness of otherwise unnoticed pregnancies, leading to more miscarriages being reported. The study also found that although many health outcomes were worse for African-American and Hispanic women, these groups had a lower risk of miscarriage than whites, especially during early pregnancy.

Gestational Diabetes Rates Vary by Diet and Race/Ethnicity. Women who consumed a diet high in animal fat and cholesterol before pregnancy were at higher risk for gestational diabetes than were women whose diets were lower in animal fat and cholesterol; this finding appeared to be independent of other dietary and nondietary risk factors. Moreover, women with healthy eating habits had between 40 and 57 percent lower risk of developing type 2 diabetes later in life. Scientists also discovered that race/ethnicity may account for differences in pregnancy complications related to gestational diabetes. The rates of gestational diabetes were highest among Asian and Hispanic women, but these two groups were the least likely to experience additional pregnancy complications. Asian women with gestational diabetes had the lowest odds of cesarean delivery and excessive weight gain in the fetus compared with women in other racial/ethnic groups who also had gestational diabetes. Black women were more likely to experience certain complications, such as preeclampsia and preterm delivery, than were women of other racial/ethnic groups.

Preterm Birth

Understanding the Body's Defenses Against Bacterial Vaginosis Infection. Scientists estimate that each year in the United States, 80,000 preterm births are related to pregnant women having bacterial vaginosis (BV), a bacterial infection in the vagina. To understand how the body's natural defenses work against BV, researchers studied a group of 126 pregnant women who self-collected vaginal swabs at two time points during their pregnancies. The swabs were analyzed for the bacteria known to cause BV and for levels of defensins, which are chemicals the body produces to protect mucosal membranes from infection. Scientists discovered that levels of a particular defensin called HBD3 were lower in the pregnant women who had either BV itself or greater numbers of some bacteria known to cause BV. Women with lower HBD3 levels could be at greater risk for BV because of lower levels of protective defensins, or possibly the BV bacteria themselves are suppressing the body's immune response. Understanding how BV takes hold could help researchers develop new strategies to prevent these infections.

Blood Test to Predict Risk for Preterm Birth. Researchers analyzed the blood serum of women the sixth and seventh weeks of their pregnancies, searching for possible protein abnormalities that could warn of early, spontaneous labor. They identified three peptides (short sections of proteins) that were present in significantly lower concentrations in the serum of women who later delivered prematurely. Two-thirds of the women with lower peptide concentrations were unable to carry their pregnancies to term. As the researchers followed the women through their pregnancies, they also found that concentrations of the peptides fell even lower as the women neared delivery.

Study Shows Additional Benefits of Progesterone in Reducing Risk of Preterm Birth. An analysis of five previous studies uncovered additional evidence of the effectiveness of progesterone, a naturally occurring hormone, in reducing the rate of preterm birth among women who have a short cervix. These women are at an increased risk of delivering early. Specifically, the analysis found that progesterone reduced preterm delivery before week 28 by half. The researchers concluded that even when the mother delivers before full term, progesterone treatment can reduce the likelihood that the infant will die (by 43 percent), have respiratory distress syndrome (by 52 percent), weigh less than 3.5 pounds (by 45 percent),

be admitted to the intensive care unit (by 25 percent), or require mechanical ventilation (by 34 percent).

Violence Against Women

Assaults on Pregnant Women Associated with Increased Risk of Low Birth Weight. Pregnant women who are assaulted by an intimate partner are at increased risk of giving birth to infants of reduced weight, according to a population-level analysis of domestic violence. Although the results showed a pattern of low birth weight among the newborns of women who had experienced an assault, the study was not designed to establish cause and effect, so it could not prove that violence caused the reduced birth weights. Infants born to women who were hospitalized for injuries received from an assault during their pregnancies weighed, on average, 163 grams, or one-third of a pound, less than did infants born to women who were not hospitalized for such assaults. Assaults in the first trimester were associated with the largest decrease in birth weight.

Gender Differences

Simple Blood Test Can Help Predict Cognitive Impairment for Females with Fragile X. Fragile X syndrome is a complex condition that often, but not always, includes intellectual disability. Fragile X syndrome is caused by mutations in a specific gene located on the X chromosome. Because women have two X chromosomes, while men have an X and a Y chromosome, the outcomes are highly variable for women and girls with either the full mutation or the premutation. Scientists evaluated a simple blood test that assessed genetic markers in 62 females with Fragile X premutations. The blood test was able to predict individuals with low IQ very accurately across the groups. For women and girls with the full mutation, the blood test measure was significantly related to IQ and verbal ability.

Gender and Crime Victimization Modify Neighborhood Effects on Adolescent Mental Health. NICHD is committed to funding research that analyzes the effects of gender on the health outcomes of individuals at all stages of life. For example, scientists found that gender and recent crime victimization alter the effects on mental health of adolescents moving from a poverty-stricken neighborhood to a more advantaged neighborhood. In particular, girls in families that had not experienced recent crime victimization had significant improvements in mental health after the move to a more advantaged neighborhood. However, the boys from nonvictimized families saw virtually no improvement in mental health from the move. Girls from families experiencing recent crime victimization were significantly less likely to achieve mental health improvement than were girls whose families had not been victims of crime. Boys from families experiencing recent crime victimization had worse distress, more behavior problems, and slightly more major depressive disorders, so much so that instead of benefitting from a move to a more advantaged neighborhood, they were actually harmed by the move.

Girls Have Poorer Outcomes than Boys in Deadly Genetic Disorder of Nervous System. Children with the deadly genetic disorder of the nervous system known as Batten disease begin in elementary school to lose vision, have seizures, and develop problems with behavior and movement. Researchers found that girls had poorer outcomes than boys in Batten disease. Girls developed symptoms about a year later than boys, but disease progression and quality of life got worse more quickly in girls than in boys. Young women with Batten disease also died sooner than did young men, the researchers found.

Sex Differences in Low Back Pain and Phantom Limb Pain. Other research on gender differences has shown that women and men have different responses to pain. For example, an examination of men and women with low back pain confirmed that men move their pelvis much earlier than women when rotating their hips, causing an increase in back pain and suggesting that physical treatment options may need to be adjusted for men and women. Another NICHD study looked at whether pain after the loss of a limb differs between men and women. In this study of over 350 people who had lost a limb, researchers assessed whether men and women differed in the type of pain,

pain intensity, or ways of coping with pain. The study found that a greater proportion of males than females reported the presence of phantom limb pain, but this difference was no longer prominent when there was control for the cause of limb loss. In contrast, women reported greater overall average pain intensity than men. Women also indicated that pain had a greater negative impact on their lives and functioning in a comparison with men.

LGBTI (Lesbian/Gay/Bisexual/Transsexual/Intersex) Research

Gender and Sexual Orientation Affect Substance Abuse or Depressive Symptoms. NICHD researchers looked at whether sexual orientation could be linked to substance abuse or depressive symptoms. Analysis of data from nonheterosexual populations of adults 24 to 32 years of age showed that health risks vary by both gender and the particular sexual orientation involved. The study looked at sexual identity, sexual behavior, and sexual attraction. The researchers found that among women, being attracted to both sexes, identifying as "mostly straight" or "bisexual," and having mostly opposite-sex sexual partners was associated with greater risk of psychological problems, stress, smoking, binge drinking, and victimization. Among men, sexual attraction was unrelated to health indicators. Men who had sexual partners of the same sex or both sexes were at lower risk for binge drinking. Another study, of adolescents 12 to 18 years of age, found that females who had sexual experiences with other females appeared to be at higher risk for substance abuse, regardless of their age or a change in how they perceived their sexual orientation.

Significant Plans for Sex/Gender Analysis

Research on the Health of LGBTI Populations (PA-12-111, 112, 113). NICHD partnered with several other NIH Institutes and Centers to solicit applications in biological, clinical, behavioral, and social processes that affect health and development among LGBTI populations and their families. The goal of this research is to focus on the development of effective supportive, preventive, and treatment interventions and health service delivery methods that will enhance the health of LGBTI populations (*http://grants.nih.gov/grants/guide/pa-files/PA-12-111.html*).

Global Network for Women's and Children's Health Research (RFA-HD-12-200, 201). NICHD continued its efforts in soliciting grant applications from investigators to participate under a cooperative agreement in an ongoing multicenter international research network. The goal of the network is to improve maternal and infant health outcomes and to build health research capacity in resource-poor settings by testing cost-effective, sustainable interventions (*http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-12-200.html*)

Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health (RFA-OD-11-003). NICHD continued to cofund applications accepted under the SCOR program developed by ORWH. These centers provide opportunities to develop to bridge basic and clinical research on sex/gender factors underlying a health issue that affects women.

Initiatives

Requests for Applications

NIH/PEPFAR Collaboration for Advancing Implementation Science in Prevention of Maternal-Child HIV Transmission (RFA-HD-12-210). NICHD, in partnership with the Fogarty International Center, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the NIH Office of Behavioral and Social Sciences Research, and ORWH, solicited grant applications for implementation science projects to inform the President's Emergency Plan for AIDS Relief (PEPFAR) as they develop more efficient and cost-effective methods to deliver proven interventions for prevention of maternal-child HIV transmission (*http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-12-210.html*).

Data Coordinating Center for the NICHD Cooperative Multicenter Maternal-Fetal Medicine Units Research Network (RFA-HD-13-013). This funding opportunity

announcement was issued by NICHD to facilitate the advancement of pregnancy care by establishing a network of academic centers that, by rigorous patient evaluation using common protocols, can study the required numbers of patients and provide answers more rapidly than can individual centers acting alone (*http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-13-013.html*).

Specialized Cooperative Centers Program in Reproduction and Infertility Research (SCCPIR)(RFA-HD-13-005). NICHD announced a recompetition of SCCPIR in support of high-quality translational research to improve human reproductive health and infertility. The centers also serve as a national resource for the training and career development of new scientists who want to pursue careers in reproduction and infertility. Center investigators are also expected to participate in important community outreach and education efforts to increase awareness of the importance of their research to the general public (*http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-13-005.html*).

Contraceptive Development Research Centers Program (RFA-HD-12-185). NICHD solicited applications for this program to conduct a wide range of research, both basic and applied, with the ultimate goal of developing clinically useful contraceptive products. These centers provide a multidisciplinary approach to high-quality translational research programs in the area of contraceptive product discovery and development. The centers will also serve as a national resource for career development of young scientists electing to pursue research in contraceptive development (*http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-12-185.html*).

Program Announcements

Pregnancy in Women with Disabilities (PAR-11-258, 259). In partnership with the National Institute of Nursing Research and ORWH, NICHD invited grant applications to investigate the incidence, course, and outcomes of pregnancy among women with physical, intellectual, developmental, or sensory disabilities. Areas of interest include strategies for addressing barriers to prenatal care, management of pregnancy, and the transition to parenthood (*http://grants.nih.gov/grants/guide/pa-files/PAR-11-258.html*).

Translational Research in Pediatric and Obstetric Pharmacology (PAR-11-246, 247, 248). NICHD solicited grant applications for translational and clinical research and clinical trials that will advance our knowledge about the underlying mechanisms of drug action, response, and safety in children at various developmental stages or in pregnant women and the developing fetus. The overall goals are to improve the safety and effectiveness of current drugs for pediatric or obstetric patients (*http://grants.nih.gov/grants/guide/pa-files/PAR-11-246.html*).

Research Opportunities in Obstetric Fistula (PA-11-141, 142, 143). NICHD solicited grant applications to investigate epidemiologic, clinical, social, and behavioral interventions for obstetric fistula. Considered a disease of poverty, obstetric fistula can lead to severe ulcerations of the vaginal tract, paralysis of the lower limbs caused by nerve damage, or infection of the fistula and stillborn babies. The goal of the initiative is to improve the identification, prevention, treatment, and social circumstances of women at risk for or currently suffering from obstetric fistula (*http://grants.nih.gov/grants/guide/pa-files/PA-11-143.html*).

Advancing Novel Science in Women's Health Research (ANSWHR) (PAS-10-226). ORWH developed and implemented this announcement, which NICHD cosponsors along with 20 other Institutes and Centers. Investigators are invited to compete for grants in all areas of women's health and sex differences research, including reproductive health, diabetes, and chronic pain (*http://grants.nih.gov/grants/guide/pa-files/pas-10-226.html*).

Vulvodynia: Systematic Epidemiologic, Etiologic, or Therapeutic Studies (PAR-10-190, 191, 192). NICHD and ORWH encourage applications that address basic, clinical, translational, epidemiologic, or behavioral research on vulvodynia and related symptom-based conditions. The goal of this initiative is to facilitate new research on diagnostic, preventive, and therapeutic approaches to vulvodynia. Such research will increase our understanding of the

pathophysiology, biologic and behavioral risk factors, natural history, and genetics of vulvodynia (*http://grants.nih.gov/grants/guide/pa-files/PAR-10-190.html*).

Model Systems for Fragile X Premutation and Primary Ovarian Insufficiency (FX-POI) (PAR-11-137). NICHD solicited grant applications to stimulate the development of new model systems and the thorough characterization of the ovarian phenotype of existing models of fragile X–associated premature ovarian insufficiency (FX-POI). New and well-characterized models of FX-POI will help answer fundamental questions about the role of the FMR1 repeat expansion in ovarian function and reproductive aging, and these models will allow the field to advance into evidence-based clinical research on Fragile X premutation carriers who are at risk for POI (*http://grants.nih.gov/grants/guide/pa-files/PAR-11-137.html*).

NICHD also partners with other Institutes on the following program announcements:

- Women's Mental Health During Pregnancy and the Postpartum Period (PA-12-215);
- Maternal Nutrition and Prepregnancy Obesity: Effects on Mothers, Infants, and Children (PA-12-061); and
- Etiology and Pathophysiology of Sleep-Disordered Breathing in Pregnancy (PA-11-122).

Conferences and Workshops (in chronological order)

Vision Themes: Reproduction Workshop (January 25–26, 2011). Hosted by NICHD, this workshop was held as part of the NICHD Scientific Vision process. The objective of the workshop was to identify visionary scientific opportunities that will impact human reproductive health globally and will shape the future scientific agenda in reproductive research for the next decade. Expanding our knowledge of reproductive biology and its clinical and behavioral applications will allow researchers to better define the gynecologic disorders, control or improve fertility, and manage the critical transitions that mark reproductive health across the lifespan of women. The workshop discussions were summarized in a white paper.

Timing of Indicated Late Preterm and Early Term Birth Workshop (February 7–8, 2011). Jointly hosted by NICHD and the Society for Maternal-Fetal Medicine, this workshop's attendees gathered and reviewed existing information on the conditions that result in medically indicated late preterm and early term births. Discussion topics included the potential risks and benefits of continued pregnancy and the optimal gestational age for delivery.

Vision Themes: Pregnancy and Pregnancy Outcomes Workshop (February 22–23, 2011). Hosted by NICHD, this workshop was held as part of the NICHD Scientific Vision process. The discussions centered on developing innovative research strategies to reduce the lifelong impact of pregnancy on women, improve the prospects of a healthy pregnancy for women with disabilities, and reduce disparities in outcomes for both mother and child. The workshop resulted in a consensus on four general themes and specific recommendations that were summarized in a white paper.

Health Disparities in Reproductive Health (May 13, 2011). The objective of this conference was to bring together leadership of the Health Disparities Special Interest Group to have discussions related to continued support and expansion of the existing research network and of research and didactic programs.

2nd International Workshop on Cyclic AMP, Phosphodiesterases, and Human Disease (June 8–10, 2011). This NICHD-sponsored workshop brought together experts in phosphodiesterases and cyclic adenosine monophosphate from a variety of disciplines to discuss refocusing research to a more translational approach. Genetic components affecting disease susceptibility and novel pharmacological and/or dietary supplement compounds affecting tissue activity were discussed.

6th International Fission Yeast Meeting (June 25–26, 2011). Researchers in the fission yeast community were brought together to exchange ideas and establish collaborations between laboratories working on Schizosaccharomyces pombe topics. Young

scientists, students, postdoctoral fellows, and junior principal investigators were provided an opportunity to present their work to a broad audience.

Vulvodynia: A Chronic Pain Condition—Setting, a Research Agenda (July 11–12, 2011). Sponsored by NICHD and ORWH, this meeting took a novel approach to understanding vulvodynia as a chronic pain condition rather than as a gynecological disorder. Researchers from various fields and areas of expertise explored the basic pathophysiology of chronic pain, creating a foundation for new, interdisciplinary collaborations and innovative approaches to studying vulvodynia.

Ovarian Reserve: Regulation and Implications for Women's Health (October 25, 2012). This conference, cosponsored by NICHD and the American Society for Reproductive Medicine, addressed current questions related to ovarian reserve, including how to critically assess biomarkers of ovarian reserve, the methods used to estimate it, and the implications for a woman's health and fertility.

Global Health Implementation Research for Unmet Need and Scale-Up of Evidence-Based Maternal and Child Health Interventions—Consultation of Experts (November 4, 2011). NICHD and the Global Network for Women's and Children's Health Research convened experts in the field of implementation science research to explore the potential development of implementation models and frameworks applicable to maternal and child health programs, services, and research in resource-poor settings.

Health Disparities and Special Populations of Women

Scientific Research Advances

Rural Women at Higher Risk of Violence and Have Fewer Resources Available. Intimate partner violence (IPV) against women is a significant health issue in the United States and worldwide. The majority of studies on IPV have been conducted in urban populations. With support from the Centers for Disease Control and Prevention (CDC) and NICHD, scientists surveyed nearly 1,500 women frequenting a women's clinic in a Midwestern U.S. state to assess whether IPV prevalence rates differ by rurality. Women in small rural and isolated areas reported the highest prevalence of IPV (22.5 percent and 17.9 percent, respectively), versus 15.5 percent for urban women. Rural women reported a significantly greater severity of physical abuse than their urban counterparts. The mean distance to the nearest IPV resource was three times as great for rural women as for urban women, and rural IPV programs served more counties and had fewer on-site shelter services. Over 25 percent of women in small rural and isolated areas lived more than 40 miles from the closest program, compared with less than 1 percent of women living in urban areas.

Initiatives

Addressing Health Disparities in Maternal and Child Health Through Community-Based Participatory Research (PAR-11-241). NICHD released a program announcement to address health disparities in research areas, including fibroid tumors and pediatric and maternal HIV/AIDS prevention through community-based participatory research (*http://grants.nih.gov/grants/guide/pa-files/PAR-11-241.html*).

Biomedical and Behavioral Research Innovations to Ensure Equity (BRITE) in Maternal and Child Health (PAR-12-093). NICHD released this program announcement to stimulate research in maternal and child health equity within institutions eligible for the Academic Research Enhancement Award (AREA) R15 program. Areas of research focus included preterm birth, uterine fibroids, violence prevention, and medical rehabilitation (*http://grants.nih.gov/grants/guide/pa-files/PAR-12-093.html*).

Career Development/Training for Women in the Sciences

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program. Along with nearly a dozen other NIH Institutes and Centers, NICHD participates in the BIRCWH program, which is led by ORWH. NICHD's Fertility and Infertility

Branch (formerly the Reproductive Sciences Branch) administers a large number of the BIRCWH awards. These research centers aim to provide bridging support to physician-scientists as they move between completion of clinical or postdoctoral training and an independent research career. Research addressed by BIRCWH spans the spectrum of women's health topics, and the program is open to all types of clinicians and nonclinicians (*http://orwh.od.nih.gov/interdisciplinary/bircwh/index.asp*).

Reproductive Scientist Development Program (RSDP). In FY 2011–2012, NICHD's Fertility and Infertility Branch (formerly the Reproductive Sciences Branch) continued to support a national career development program, with the goal of developing a cadre of reproductive physician-scientists based in academic departments who could employ cutting-edge cell and molecular technologies to address important problems in the field of obstetrics and gynecology. The mentored research experiences this program offers are intended to assist junior faculty in their transition to productive, independent physician-scientists who are highly competitive for research funding. The program accepts approximately four scholars each year for a 5- to 6-year training period (*http://www.nichd.nih.gov/research/supported/pages/rsdp.aspx*).

Women's Reproductive Health Research (WRHR) Career Development Program. NICHD and ORWH solicited applications to continue to support a national program of mentored institutional career development programs for junior faculty who have recently completed postgraduate clinical training in obstetrics and gynecology and are committed to an independent research career in women's reproductive health. The supervised research training will assist junior faculty in their transition into productive physician-scientists in areas related to obstetrics and gynecology and its subspecialties (*http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-026.html*).

Postdoctoral Research Training in Obstetric and Fetal Pharmacology (PAR-11-183). NICHD and ORWH cosponsored a program announcement to recruit a cadre of diverse, highly trained academic clinical and nonclinical scientists who will conduct basic, translational, and clinical research in maternal and fetal pharmacology and therapeutics. The goal is to have well-trained scientists assume leadership roles related to the nation's maternal-fetal pharmacology research agenda and make contributions to this field to improve pharmacotherapy for pregnant women and prevent and reduce risk and harmful effects for mothers and their unborn babies (*http://grants.nih.gov/grants/guide/pa-files/PAR-11-183.html*).

Two Featured Programs and Objectives in Support of the NIH Strategic Plan for Women's Health Research

NIH Research Plan on Vulvodynia (2012). NICHD is in collaboration with other Federal, private, and nonprofit agencies, as well as researchers in the field, to lay out an agenda for the rigorous scientific research needed to answer questions and fill in knowledge gaps about vulvodynia, a pain condition that affects the vulva. Although vulvodynia is thought to affect 9 to 18 percent of women aged 18 to 64, there are few definitive answers about the cause, diagnosis, and treatment of this condition. Current researchers in vulvodynia have emphasized the need for more basic physiological research, both on vulvodynia specifically and in the broader context of other pain disorders. Short-term objectives are aimed at increasing scientific outreach efforts to the broader pain research community.

The NIH Research Plan on Vulvodynia supports ORWH Strategic Goal 4: "Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research." Specifically, the Research Plan meets Objective 4.2: "Establish new ventures and initiatives with a wide cross-section of partners, including NIH Institutes, Centers, and Offices; academia; other Federal agencies; international organizations; private foundations; and industry."

Gynecologic Health and Disease Branch. This newly formed branch within NICHD's Division of Extramural Research supports research related to gynecologic health in women and adolescent girls. Program areas

include gynecologic diseases and disorders, reproductive and gynecologic health issues, pelvic floor disorders, and adolescent gynecology. The Gynecologic Health and Disease Branch (GHDB) supports the Pelvic Floor Disorders Network and the Women's Reproductive Health Research (WHRH) Career Development Program.

The GHDB supports ORWH Strategic Goal 2: "Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs." Specifically, the GDBH meets Objective 2.4: "Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls." The GDBH also meets Objective 2.7: "Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls."

National Institute on Deafness and Other Communication Disorders

Executive Summary

The National Institute on Deafness and Other Communication Disorders (NIDCD) conducts and supports research and research training on the normal mechanisms as well as the diseases and disorders of hearing, balance, smell, taste, voice, speech, and language. NIDCD also conducts and supports research and research training that is related to disease prevention and health promotion.

NIDCD addresses special biomedical and behavioral problems associated with people who have communication impairments or disorders. The Institute supports efforts to create devices that substitute for lost or impaired sensory and communication functions.

A number of diseases, disorders, or conditions within the mission of NIDCD affect women (and men) disproportionately. Examples of significant research programs have been selected for inclusion in this report. Highlights of the latest research advances and plans for the future in these areas follow.

Accomplishments

Cytomegalovirus

Cytomegalovirus (CMV) infection is the leading cause of nonhereditary deafness. Maternal transmission of CMV is well recognized as a common cause of sensorineural hearing loss (SNHL). CMV is also recognized as the most common cause of human congenital infection, occurring in up to 2.5 percent of all live births. It is estimated that the sequelae of congenital CMV infection may account for as many as 40,000 new cases of SNHL per year. NIDCD-sponsored scientists continue to make significant progress in fully characterizing the effects of CMV on SNHL as well as the mechanisms and epidemiology of CMV maternal transmission. Recent results demonstrate a highly significant effect of CMV infection on the development of late-onset SNHL.

NIDCD-supported investigators conducted a preclinical animal trial of delivering antiviral drugs to the inner ear via an intratympanic route. Drawing upon the vast otologic experience with intratympanic administration of drugs (such as corticosteroids or aminoglycosides) to treat the cochlea and inner ear, the investigators proposed that the intratympanic delivery of two antiviral agents (ganciclovir and cidofovir) can be used to effectively treat CMV-related hearing loss while avoiding the numerous and significant potential side effects of these drugs. They tested this hypothesis using their well-developed guinea pig model of CMV infection and hearing loss. CMV-related hearing loss was first induced by directly inoculating the cochleas of guinea pig pups with guinea pig CMV (GPCMV) or newly generated chimeric GPCMV. The experimental antiviral treatment groups then received intratympanic doses of drug, and the effects of therapy were monitored by performing auditory brainstem response testing and histopathologic examination of the cochleas. By executing this research plan, the investigators generated novel data that will serve as the foundation for early clinical trials

administering antiviral drugs to the middle ear space in order to treat CMV-related inner ear disease. The potential benefits of delivering antivirals intratympanically include advantages in efficacy as well as reduced toxicities.

Voice Disorders

Voice disorders affect millions of Americans, adversely influencing their quality of life and impairing their ability to communicate effectively and to function in our society. A number of voice disorders appear to affect women more frequently than men. NIDCD currently supports numerous projects focused on normal and disordered voice processes. Of note are studies examining behavioral vocal hyperfunction. Vocal hyperfunction is not organic in origin but is rather a result of a habitual pattern of voice use that may be traumatic to laryngeal tissue and function.

Data in the literature clearly identify voice disorders as the primary occupational risk of teachers not only in the U.S. but also internationally. Moreover, voice problems constitute a global concern in women's health. Until recently, few reports have been available concerning the treatment of these problems in teachers, and even fewer have addressed the equally important question of prevention. NIDCD-supported investigators are conducting a study within the context of a long-range goal to identify effective intervention methodologies for the prevention and treatment of voice problems in teachers while taking into consideration multicultural and linguistic factors.

Spasmodic dysphonia (SD) is a neurological disorder (dystonia) affecting the voice muscles in the larynx. The vast majority of those affected are female, with estimates as high as 80 percent. In SD, the muscles inside the vocal folds experience sudden involuntary movements, called spasms, which interfere with the ability of the folds to vibrate and produce voice. SD causes voice breaks and can give the voice a tight, strained quality. People with SD may have occasional breaks in their voice that occur once every few sentences. Usually, however, the disorder is more severe, and spasms may occur on every other word, making a person's speech very difficult to understand. At first, symptoms may be mild and occur only occasionally, but they may worsen and become more frequent over time. SD is a chronic condition that continues throughout a person's life, and it can affect virtually anyone. It is a rare disorder, however, occurring in roughly 1 to 4 people per 100,000. The first signs of SD are found most often in people between 30 and 50 years of age. NIDCD released two program announcements (R01, R21) on SD in March 2010, and a number of applications in response to these solicitations were awarded in 2011–2012.

The diagnosis of SD has proven to be difficult, because it often presents with symptoms similar to muscle-tension dysphonia (MTD). That disorder is caused by abnormal phonation believed to be in response to the swelling of vocal fold tissue. Misdiagnosis is not uncommon and can lead to inappropriate treatment. SD is treated primarily with injections of botulinum toxin, while MTD is treated with behavioral therapy. The current gold standard for diagnosis uses an elaborate, time-intensive, and costly three-step approach involving a questionnaire, a clinical-perceptual evaluation, and a naso-endoscopic evaluation. Recent research has documented that patients with focal dystonia affecting head and neck musculature, such as blepharospasm and torticollis, reveal kinesthetic deficits in the nondystonic musculature of their upper limbs, suggesting a central origin of these disorders. NIDCD-supported investigators are examining whether SD also presents with kinesthetic deficits in nondystonic limb systems that are clinically symptom free. If, in contrast, MTD patients have normal limb kinesthesia, then kinesthetic loss would be a potential marker for SD that could help to differentiate between SD and MTD. The health significance of showing that SD, but not MTD, is associated with a general kinesthetic loss is that it opens the avenue to develop easy-to-administer, standardized, time-efficient clinical tests for the diagnosis of SD (and focal dystonia) that complements the current diagnostic arsenal and reduces the risk of a misdiagnosis.

Another ongoing project is attempting to identify brain abnormalities in SD and

SD/VT (vocal tremor) patients as the basis for characterization of the central mechanisms underlying symptom improvement following the use of sodium oxybate, a novel pharmacological agent for treatment of ethanol-responsive dystonia. The central hypothesis is that, compared with SD patients, SD/VT patients will have additional brain abnormalities within the sensorimotor brain circuits that control voice production, circuits that are being modulated to a greater extent with sodium oxybate treatment. The investigators postulate that clinical efficacy of sodium oxybate treatment will correlate with its central modulatory effects. The rationale for the proposed research is that identification of distinct brain mechanisms underlying SD and SD/VT clinical manifestations would provide the necessary insights into the pathophysiology of these disorders, while understanding the neural correlates of sodium oxybate action would allow establishment of a scientific rationale for the use of a novel treatment in these problems.

Stuttering

Stuttering is a speech disorder in which sounds, syllables, or words are repeated or prolonged, disrupting the flow of speech. These disruptions may be accompanied by struggling behaviors, such as rapid eye blinks or tremors of the lips. Stuttering can make it difficult to communicate with other people. Boys are twice as likely to stutter as girls. Whereas stuttering is not a condition that is life-threatening, it is a disorder that is life-altering. NIDCD intramural and extramural researchers continue to study stuttering and increase our understanding of this condition.

There is a fundamental gap in understanding the neural bases for childhood developmental stuttering, particularly with respect to:

Why certain children recover naturally whereas others continue to stutter throughout life; and

Why there is a greater probability of recovery among girls than boys.

One NIDCD-supported project aims to identify neural markers for stuttering and to develop interventions that lead to behavioral and neurophysiological normalization in speech. The overall objective is to identify structural and functional neural markers of stuttering close to the onset of symptoms and to determine gender-specific brain developmental trajectory markers that would serve to differentiate those children who recover from stuttering from those who do not.

Initiatives

A number of funding opportunity announcements have been released in the areas of SD, hearing health care, development of measures that determine hearing outcomes, nonverbal school-aged children with autism, and translation of basic research into clinical tools among others.

National Institute of Dental and Craniofacial Research

Executive Summary

The mission of the National Institute of Dental and Craniofacial Research (NIDCR) is to promote the general health of the American people by improving dental, oral, and craniofacial health through research. This includes funding clinical and basic research to understand, prevent, and treat oral and craniofacial diseases and conditions that disproportionately or solely affect women. These diseases include orofacial pain, temporomandibular joint disorder (TMJD), osteoporosis of the craniofacial complex, salivary gland diseases, and oral diseases of pregnant women. This report highlights accomplishments and initiatives in the areas of chronic pain and TMJD, osteoporosis and basic bone biology, osteonecrosis of the jaw, the oral health of pregnant women, oral health disparities, Sjögren's syndrome, human immunodeficiency virus (HIV) infection, and craniofacial anomalies.

NIDCR women's health clinical initiatives in FY 2011 and FY 2012 included large studies designed to identify risk factors and characterize diseases affecting women. One study is following a cohort to learn more about women who develop TMJD, and then to determine genetic, clinical, and behavioral

risk factors that contribute to chronic TMJD. Other researchers investigated potential treatments for TMJD. Another large NIDCR-supported study described and assessed individuals with Sjögren's syndrome, an autoimmune disease with dramatic oral health consequences, and developed new disease classification criteria provisionally endorsed by the American College of Rheumatology (ACR). This marks the first time that the ACR has approved classification criteria for Sjögren's syndrome. In a separate effort, interventional studies are seeking to help pregnant women care for their own teeth as well as their new babies' teeth. By exploring the most effective methods of health education and oral health interventions, the studies seek to increase awareness of how the oral health of the mother affects her general health and the health of the newborn, and to decrease the oral health complications associated with pregnancy.

NIDCR also supports basic science studies examining the growth and development of teeth, cartilage, and bone. These studies are advancing research in biomaterials and in the emerging field of tissue engineering, which uses the body's own cellular and molecular processes to repair and regenerate tissues and organs.

Recognizing the importance of gene-to-gene, gene-environment, and behavioral interactions, the Institute has long emphasized genetic, behavioral, social science, and epidemiological research. Researchers supported by NIDCR during FY 2011 and FY 2012 continue to define genes associated with craniofacial anomalies, such as cleft lip and palate, and with other problems with facial development, such as craniosynostosis.

Accomplishments

Pain Research

For many years, NIDCR-supported research has explored many aspects of pain, ranging from basic studies to efforts to develop new therapies for acute and chronic pain, including conditions that primarily affect women. Findings from these studies demonstrate that men and women respond differently to painful stimuli and that women are more likely to develop certain chronic pain conditions. Human and animal studies include research in the areas described below.

Opioid drugs, such as morphine, are usually given peripherally—that is, by injection or intravenously. This sometimes results in serious side effects, including breathing problems, nausea, constipation, addiction, and tolerance. However, by injecting the drugs centrally (directly into the cerebrospinal fluid), excellent pain relief can be achieved using much smaller doses, reducing the risk of these side effects. It was known from previous research that centrally administered opioids are more potent in males than in females. However, little was known about possible sex differences when opioids are given peripherally. Recently, NIDCR-funded investigators showed that sex differences are also present when a specific subtype of opioid is given by the peripheral route. Using this particular type of opioid has many advantages, including reduced side effects. However, the drug was confirmed to be much more effective in alleviating pain in male rodents than in females, suggesting that alternative drug treatments precisely tailored for men and women are needed.

Temporomandibular Joint and Muscle Disorders

Temporomandibular joint and muscle disorders (TMJD) are a diverse group of orofacial conditions associated with persistent orofacial pain and jaw dysfunction. Approximately 5 to 10 percent of the adult population report symptoms of TMJD at any one time. While most cases resolve with minimal or no treatment, some individuals develop a chronic, painful disorder that takes a high functional, emotional, and financial toll. Despite its high societal cost, the natural history of TMJD is not well characterized, and treatments for chronic TMJD need improvement.

More women have TMJD and report more pain than men in experimental settings. This suggests that sex hormones may play a role in disease onset and pain sensitivity. Understanding how sex hormones affect disease and pain sensitivity could guide design of individualized treatments for TMJD. An NIDCR-funded research team, using a rodent

model of acute inflammatory pain, showed that the female sex hormone estradiol has a profound effect on numerous genes that are important in pain modulation and regulation of nerve inflammation. These effects were seen throughout the trigeminal system that controls the sensory and motor functions in the face, teeth, mouth, nasal cavity, and the TM joint itself. The genes involved are likely targets for relieving chronic TMJD pain.

In 2004, NIDCR funded the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study, the first large, multisite prospective clinical study that seeks to identify biological, psychological, and social factors that increase risk of developing TMJD and chronic TMJD. During the past year, initial results suggested there are two components of how pain is perceived: Pain amplification and psychological distress. These interact with environmental and genetic factors to lead to TMJD pain persistence. This study identified new risk factors and confirmed others previously reported.

For example, consistent with previous results, researchers found that chronic TMJD is more common in women and the non-Hispanic White population. But contrary to other findings, they found that increasing age within the range of 18 to 44 years is associated with higher levels of chronic TMJD. Signs and symptoms associated with increased chronic TMJD risk include greater facial pain, pain-related interference with function, greater limitations in jaw function/movement, past jaw injury, and a higher frequency of other pain conditions such as fibromyalgia. Major psychosocial risk factors strongly associated with chronic TMJD include somatic awareness (sensitivity to physical sensations and bodily activity), active distress and catastrophizing. When tested in the laboratory, those with chronic TMJD had different quantitative pain scores, and there are suggestions that autonomic system dysfunction, where the nervous system that controls most involuntary functions breaks down, plays a role in chronic TMJD. In addition, this study looked for genetic risk factors. A screen of approximately 320 candidate genes identified several genetic changes associated with higher risk of chronic TMJD; these included changes in a number of genes associated with pain signaling and genes for various types of pain receptors. In addition, this study confirmed the role of COMT, a much-studied enzyme that helps to inactivate certain neurotransmitters, as a risk factor for TMJD. Cumulatively, these results demonstrate that there is a group of factors that influence a person's risk for chronic TMJD. These results will be confirmed with data generated in the second phase of OPPERA, OPPERA II, which is following a group of individuals who have just developed TMJD (termed first-onset TMJD). In the near future, a second set of manuscripts will be published detailing the risk factors for first-onset TMJD.

OPPERA II was funded in FY 2012 to continue following those recruited in OPPERA I. OPPERA II will explore in greater depth genetic risk factors for chronic and first-onset TMJD and determine the prevalence of other chronic pain conditions that frequently co-occur with TMJD and can also disproportionately affect women, such as headache, irritable bowel syndrome, chronic low back pain, and chronic widespread pain.

Other examples of NIDCR-supported TMJD research include the following:

- A study to improve the reliability and validity of the widely used Research Diagnostic Criteria for TMJD (RDC/TMD), which developed a reliable six-item screening tool for practicing dentists to more reliably diagnose and treat these disorders. Having a reliable and concise instrument increases its utility in routinely assessing patients who may have pain-related TMJD in clinical and research settings.
- NIDCR-funded researchers recently launched a study to evaluate the utility of TMJ imaging in diagnosing and managing TMJD. Old TMJ images of approximately 600 patients (mostly female) treated for TMJD over the past 6 to 10 years will be compared with new images, to determine the degree to which progressive change in joint structures contributes to pain and dysfunction in TMJD patients.
- NIDCR is supporting a study to assess the ability of a brief survey to predict whether a patient with acute TMJD is likely to

progress to chronic disease, and to determine the best therapy for those most likely to develop chronic TMJD.

Reconstruction of the TMJ

Severe TMJD can lead to degeneration of the jaw joint itself. The TMJ is a complex joint that includes bone, cartilage, and muscle. Tissue engineering provides a promising approach to regenerating tissues of the joint in patients affected by TMJD. Studies are mapping the characteristics of the TMJ disk and its attachments at cellular and tissue levels. This knowledge is key to engineering a TMJ disc prototype that approximates the normal anatomical structure and function of the TMJ, which will be tested in large animal models and, if successful, will move into human clinical trials for treatment of advanced TMJ destruction. Additionally, researchers are exploring strategies for TMJ disc regeneration using natural extracellular matrices. Other studies are developing stem cell-based approaches for regenerating the TMJ and creating optimal biomaterials, scaffolds, and bioreactors for TMJ bone tissue engineering and regeneration. Research in the area includes the studies described below:

- The porcine (pig) TMJ is structurally very similar to that of higher primates. NIDCR-funded researchers are taking advantage of these biological similarities and investigating the biochemical content, mechanical properties, and ultrastructural tissue organization of the porcine TMJ disc. This work will further advance the utility of this animal model and shed light on TMJ disc-specific structure/function relationships. Additional work is studying not only the biochemical composition but also the biomechanical properties and cellular populations of TMJ disc attachments for engineering an entire anatomically shaped TMJ disc complex. The investigators plan to test the function of their TMJ constructs in a porcine model with typical TMJ disc defects, providing a potential clinically relevant solution for TMJ disc damage.
- Advanced tissue engineering devices that simulate the physiological environment, so-called bioreactors, are being developed to derive functional composite tissue-engineered TMJ constructs that approximate the size and anatomy of the human TMJ. The bioreactors have a two-compartment design; one compartment is designed to promote cartilage growth, while the other is designed to optimize bone regeneration. The investigators expect that their advanced bioreactors will generate models for testing tissue engineering-based strategies for treatment of TMJD.
- Work is under way to develop stand-alone cultures of specialized cells for generating a biomimetic TMJ meniscus and mandibular cartilage, and to utilize scaffolds composed of natural extracellular matrices to stimulate formation of a disc that closely mimics the composition, structure, and mechanical properties of native TMJ disc material.

Mineralized Tissue Studies in Health and Disease

The study of teeth, bone, and other mineralized tissues has been a mainstay of NIDCR-supported research since the Institute's inception, because of its importance not only to oral health but also to the growth and development of the entire body.

Bone is an active and dynamic tissue that continuously remodels itself throughout life. The process of bone remodeling consists of cycles of bone formation and resorption. An imbalance between bone formation and resorption will lead to a change in bone mass. In children and young adults (< 20 years old), bone formation dominates resorption, resulting in bone growth and development. In healthy adults (20 to 40 years old), the processes of bone formation and resorption are delicately equilibrated, and no increase or decrease in bone mass occurs. However, in aging bone, an imbalance of resorption over formation often induces loss of bone mass and can lead to osteoporosis, a skeletal disease that affects bone architecture and increases the risk of fracture. Osteoporosis disproportionately affects women, who are four times more likely than men to develop the disease.

Diseases that affect mineralized tissues of the craniofacial complex include periodontal disease, osteoporosis, and bisphosphonate-associated osteonecrosis. Advances in this

area include clinical studies defining risk factors for osteonecrosis of the jaw. NIDCR-funded investigators are studying the basic biological processes involved in the development and maintenance of bone, cartilage, and/or teeth.

- Defining the roles of bone cells, namely osteoblasts, osteoclasts, and osteocytes, has been a primary focus in studies of bone remodeling. How they regulate bone mass through a balance of their activities is well described; however, the molecular nature of the regulation of bone quality remains unclear. A group of NIDCR-funded investigators sought to study proteins that might participate in active regulation of bone quality in response to biological stimuli. A strong candidate in maintaining bone quality was the extracellular collagen-degrading matrix metalloproteinase (MMP-13). Results from the experiments of these researchers led to the discovery of a novel role for MMP-13 in the remodeling of cortical bone matrix. The investigators found this was particularly true during lactation, when there is great demand to release calcium stores from bone. The finding that MMP-13 is essential for bone quality could help lead to therapies to prevent or reverse compromised bone fracture toughness. This work also has significant implications for understanding the bone changes and fragility that accompany steroid-induced osteoporosis, since these commonly prescribed drugs can regulate MMP-13 expression.
- Bone growth, development, and mineral balance are orchestrated by a complex repertoire of molecular switches. Problems with any of the components may lead to debilitating bone disorders and serious consequences, such as fractures. Several ongoing projects are studying candidate genes and cellular pathways critical for the maintenance of bone-forming and resorbing cells (osteoblasts and osteoclasts). Estrogen has been known to regulate the gene known as TGFβ inducible early gene (TIEG) in osteoblasts, and studies are under way to understand why mutation of TIEG leads to smaller and weaker bones in female, but not male, mice. Potential targets for therapeutics may emerge from large datasets being generated through the study of other novel genes and proteins involved in bone growth and regulation.
- Bone homeostasis is the tightly controlled biological program of bone formation and bone resorption maintained by a healthy body. It is often affected by factors that influence the genes, called epigenetic factors. Each step of this program is regulated by a series of activators and inhibitors. One project studying control of gene regulation in bone focuses on a metabolic pathway that serves as a major conduit for extracellular signals influencing bone cell response to hormones or mechanical loading. In other studies, microRNAs, which are small, noncoding RNAs that regulate protein expression, were found to influence the formation of osteoblasts, the cells that form new bone. MicroRNAs were also found to regulate the differentiation of certain stem cells into osteoblasts, cartilage-forming cells, and even fat-forming cells. These studies showcase the importance and value of functional studies that follow up on evidence generated from high-throughput screening assays. Investigations of new molecular pathways and networks continue to enhance our understanding of bone homeostasis.

Bisphosphonates (BPs) are drugs that inhibit the activities and functions of osteoclasts and perturb the differentiation of osteoblasts. Intravenous BPs are used primarily to treat and control pain associated with cancer metastasis to bone, Paget's disease, and multiple myeloma. Oral BPs are used to prevent bone loss and are prescribed for patients with osteoporosis or osteopenia. In 2003, case reports began to appear suggesting that use of BPs could lead to the development of non-healing, exposed necrotic bone in the upper or lower jaw. The clinical condition was named osteonecrosis of the jaw (ONJ). Most cases of ONJ are related to the intravenous use of BP in cancer patients, but several cases are associated with oral BPs. In 2009, cases began to surface of ONJ in patients treated with the drug denosumab, which inhibits the osteoclastogenic factor RANKL and is not a BP. Patients with ONJ present with

painful, exposed, and necrotic bone, which may develop spontaneously or after invasive dental procedures, radiation, or chemotherapy. These lesions may be nonhealing or very slow to heal. NIDCR has funded studies examining the etiology and epidemiology of the problem.

Through solicitations for research on the pathophysiology of ONJ and for clinical studies of ONJ, a number of projects have been added to the NIDCR program portfolio. These include investigations into the risk factors for development of ONJ, how ONJ involves the oral mucosa and the immune system, epidemiological assessment of ONJ in osteoporotic/osteopenic patients and cancer patients using BPs, and studies of the pathophysiological mechanisms of ONJ. This research includes studies of BPs and the newer biological antiresorptive agents, such as denosumab, that have also been associated with ONJ. Some investigators are focused on developing animal models for ONJ.

Using dental records from dentists in the three NIDCR dental practice-based research networks, one study investigated which dental procedures were associated with ONJ. This study was important to both dentists and their patients because some previous studies had suggested that "dental problems" play a significant role in the development of these lesions. In many publications, dental histories were poorly documented, leaving clinicians and their patients taking BPs uncertain about which dental procedures increase the risk for ONJ. The investigators found that, among patients taking oral BPs, extraction was the only dental procedure associated with subsequent ONJ development. Results of this study suggest that routine dental procedures are not associated with the development of ONJ in patients taking BPs.

Another research team investigated the effects of BPs on the healing of oral mucosal tissue. When pamidronate, a BP commonly prescribed to cancer patients, was added to cultures of normal oral keratinocytes and fibroblasts, these cells aged and died. The results suggest that these cellular changes might be partly responsible for the poor tissue healing observed in ONJ. Other researchers are trying to establish why ONJ occurs primarily in the oral cavity by studying bone cells from the jaw. To date, these investigators have found that pamidronate significantly decreased cell viability, proliferation, osteogenesis, and wound healing in tissue cultures of these cells.

Oral Health Disparities Research

NIDCR's strategic plan includes as a goal the elimination of disparities in oral health. Vulnerable populations include women of racial and ethnic minority backgrounds, the poor, and those with developmental or acquired disabilities.

- The oral health status of the overall U.S. population has improved in recent decades, but the prevalence of dental disease in African-American, Hispanic, and American Indian/Alaska Native subpopulations has remained high. While no single factor can explain the disparities in oral health status, NIDCR-sponsored research has considered the role of oral health literacy in oral health. In one study investigating this relationship, 1,158 low-income female caregivers were interviewed about their knowledge of oral health, oral health behaviors, and the reported oral health status of their young children. Lower caregiver literacy was associated with deleterious oral health behaviors, including nighttime bottle use for children and no daily brushing/cleaning of their children's teeth.
- In a study of adolescents and their mothers, NIDCR-supported investigators found that early maternal enabling factors that contributed to adolescent caries (tooth decay) are mediated by maternal psychosocial factors (stress, coping, social support). Greater social support when the child was 3 years old was directly associated with lower levels of tooth decay at age 14. Further research is needed to determine how to support parents with poor enabling factors to better address their children's oral health issues.
- There is a complex relationship between maternal behaviors and maternal oral health and children's oral health. Three interventional studies supported by NIDCR are testing behavioral interventions

directed at pregnant women or mothers of very young children to determine whether the interventions will reduce dental decay in the participants' children. Another study is testing an intervention to reduce untreated dental decay in pregnant women who are eligible for Medicaid.

Oral Health of Pregnant Women

The National Maternal and Child Oral Health Resource Center (OHRC) published "Oral Health Care During Pregnancy: A National Consensus Statement—Summary of an Expert Workgroup Meeting" in 2012 (see *http://www.mchoralhealth.org/materials/consensus_statement.html*). A portion of the evidence in this document came from two large Phase III clinical trials sponsored by NIDCR that were designed to determine whether treatment of periodontal disease during pregnancy would reduce preterm birth. While both trials found that periodontal disease treatment during the second trimester of pregnancy did not reduce preterm birth, the trials did not find that dental treatment during pregnancy was unsafe. This document is intended to help professionals working in states and communities plan, develop, and implement programs to help ensure that pregnant women receive optimal oral health services.

Salivary Hypofunction (Dry Mouth)

The salivary glands produce saliva, a complex fluid that is central to the maintenance of oral health. If insufficient quantities of saliva are made, oral health deteriorates. Problems can include dramatic increases in dental caries; difficulty in swallowing, chewing, and speaking; loss of enjoyment of food; mouth sores; mucosal infection with *Candida* species; and reduced quality of life. Many diseases and conditions can reduce salivary gland function. Patients with Sjögren's syndrome, an autoimmune disease with much higher prevalence in women, often have salivary dysfunction that is thought to be caused by an infiltration of the salivary glands by white blood cells.

Salivary gland cells are polarized, allowing for a directed flow of the production and delivery of saliva. The molecular mechanisms underlying this polarity are not well understood. Recent research employed an organ culture of mouse embryonic salivary glands to explore the roles and interactions of the enzyme Rho kinase (ROCK) and the known polarity protein PAR-1b in coordinating the organization of salivary gland cells. ROCK was found to coordinate tissue polarity by localizing PAR-1b activity on specialized structural cells. Inhibition of ROCK resulted in the disorganization of these structural components and abnormal gland structure. Other abnormalities were found when PAR-1b was overexpressed. These findings provide insight into mechanisms of salivary gland development and can lead to improved salivary gland engineering and tissue regeneration strategies.

Head-and-neck cancer treatment sometimes includes radiation therapy, which can cause irreversible loss of salivary gland function. This is in part due to death of salivary gland stem cells. A particular cellular signaling pathway (called the Wnt/B-catenin pathway) is known to be essential for maintenance and activation of various adult stem cells. If salivary glands are mechanically damaged, this pathway activates, causing increased production of salivary gland stem cells and leading to healing. However, radiation therapy causes a different outcome, which interferes with healing. An interesting additional finding was that the radiation-induced effect was seen only in male mice; further research is planned to explore Wnt activation on submandibular glands of female mice.

Autoimmune Diseases and Sjögren's Syndrome

Autoimmune disorders cause an unintended destruction of the body's own tissues and disproportionately affect women. Sjögren's syndrome (SS), an autoimmune disease characterized by reduced secretions from salivary and lacrimal glands, is the second most common autoimmune disease in the United States. SS affects an estimated 1 to 4 million people, 90 percent of whom are women. Typically, patients with SS have increased numbers of lymphocytes and other immune cells in their salivary and lacrimal glands, changes thought to result in the ultimate

reduction of saliva and tear production. The most serious complication of SS is the greatly increased risk for developing malignant lymphoma, which occurs an estimated 40 times more frequently in these patients than in the general population.

In 2003, NIDCR, the National Eye Institute, and ORWH provided support for the Sjögren's International Collaborative Clinical Alliance, or SICCA. SICCA is an integrated research network that spans seven countries (Argentina, China, Denmark, India, Japan, United Kingdom, and the United States). By sharing their scientific resources, the researchers in this network assembled the first large international SS patient registry, a major step forward in studying this condition. The registry, designed by an international expert panel of ophthalmologists, rheumatologists, and oral medicine/pathology specialists, used standardized tests to evaluate over 1,400 participants enrolled in the SICCA Registry. All had possible signs and/or symptoms of SS, were typical of patients seen in a clinical practice, and were drawn from ethnically diverse patient populations worldwide. The goal of this activity was to develop new diagnostic criteria for SS that could be used by clinicians and researchers developing new therapies for this condition. The new criteria were published in 2012 and, importantly, the American College of Rheumatology (ACR) voted to accept the SICCA criteria. This marks the first time ever that the ACR has approved classification criteria for SS, despite its recognition as a distinct condition for more than 80 years. This registry is also beginning to analyze DNA of subjects to determine the genes associated with SS and to determine the frequency of other types of diseases in this population. In addition, the registry has distributed biospecimens to 23 other investigators for different research projects studying this disease.

NIDCR intramural scientists continue to evaluate patients with SS at the Bethesda campus. The goal of their natural history protocol is to identify the genetic disease mechanisms of SS by carefully studying the clinical features of SS patients, and patients with Sjögren's-like conditions, over time, as well as to collect serum and tissue samples for analysis in the laboratory under future study protocols. In 2011, they reported that microRNA profiles in salivary gland biopsies might be good biomarkers of disease activity in the glands. MicroRNA are small, noncoding RNA molecules that can regulate gene expression; variation in measured microRNA levels can reflect physiologic and pathologic processes and may be used as biomarkers of concurrent pathophysiologic events in complex settings, such as autoimmune diseases. In their study, microRNA expression patterns accurately distinguished salivary glands from control subjects and patients with SS, and these patterns could also differentiate between patients with low-degree inflammation and those with high-degree inflammation. In other studies, these investigators demonstrated that saliva is highly enriched in microRNAs, suggesting that saliva, rather than minor salivary gland biopsies, could be used to assess salivary gland inflammation in these patients. Other clinical studies from this group of investigators found differences in mRNA expression of minor salivary glands of healthy women versus healthy men in a diverse set of genes involved in immune function, inflammation, and healing. These differences may help in defining why women develop SS nine times more frequently than men.

The hallmark of SS is an autoimmune attack on the salivary glands; progressive lymphocytic infiltration into the salivary and other exocrine glands leads to tissue damage and secretory defects. This year, NIDCR intramural scientists reported that mice with deficiencies in two genes, known as STIM1 and STIM2, develop spontaneous and severe SS-like autoimmune disease, displaying major hallmarks of the disease. In mice, diffuse lymphocytic infiltration was seen in submandibular glands, a major feature of SS, by age 6 weeks, progressing to severe inflammation by age 12 weeks. SS-specific autoantibodies were detected in the serum, and progressive salivary gland destruction and loss of fluid secretion were also seen. Importantly, the scientists also found that tissue samples from SS patients are deficient in the same two genes. Calcium metabolism was also reduced in the white blood cells of SS patients compared with those from healthy controls. Thus, deficiency of STIM1

and STIM2 proteins in white blood cells, and consequent defects in calcium signaling, are associated with salivary gland autoimmunity in STIM1/2-deficient mice and SS patients. These data reveal a previously unreported link between STIM1 and STIM2 proteins and SS.

To understand the pathogenesis of SS, researchers have turned to animal models that capture many aspects of the disease. However, the complex nature of the syndrome itself complicates the translation of findings in mice to humans. To identify common signaling pathways and molecular targets, gene expression microarrays from the salivary glands of human SS patients, non-Sjögren's human controls, and a Sjögren's mouse model were examined for coexpression of gene modules. A weighted gene coexpression network analysis evaluated human modules that could also be found in mouse data. Several coexpression modules from human parotid gland samples could discriminate Sjögren's patients from unaffected individuals. One of these modules was found to be highly preserved in the mouse model and led to the identification of genes associated with immune function and lymph node structure, both important elements in the normal immune response. This research points towards the future use of systems biology and computational analysis to assist in the direct comparison of data between humans and animal models and to identify common pathways for future target-based research and therapies.

In other studies, intramural investigators have employed the non-obese diabetic (NOD) mouse to study SS and possible therapies for this disorder. Using gene therapy, they used a molecule to block intercellular adhesion molecule-1 (ICAM-1), which is involved in migration and costimulation of two kinds of immune cells. Their results indicated that blocking ICAM-1 early in disease decreased salivary gland infiltrates, but that administration of the blocking molecule to mice with established disease increased the amount of T cell infiltrates. Neither group had improvements in salivary gland function. These data indicate that caution must be taken in treating human SS with therapies targeting the ICAM-1, because it is likely that most patients are diagnosed and request treatment in a more progressed stage of the disease.

In Vitro Studies of Autoimmune Diseases

The mechanism by which Sjögren's syndrome destroys the salivary glands is not well understood, but it is known that salivary gland cells become subject to programmed cell death, or apoptosis. NIDCR-supported investigators recently explored the use of a small interfering RNA (siRNA) molecule that was bound to carbachol, which binds to salivary gland signal receptors. The carbachol serves to direct the siRNA to the salivary gland, where the carbachol/siRNA conjugate can then target and knock down expression of caspase 3, a key protein in cell death in human salivary gland cell cultures. In laboratory conditions, the caspase 3 gene and protein expression were knocked down by 50 percent in conjugate-treated cells, indicating that the conjugate successfully entered cells and that the siRNA successfully reduced caspase 3 expression. The ability of the siRNA conjugate to target salivary gland cells via ligand receptor binding holds promise for site-specific delivery of a therapeutic treatment that could protect salivary gland cells from cell death and thus maintain secretory function.

Human Immunodeficiency Virus (HIV)

The study of the oral manifestations of HIV infection has been of great interest to NIDCR, because oral changes in HIV-infected individuals are frequent, varied, and among the first symptoms of infection. The impact of HIV/AIDS on women has grown substantially since the beginning of the epidemic.

One component of the AIDS Clinical Trials Group (ACTG), the largest HIV clinical trials organization in the world, is the Oral HIV/AIDS Research Alliance (OHARA). Its main objective is to investigate oral complications associated with HIV/AIDS, in particular the effects of antiretroviral drugs on the development of mouth sores and associated fungal and viral pathogens. Observational studies and clinical trials are being implemented at ACTG-affiliated sites in the U.S. as well as in resource-poor countries. These studies

will also determine differences in the oral manifestations and therapeutic outcomes of HIV-infected men and women. Recently updated definitions for HIV-related oral diseases will be used to measure standardized clinical endpoints in OHARA studies. Implementation of these new endpoints will allow researchers to determine which HIV medications have the biggest impact on the oral health symptoms of HIV.

In 2011, NIDCR, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, began the project "Oral Health Among Participants in the Pediatric HIV/AIDS Cohort Study," a multicenter subproject of the Pediatric HIV/AIDS Cohort Study (PHACS). This observational study will examine the oral health of adolescents, including girls, with the following objectives: (1) to estimate and compare the prevalence of dental, periodontal, and oral mucosal diseases in HIV-infected and uninfected children; and (2) to explore the associations between these oral outcomes and indicators of overall health, quality of life, neurocognition, and, for HIV-infected children/adolescents, HIV disease severity and use of antiretroviral therapy.

Craniofacial Anomalies

NIDCR supports research designed to identify the genetic and molecular mechanisms underlying oral health problems and craniofacial disorders. Craniofacial abnormalities, such as cleft lip and cleft palate, ectodermal dysplasias, craniosynostosis, and amelogenesis and dentinogenesis imperfecta, may be the result of spontaneous or inherited genetic mutations. Often, the causes are complex, involving environmental factors and gene-gene and gene-environment interactions. Advances in this area were numerous between 2011 and 2012.

Craniosynostosis, which results from premature fusion of 1 or more cranial sutures, occurs at a rate of approximately 3 to 5 out of every 10,000 live births. In most instances, craniosynostosis occurs with no other major malformations (such as nonsyndromic craniosynostosis [NSC]). Rare genetic variants in a few genes have been associated with NSC, occurring in a small proportion of individuals with NSC. Sagittal craniosynostosis is the most common type of NSC; because the sagittal suture lies along the midline of the skull, the premature fusion in sagittal craniosynostosis prevents the head from growing in width to accommodate the expanding brain. In a recent publication, investigators reported on a study to identify the genes that affect susceptibility to sagittal nonsyndromic craniosynostosis (sNSC); published literature suggests that both genetic and environmental factors affect development of sNSC, but little is known about the specific genes that may be involved. These researchers conducted a genome-wide search in 214 families with at least 1 individual with sNSC. The genome-wide search yielded two regions with statistically significant results in proximity to two genes involved in skeletal development (BBS9 and BMP2). Researchers are continuing to explore the role these genes may play in the development of craniosynostosis.

Other groups have continued to expand our knowledge of the genetic contribution to nonsyndromic cleft lip with or without cleft palate (NSCL/P), one of the most common birth defects. Genetic studies have identified several genomic regions or genes that affect susceptibility. A recent study combined data from two large previous studies to advance understanding of genetic factors contributing to susceptibility to NSCL/P. The researchers confirmed associations with all previously identified loci and identified six additional susceptibility regions. Analysis of phenotypic variability identified the first specific genetic risk factor for NSCL plus cleft palate. Future studies are needed to identify the specific genes and variants involved and to understand the ways in which these genes affect craniofacial development and development of NSCL/P.

NIDCR Activities that Support the Goals of the NIH Strategic Plan for Women's Health Research

Many investigators supported by NIDCR conduct studies that support the goals of the NIH Strategic Plan for Women's Health Research.

Examples below support Goal 1, "Increase Sex Differences Research in Basic Science Studies," and selected objectives.

1.2: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems

Sjögren's syndrome (SS), an autoimmune disease that leads to inflammation and dysfunction in the lachrymal and salivary glands, is diagnosed nine times more frequently in females than in males. Investigators hypothesized that differential mRNA transcription in salivary glands may be linked to the sex distribution of the disease. NIDCR researchers used RNA from minor salivary glands collected from nine healthy volunteers (four men and five women) to compare the transcriptomes of the two sexes. They identified a number of sex, species, and tissue-specific gene expression patterns. These differences included, but were not limited to, a diverse set of genes involved in immune modulation, chemotactic control, inhibition of complement, metabolism, and neurogenesis. Analysis of these changes provides insight into the protective and predisposing molecular factors that may be involved in the development of SS. Some of the gene changes observed in this study correlate with previously observed sex differences in salivary gland function and illustrate several new targets for further investigation.

1.5: Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders

Temporomandibular joint disorders (TMJD) are a heterogeneous group of orofacial conditions associated with persistent orofacial pain and jaw dysfunction. Most individuals with TMJD are women, and women report more pain than men in experimental settings. As described above, this suggests that sex hormones may play a role in disease onset and pain sensitivity. A NIDCR-funded research team, using a rodent model of acute inflammatory pain, has shown that physiological levels of the female sex hormone estradiol have a profound effect on the expression levels of numerous genes important in pain modulation and regulation of neuroinflammation. These effects were seen throughout the trigeminal system—which controls the sensory and motor functions in the face, teeth, mouth, and nasal cavity—including the TM joint itself, the trigeminal ganglion, and the trigeminal nucleus in the brain stem.

Other studies are investigating the role of the estrogen axis on the regulation of cartilage growth induced by mechanical loading. NIDCR envisions that this work will aid in the understanding of how estrogen and mechanical loading interact to influence development of TMJD.

In addition, as described above, NIDCR supports research investigating the sex-specific differences in response to opioids.

The primary activity supporting Goal 5, "Develop and Implement New Communication and Social Networking Technologies to Increase Understanding and Appreciation of Women's Health and Wellness Research," is NIDCR's participation as a "Text4baby Partner."

Under the auspices of DHHS, NIDCR is now a Text4baby partner. Text4baby is a free health text messaging service for pregnant women and new moms. Those who text "BABY" (or "BEBE" for Spanish) to 511411 receive weekly text messages, timed to their due date or their baby's birth date, through the baby's first year. The messages, which have been vetted by both government and nonprofit health experts, deal with topics such as nutrition, immunization, birth defect prevention, and oral health. Text4baby oral health messages were reviewed by NIDCR, the Centers for Disease Control and Prevention, American Academy of Pediatric Dentistry, American Academy of Pediatrics, and Duke Pediatric Dentistry. Since its February 2010 launch, more than 285,000 individuals have enrolled in Text4baby. Text4baby is run by the nonprofit Healthy Mothers Healthy Babies Coalition (HMHB) in partnership with the private sector and government partners, including DHHS and the White House Office on Science and Technology Policy.

Initiatives

Funding Opportunity Announcements (FOAs)

Advancing Novel Science in Women's Health Research (ANSWHR), PAS-10-226. The purpose of this FOA, issued by the Office of Research on Women's Health (ORWH) and cosponsoring NIH Institutes and Centers (ICs), is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences.

Mechanisms, Models, Measurement, & Management in Pain Research (R01), PA-10-006; (R21), PA-10-007; (R03), PA-10-008. The purpose of this FOA, issued by the National Institute of Nursing Research (NINR) in conjunction with members of the NIH Pain Consortium, is to inform the scientific community of the pain research interests of the various Institutes and Centers (ICs) at the NIH and to stimulate and foster a wide range of basic, clinical, and translational studies on pain as they relate to the missions of these ICs.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment (R01), PAR-12-032 and (R21), PAR-12-033. This FOA, issued by the ORWH and cosponsoring Institutes and Centers (ICs) of the NIH, encourages investigator(s)-initiated applications that propose to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS), sometimes referred to as myalgic encephalomyelitis, in diverse groups and across the lifespan.

NIDCR Institutional Career Development Award for Enhancing Research Capacity in Temporomandibular Joint Disorders and Orofacial Pain (K12), PAR-11-289. The purpose of this FOA is to expand and strengthen the community of investigators engaged in research on temporomandibular joint disorders (TMJDs) and orofacial pain.

Pathophysiology and Clinical Studies of Osteonecrosis of the Jaw (R01), PAR-11-082; and (R21), PAR-11-083. The purpose of this FOA is to stimulate research regarding clinical and basic science research to examine the etiology, diagnosis, and pathophysiology of medication-induced osteonecrosis of the jaw.

Trans-NIH Blueprint for Neuroscience Grand Challenge on Pain (R01), RFA-DE-11-002. Division of Extramural Research staff continue to head the Trans-NIH Blueprint for Neuroscience Grand Challenge on Pain initiative. Twenty-six applications were received in response to a FOA issued in May 2010 (RFA-DE-11-002). The FOA encouraged multi-principal investigator grant applications from pain and non-pain neuroscientists that will explore mechanisms underlying the transition from acute to chronic neuropathic pain.

Conferences, Symposia, Workshops, Consortia and Working Groups

2011 Gordon Research Conference on Salivary Glands & Exocrine Secretion. This conference brought together investigators to present and discuss the most recent progress in understanding the molecular basis of development, function, and dysfunction of salivary and related exocrine glands.

National Institutes of Health 6th and 7th Annual Research Symposium for Advances in Pain Research. This annual symposium highlights advances in NIH-supported pain research. The theme of the sixth symposium was the mechanisms and management of overlapping chronic pain and associated conditions, while the seventh symposium focused on novel approaches and therapy development for pain management.

Sixth Scientific Meeting of the TMJ Association. Held June 5–7, 2011, in Bethesda, Maryland, this meeting built upon evidence from the five previous meetings demonstrating that temporomandibular disorders (TMD) are a complex family of conditions influenced by genetics, gender, and environmental and behavioral triggers mediating the vulnerability of patients to TMD and typically manifesting as more than jaw and muscle pain and jaw dysfunction. The sixth meeting focused on the pathophysiological processes underlying the chronic pain conditions that coexist with TMD and constitute comorbid chronic pain conditions.

National Institute of Diabetes and Digestive and Kidney Diseases

Executive Summary

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports basic and clinical research on diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases. Within NIDDK's research mission, diseases and health risks that disproportionately, predominantly, or solely affect women include gestational diabetes mellitus, obesity (especially in racial and ethnic minority populations), cardiovascular and end-stage renal disease associated with diabetes, eating disorders, irritable bowel syndrome (IBS) and other functional gastrointestinal disorders, osteoporosis, thyroid diseases (including Grave's disease and hypothyroidism), hyperparathyroidism, gallstones, primary biliary cirrhosis, interstitial cystitis/painful bladder syndrome (IC/PBS), urinary tract infections (UTIs), urinary incontinence, and lupus nephritis (the kidney disease of systemic lupus erythematosus). Some NIDDK-supported research, such as study of the relationship of obesity to cardiovascular disease, may also have an important impact on diseases that are primarily within the mission of other Institutes and Centers. NIDDK supports research on ways to improve women's health and to advance understanding of sex/gender differences in health and disease, both through basic research directed at understanding underlying disease processes and through clinical research that translates this understanding into therapies and preventive interventions. In fiscal years 2011 and 2012, the Institute has made progress in the following areas important to women's health, all of which are highlighted in this report: prevention and treatment of diabetes and its complications, obesity, thyroid conditions, metabolic health in pregnancy, IBS and other functional gastrointestinal disorders, kidney disease, IC/PBS, UTIs, and urinary incontinence. The Office of Research on Women's Health has worked with NIDDK to foster research in many of these areas.

Introduction

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports biomedical and behavioral research to address some of the most common, costly, and chronic diseases and conditions affecting U.S. and global populations. Many of these diseases and conditions affect women solely, disproportionately, or in unique ways. For example, only women develop gestational diabetes mellitus (GDM); women lose their comparative protection against the risk of cardiovascular disease when they develop chronic diabetes; African-American women experience the highest rates of obesity; obesity increases risk for myriad health problems of special interest to women, including cardiovascular disease, gallbladder disease, and GDM; women are more prone to autoimmune disorders, including autoimmune thyroid and liver diseases; lupus, and hence kidney disease of lupus (lupus nephritis), predominantly occurs in women; bowel and bladder control problems are much more prevalent in women; and women are more highly affected by pelvic pain syndromes associated with the bladder and gut. NIDDK supports a diverse portfolio of research important to women's health, including studies in the following areas:

- Diabetes in women (including type 1, type 2, and gestational diabetes)
- Diabetes health complications, including sexual dysfunction and depression
- Obesity prevention and treatment
- Thyroid and parathyroid conditions and diseases
- Bone metabolism and osteoporosis
- Irritable bowel syndrome (IBS)
- Interstitial cystitis/painful bladder syndrome (IC/PBS)
- Fecal and urinary incontinence
- Kidney diseases and kidney failure
- Liver and biliary diseases
- Urinary tract infections (UTIs)

Research on sex/gender differences is also revealing new information about how

susceptibility, onset, progression, or treatment efficacy for diseases and conditions within the NIDDK mission may differ between women and men.

The scope of NIDDK women's health research crosses the Institute's three extramural research divisions—the Division of Diabetes, Endocrinology, and Metabolic Diseases; the Division of Digestive Diseases and Nutrition; and the Division of Kidney, Urologic, and Hematologic Diseases—as well as NIDDK's Intramural Research Program. Their efforts are enhanced by activities of NIDDK's Office of Obesity Research and Office of Minority Health Research Coordination and by the Division of Nutrition Research Coordination, which is housed within NIDDK. NIDDK promotes public health education and awareness through its Office of Communications and Public Liaison, whose key efforts include the National Diabetes Education Program (NDEP), a joint effort of NIDDK and the Centers for Disease Control and Prevention (CDC); the National Kidney Disease Education Program; and the Weight-control Information Network. Finally, NIDDK conducts strategic planning efforts for research in major areas of its portfolio on a regular basis; many of these are germane to women's health and include input and/or partnership from the NIH Office of Research on Women's Health (ORWH).

The NIDDK scientific staff includes a newly hired Program Director for Women's Urologic Health, who is bringing a greater focus on prevention research for women's urologic health. NIDDK has also established a Healthy Pregnancy Program (described under "Accomplishments") that involves the efforts of program directors from two extramural research divisions plus the Office of Obesity Research. A Women's Health Liaison to ORWH in NIDDK's Office of Scientific Program and Policy Analysis coordinates efforts across the Institute and works with ORWH to foster partnerships in areas of joint interest in women's health. Highlights of accomplishments in women's health research supported by NIDDK follow.

Accomplishments

Diabetes

Type 2 Diabetes Prevention—Understanding Risk Factors in Women

Information important to diabetes prevention in women continues to emerge from the Diabetes Prevention Program (DPP) and its long-term follow up, the DPP Outcomes Study (DPPOS). In 2002, the DPP clinical trial results showed that, in a racially, ethnically, and age-diverse cohort of adult women and men, a lifestyle intervention (exercise and diet to induce moderate weight loss) reduced risk of developing type 2 diabetes by 58 percent. The diabetes drug metformin reduced diabetes risk by 31 percent. A recent report from the DPPOS has shown that using either of these interventions would be a very cost-effective way to improve health and quality of life for people at high risk for type 2 diabetes. Sixty-eight percent of the DPP study participants were women, of whom 16 percent had a history of GDM, which has enabled researchers to study the efficacy and long-term effects of DPP interventions in women with this risk factor; ORWH support of the DPP facilitated recruitment and retention of these women. Another sex-specific factor, menopause, may influence diabetes risk by affecting glucose metabolism; knowing the effect of menopause is important to tailoring diabetes prevention strategies in women. In a recent study, scientists found that natural menopause did not further increase diabetes risk in DPP participants, nor did it interfere with their response to DPP interventions. NIDDK and ORWH have also supported a study in the DPP population of the mechanistic and predictive role of endogenous sex hormones and sex-hormone binding globulin (SHBG) in the development of type 2 diabetes in women and men. Recent advances emerging from this study include the finding that, among postmenopausal women in the DPP not using estrogen, the DPP lifestyle intervention (but not metformin) increased SHBG levels and lowered levels of the sex steroid dehydroepiandrosterone (DHEA) between baseline and 1 year—changes that were associated with

lower glucose levels independent of adiposity and insulin. Also, the scientists found significant racial and ethnic differences in both baseline levels of sex hormones and changes in levels of these hormones in postmenopausal DPP participants at baseline and after 1 year, information that can now be further investigated for clinical significance.

Treating Diabetes in Youth

An increase in childhood obesity and other factors have led to a significant rise in cases of type 2 diabetes in people under 20 years of age. Girls are disproportionately represented in the pediatric population with type 2 diabetes, a difference not observed in adults with the disease. Researchers are seeking optimal treatments for type 2 diabetes in youth to help avert the long-term complications of the disease. Currently, metformin is the only oral drug approved for treating type 2 diabetes in children. The nationwide Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study compared the efficacy of three treatment arms, using time to treatment failure based on glycemic control as the measure of efficacy. The three treatment regimens were metformin alone; metformin plus another diabetes drug, rosiglitazone; and metformin plus an intensive lifestyle intervention. Participants were randomized within 2 years of the diagnosis of type 2 diabetes, were 10 to 17 years of age, and were followed for a minimum of 2 years. At the start of the study, the 699 participants were either overweight or obese, and about 65 percent of the randomized cohort was female. Unfortunately, metformin alone failed to maintain acceptable, long-term blood glucose control in over half of the youth over an average follow-up of 46 months—a much higher failure rate than expected. The addition of lifestyle intervention to metformin did not significantly improve outcomes. The combination of metformin plus rosiglitazone was significantly better and was most effective in girls, but still it failed 38.6 percent of the time over the follow-up period. (Note: current U.S. Food and Drug Administration restrictions on rosiglitazone implemented after the trial began mean that this drug is not recommended for use in children.) The results suggest that treatment with metformin alone may be inadequate for a majority of youth with type 2 diabetes and that type 2 diabetes is actually a more aggressive disease in youth than in adults. The TODAY cohort represents the largest cohort of newly diagnosed youth with type 2 diabetes. Following the trial, a follow-up study (TODAY2) was initiated to understand the durability of treatment effects and the clinical course of diabetes in those diagnosed at an early age. Of particular concern for girls is the effect of the disease on pregnancy; in adult women, uncontrolled diabetes is associated with adverse pregnancy outcomes. TODAY2 is collecting prospective data on pregnancy outcomes from girls who participated in TODAY to learn more about the impact of type 2 diabetes on pregnancy in youth.

Finding Ways to Combat Self-Imposed Insulin Restriction in Women with Type 1 Diabetes

Researchers have identified factors linked with some women's decisions to take insufficient insulin to properly manage their type 1 diabetes (insulin restriction). Some women with type 1 diabetes intentionally take less insulin than prescribed by their doctors—usually because of the fear of gaining weight and problems with diabetes self-care—and thus do not achieve optimal blood glucose control. An 11-year follow-up study of women with type 1 diabetes showed previously that insulin restriction was associated not only with increased rates of diabetes complications, but also with increased risk of premature death. In new research in the same population, scientists looked at factors associated with decisions to start or stop insulin restriction over the 11-year follow-up period. The results show that women who stopped insulin restriction reported improved diabetes self-care, fewer problems with diabetes self-management, and less fear that taking insulin would cause weight gain. In contrast, women who started restriction during the follow-up period were fearful of weight gain. Overall, fear of weight gain and problems with diabetes self-care were core issues associated with women's decisions to start or stop insulin restriction. The researchers also examined actual weight gain and found that the result was the exact opposite of the fears:

women who stopped restricting did not gain weight, while the insulin restrictors gained weight, an observation that could potentially be used by physicians as a tool to help women with type 1 diabetes manage their concerns about weight gain and thus help avoid insulin restriction. This study sheds light on core issues surrounding women's decisions to restrict insulin and highlights the importance of health care providers' assessing and addressing insulin management as well as any weight concerns or symptoms of eating disorders when treating women with type 1 diabetes.

Impact of Diabetes on Sexual Function in Women

While the impact of diabetes on men's sexual function is known to be significant, the impact of diabetes on sexual function in women has been poorly understood. In a recent study, scientists investigated sexual function in an ethnically diverse cohort of middle-aged and older women who either had diabetes treated with insulin, diabetes not treated with insulin, or did not have diabetes. Using both self-administered questionnaires and in-person interviews, the researchers assessed multiple aspects of sexual function, including sexual activity, desire, satisfaction, and problems. Among women with diabetes, the investigators also examined associations between sexual function and use of diabetes medications, end-organ complications, and other markers of disease severity. Although women with and without diabetes reported similar levels of sexual desire and frequency of sexual activity (after adjustment for other demographic and clinical factors), women with diabetes were more likely to report lower overall sexual satisfaction than were their nondiabetic counterparts. Moreover, diabetic women treated with insulin had more problems with lubrication and orgasm than did their counterparts without diabetes. In addition, women with diabetes who had peripheral neuropathy, renal dysfunction, stroke, or heart disease were more likely to report lower sexual activity or sexual satisfaction, indicating that these end-organ complications may significantly affect women's sexual quality of life. While more research is needed to understand changes in these outcomes over time and any possible causal relationships, these findings suggest that health care providers may wish to consider assessing sexual function in their female patients with diabetes, especially those taking insulin, and that preventing end-organ complications may be important to preventing sexual dysfunction in women with diabetes.

Bidirectional Association of Type 2 Diabetes and Depression in Women

Depression is a known comorbidity of diabetes, but the exact nature of the risk relationship between the two conditions—whether, for example, each increases risk for the other—has not been well understood. In a 10-year, prospective observational study of more than 65,000 participants in the Nurses' Health Study who were aged 50 to 75 years at baseline, scientists sought to determine the bidirectional relationship between type 2 diabetes and depression in women. The study captured the baseline presence and/or later onset of clinical depression, depressed mood, and/or type 2 diabetes, as well as a number of other factors that could influence either condition. The researchers conducted two analyses: (1) in one they looked at depression status and incidence of type 2 diabetes in women free of type 2 diabetes at baseline; (2) in the other they looked at the severity of type 2 diabetes and the incidence of clinical depression in women who were not clinically depressed at baseline. They found that women with depression were at increased risk for type 2 diabetes and, of women in that group, those on antidepressant medications had the greatest increase in risk relative to women without depressive symptoms. They also found that women with type 2 diabetes were at greatly increased risk for developing clinical depression compared with women without diabetes, and that those on insulin therapy had the greatest risk. These results appeared to be independent of diet, lifestyle, and sociodemographic factors, although they were possibly influenced by disease comorbidities. Thus, these findings suggest that type 2 diabetes and depression are reciprocally related in women, and the degree of risk each confers depends on the disease severity or treatment regimen for each condition. While

additional research needs to be conducted to identify mechanisms underlying this bidirectional relationship, this advance adds to the growing body of knowledge about the relationship between depression and type 2 diabetes, especially in women.

Obesity

Look AHEAD (Action for Health in Diabetes) Shows Many Health Benefits of Intensive Lifestyle Intervention

The long-term, multicenter Look AHEAD (Action for Health in Diabetes) clinical trial has sought to determine whether lifestyle intervention can improve cardiovascular outcomes in obese patients with type 2 diabetes. More than 5,100 participants, nearly 60 percent of whom are women, were randomly assigned to either an intensive lifestyle intervention group or a diabetes support and education group. In addition to tracking cardiovascular disease outcomes, Look AHEAD researchers have examined myriad other health outcomes. After 4 years of the study, Look AHEAD showed a number of important health benefits of the intensive lifestyle intervention, including, most recently, helping to maintain physical mobility. Intensive lifestyle intervention slowed the decline in mobility by nearly 50 percent in comparison with diabetes support and education. Weight loss was a slightly stronger predictor of better mobility than was improved fitness, but both contributed significantly to the observed reduction in risk. These results are consistent with previous analyses showing that participants in the intensive lifestyle intervention group lost significantly more weight than did those in the diabetes support and education group, and that they also had improved fitness, glucose control, blood pressure, and HDL (high-density lipoprotein) cholesterol values with less use of medication. The new findings show that intensive lifestyle intervention programs can slow the decline of mobility in overweight or obese people with type 2 diabetes, a result with significant implications for improving quality of life as people age. The findings may be particularly important for women, who were relatively overrepresented among those categorized with the most severe mobility-related disability in the study. In September 2012, the intervention was discontinued when it was found that intensive lifestyle intervention in overweight/obese adults with long-standing type 2 diabetes did not reduce cardiovascular events such as heart attack and stroke—the primary study outcome. However, although the intervention was discontinued, follow-up of all study participants will continue to evaluate their long-term health and effects of the weight-loss intervention. Look AHEAD is spearheaded by NIDDK and cosponsored by the National Heart, Lung, and Blood Institute (NHLBI), National Institute of Nursing Research, ORWH, National Institute on Minority Health and Health Disparities, and CDC.

Weight Loss Surgery for Obesity—Emerging Knowledge of Benefits, Risks, and Sex/Gender Differences

One treatment approach for extreme obesity is bariatric surgery—a form of weight-loss surgery that involves reducing stomach size and, in some cases, bypassing part of the small intestine (gastric bypass). More than 80 percent of persons undergoing this surgery are female, and the majority of patients are White. A study has shown that bariatric surgery can help control type 2 diabetes more effectively than can medical therapy alone, and can help reduce the need for medications to lower blood glucose concentrations, lipid levels, and blood pressure. This study focused on two specific procedures: a variation of gastric bypass surgery, called Roux-en-Y surgery, in which the top portion of the stomach is connected directly to a lower portion of the small intestine; and sleeve gastrectomy, in which the majority of the stomach is removed, leaving a comparatively narrow "sleeve." After 12 months, blood glucose was reduced to levels below the diabetic range in only 12 percent of participants who received medical therapy alone, compared with 42 percent in the gastric bypass group and 37 percent in the sleeve gastrectomy group. This study adds to existing evidence that bariatric surgery may be a reasonable approach for treating some patients with obesity and uncontrolled type 2 diabetes. Another report has provided insights into the benefits and

risks of bariatric surgery over the longer term. In this study, researchers recruited more than 400 individuals who were extremely obese and who had Roux-en-Y gastric bypass surgery, and compared them to a similar group of individuals who did not undergo surgery; a majority of the study volunteers were women. The researchers found that the surgery led to a number of health benefits that persisted for years, including better weight-loss maintenance 6 years post-surgery, a 62 percent rate of type 2 diabetes remission 6 years post-surgery, and a reduced risk for type 2 diabetes among those who had surgery versus those who did not. Other outcomes after surgery included improvements in cholesterol and triglyceride measures and better blood pressure. Approximately 8 percent of surgery patients required further hospitalization postoperatively, and there were four suicides reported among surgery patients. The reasons for the small but significantly increased incidence of suicides in the surgical group versus the control population are unknown, but this finding indicates a need for greater attention to patients' psychological health before and after surgery. In a similar vein, another study showed that adults who had Roux-en-Y surgery had a significantly higher risk of alcohol-use disorders 2 years after surgery compared with before surgery and that men and younger adults were more likely to develop these disorders. Interestingly, patients who underwent another common type of weight-loss surgery, laparoscopic adjustable gastric banding, did not report an increase in symptoms of alcohol-use disorders. These findings emerged from research conducted in the Longitudinal Assessment of Bariatric Surgery (LABS), a prospective study of patients undergoing weight-loss surgery at one of 10 different hospitals across the United States; NIDDK is also supporting a similar study, Teen-LABS, to assess the short- and longer-term safety and efficacy of bariatric surgery in adolescents compared with adults. The majority of participants in the three studies were non-Hispanic Whites, and thus additional research will need to be conducted to see whether results are similar in diverse racial and ethnic groups; however, the findings from these studies have already added important data to current knowledge about bariatric surgery and can help individuals and their health care providers with treatment decisions.

Sex Differences in Brown Fat Accumulation in Childhood Development

In contrast to white adipose (fat) tissue, which stores energy and provides insulation, brown fat "burns" fat to release heat and help maintain body temperature. While in humans such fat is predominantly found in neonates, recent studies have found that some adults retain significant amounts of brown fat, which could have important implications for metabolic health. Brown fat appears to be closely related to skeletal muscle on the cellular level. Researchers previously found a positive association between amounts of brown fat and muscle volume in pediatric patients. Examining this relationship further through a cross-sectional study utilizing a population of girls and boys spanning childhood to the final stage of puberty, the researchers have now found a positive correlation between the presence of brown fat and advancing pubertal stage. While there was no difference by sex in the prevalence of detectable brown fat in this study population, the changes in brown fat were significantly greater in boys than in girls and were closely related to muscle volume. Interestingly, this is in contrast to studies that have reported greater prevalence and amounts of active brown fat in women than in men. These findings add to knowledge about brown fat, which is still not well understood, and open the door to future research to understand the mechanisms underlying both the expansion of brown fat during puberty and the observed sexual dimorphism in its volume.

Sex Differences in Metabolism When Fasting

When fed, the body relies primarily on glucose for energy; during a fast or starvation, fatty acids are released by fat tissue into the circulation and picked up for use or for storage as triglycerides by liver and skeletal muscle (lean tissue). Women release relatively more fatty acids during fasting and starvation than do men, which may result in sexually dimorphic lipid and glucose

metabolism in skeletal muscle and liver. However, little has been known about the magnitude of fatty acid disposition to liver and muscle in humans and any metabolic consequences of this event. In a new study conducted in men and premenopausal women, researchers examined changes in lean-tissue triglyceride content during a 48-hour fast. They found that, during the fasting period, men experienced an increase in triglycerides in the liver, and women experienced an increase in triglycerides in skeletal muscle. In contrast, they did not observe sex differences in whole-body or liver-glucose or energy metabolism, indicating that the key difference lay in tissue uptake and the conversion of free fatty acids to triglycerides. This novel finding of sex-based differences in fatty acid disposition to liver and skeletal muscle may provide insight into different pathological susceptibilities between women and men—e.g., compared with women, men have a modestly increased vulnerability to fatty liver disease—and can now be investigated further for its clinical relevance for both women and men.

Healthy Pregnancy Program

Pregnancy is a key period of study and potential intervention to protect the metabolic health of women and their offspring. Numerous observational studies have linked pre-existing overweight/obesity and/or excessive gestational weight gain during pregnancy to short-term and long-term adverse health consequences in both mothers and their offspring. However, additional research is needed to identify effective interventions that will improve weight, glucose levels, and other pregnancy-related outcomes in mothers and to determine whether these interventions affect obesity and metabolic abnormalities in the offspring. Five to seven percent of women will develop GDM during pregnancy, placing them at greatly increased risk for developing type 2 diabetes in the 5 to 10 years post partum, and increasing risk for obesity and diabetes in their offspring. Moreover, results from the Hyperglycemic and Adverse Pregnancy Outcome (HAPO) study have suggested that elevated maternal glycemia, even below levels diagnostic of GDM, is associated with adverse pregnancy outcomes.

To help address these key issues surrounding obesity and diabetes/hyperglycemia during pregnancy, NIDDK has established a Healthy Pregnancy Program that encompasses the following:

- **The LIFE-Moms (Lifestyle Interventions for Expectant Moms) Consortium:** This consortium is testing lifestyle interventions in overweight and obese pregnant women that may reduce inappropriate gestational weight gain and/or improve metabolic status, with potential short-term and long-term health benefits for mothers and offspring. The consortium consists of seven clinical studies in a broad range of populations, including minority and socioeconomically disadvantaged groups, and a research coordinating unit. This effort is cosponsored by NIDDK (the lead), NHLBI, the National Institute of Child Health and Human Development (NICHD), the National Center for Alternative and Complementary Medicine (NCCAM), ORWH, and the Office of Behavioral and Social Sciences Research (OBSSR).
- **HAPO Follow-Up Study (HAPO FUS):** This multisite observational study, conducted at 10 of the original HAPO sites, will leverage the well-characterized HAPO study population to determine whether hyperglycemia during pregnancy that is less severe than GDM influences later levels of body fat in children and the development of diabetes in mothers after giving birth. This study is cosponsored by NIDDK and NICHD.
- **Post-Gestational Diabetes Awareness Campaign:** This educational initiative, an ongoing effort of the NDEP and part of its "Small Steps, Big Rewards. Prevent Type 2 Diabetes" campaign, targets women with a history of GDM, their families, and health care providers. The program goals are to decrease incidence of type 2 diabetes among women with a history of GDM, increase awareness of health risks among families with children whose mothers were diagnosed with GDM, and improve the reach of information and the delivery of health care professional counseling regarding future health risks and the importance of adopting and maintaining healthy behaviors among these families.

In a related effort, NIDDK and ORWH cofunded a study to develop the measurement of serum levels of a factor called glycated complement regulatory protein, CD59 (glyCD59), as a replacement for the 3-hour oral glucose tolerance test in the diagnosis of GDM. If ultimately successful, this method could provide a less burdensome approach to diagnosis of this condition in women.

Endocrinology

Advances in Treating Thyroid Conditions

The thyroid gland secretes two hormones that affect nearly every part of the body, as they influence metabolism, body temperature, muscle strength, skin and hair, menstrual cycles, weight, and cholesterol levels. Insufficient (hypo) or excess (hyper) production of thyroid hormones can thus have negative effects on health. Symptoms of hypothyroidism include fatigue, weight gain, facial "puffiness," and intolerance of cold. A new report finds that some patients who continue to experience symptoms of hypothyroidism despite receiving conventional therapy may benefit from administration of a synthetic form of triiodothyronine (T3). Current standard therapy for hypothyroidism is a once-daily pill containing a synthetic form of thyroxine (T4). T4 is a less potent but more stable form of thyroid hormone that is converted to T3 by various tissues throughout the body. However, experiments in mice suggest that T4 treatment does not result in sufficient T3 levels in some tissues, which may explain why a subset of people with hypothyroidism continue to experience some of its symptoms even when receiving what should be an adequate dose of T4. In a study comparing therapy with T4 alone to therapy with T3 alone in a thrice-daily, orally administered dosing regimen in 14 people (13 female) experiencing these refractory symptoms, researchers found that participants lost weight on T3 relative to T4, showed significant improvement in their levels of cholesterol and other blood fats, and experienced no serious side effects. Although a longer, larger trial will be necessary to determine the long-term safety and efficacy of this approach, this preliminary study suggests that, while T4 remains an excellent approach for most people with hypothyroidism, a thrice-daily dosing regimen of T3 might be a good alternative for those who continue to experience symptoms. In another advance, scientists have identified a small molecule that may be able to treat Graves' disease, the most common cause of hyperthyroidism in the United States. Current treatment choices include radioiodine therapy, surgery, or drugs that block the action of thyroid hormone but can have serious toxicity, although that would be a rare event. In Graves' disease, the immune system makes antibodies that inappropriately activate the thyroid-stimulating hormone receptor (TSHR), causing the thyroid to make too much thyroid hormone. In new research, scientists synthesized and tested several small molecules, and identified one that directly blocks thyroid-stimulating antibodies from activating the TSHR. The molecule has not yet been tested in clinical trials with people who have Graves' disease, but this exciting research has opened up a potential new approach for treatment.

Digestive Conditions and Diseases

Understanding and Treating Irritable Bowel Syndrome

The functional gastrointestinal disorder IBS causes pain and constipation or diarrhea and is especially common in women. While diet and stress contribute to this disorder, the underlying causes are unknown. Symptoms may be influenced by abnormal functioning of the intestinal nervous system and altered perception of intestinal stimuli by the brain. People with IBS have a colon that seems to respond strongly to stimuli that would not bother most individuals. A key goal for research is to understand the interplay of gut and brain pathways in these disorders and to build upon this knowledge to design effective treatments. Researchers have also been examining sex and gender differences in this interplay. Pivotal work in this area has been conducted by investigators at a Specialized Center of Research (SCOR) at the University of California, Los Angeles, cofunded by NIDDK and ORWH, which has been competitively renewed for another 5-year funding cycle. Research from this

center previously found that pain responses are heightened in women with IBS who have experienced physical abuse. More recently, scientists at the center examined other types of early adverse life events, several of which were found to have effects on the probability of IBS. Compared with controls, people with IBS reported a higher prevalence of general trauma, physical punishment, emotional abuse, and sexual events. These significant differences were mainly observed in women. Of the four events, emotional abuse was the strongest predictor of IBS. Psychological distress and somatic symptoms might also contribute to the relationship between early adverse life events and IBS. Thus, these findings suggest that, when appropriate, early adverse life events and non-gastrointestinal symptoms should be assessed in IBS patients. Encouragingly, a SCOR study with more than 100 participants found that a cognitive behavioral therapy (CBT) protocol for the treatment of IBS that directly targets visceral sensations may be particularly effective for this condition, compared with other CBT approaches not specifically focused on these sensations. Also, building upon increasing understanding of the brain-gut pathways that may be involved in IBS, researchers at the center conducted a pilot study in women with IBS of a drug targeting the substance P/neurokinin-1 receptor system, which is implicated in the regulation of both pain and anxiety. The study results indicate that chronic treatment with this drug is associated with improved mood and pain ratings and with decreased activity of brain regions related to emotional arousal, suggesting that this pathway may be a good therapeutic target in IBS. All of these findings provide hope for improved treatment strategies and outcomes for IBS in women.

Bioengineered Approaches to Treating Fecal Incontinence

In research that may have implications for future treatment for fecal incontinence, scientists have successfully implanted a physiologically functional bioengineered internal anal sphincter (IAS) in mice. The IAS is a ring-like muscle located just inside the rectum; along with the external anal sphincter, these two muscles keep the anus closed and maintain fecal continence. Loss of IAS muscle tone is a primary cause for the uncontrolled release of stool that occurs in people with fecal incontinence. Using smooth muscle cells obtained from the human IAS and nerve cells from mice, scientists bioengineered three-dimensional IAS rings. The rings were surgically implanted into a small pocket under the skin of a mouse. After allowing the bioengineered sphincters to develop for nearly 1 month, the researchers removed and examined them. They found that the IAS rings had developed an ample blood supply and nerve connections. The rings exhibited appropriate muscle tone, and relaxed and contracted in response to various chemical stimuli. All of these observations suggest that the bioengineered IAS is physiologically functional. This study is the first to demonstrate implantation of a bioengineered human IAS in a mouse in which both the muscular and nerve components were viable and responsive to stimuli. This study may be translated into a bioengineered IAS for people suffering from fecal incontinence. This would be of enormous benefit, greatly improving the daily lives of these individuals and alleviating the social and financial burdens associated with this disorder.

Kidney Disease

Switch in Sex Differences in Diabetic Kidney Disease

Kidney disease (nephropathy) is one of several serious health complications of diabetes and can ultimately lead to kidney failure, or end-stage renal disease (ESRD). Research has led to advances in diabetes management that are helping to reduce the burden of diabetic nephropathy and other complications, but these problems remain an enormous health burden. Data from earlier research indicated that, among people with type 1 diabetes, women were relatively protected from diabetic nephropathy relative to men, but more recent data have suggested that that may no longer be the case. In a new study, researchers examined kidney disease and kidney failure in two cohorts of people with type 1 diabetes distinguished by diagnosis interval (one cohort diagnosed in 1950–1964 and the other in 1965–1980). They found that in the

earlier cohort, ESRD incidence was significantly higher in men than in women with diabetes of 25 or 30 years' duration, but in the more recent cohort, incidence was higher in women. The switch reflects the fact that there was a significant overall drop in ESRD incidence in men in the more recent cohort compared with the earlier cohort (a threefold to fourfold reduction), while the reduction in incidence for women in the more recent cohort versus the earlier cohort was not significant. The reason for this dramatic switch is not yet clear, but it will be important to explore to determine whether there are specific risk factors for advanced diabetic nephropathy in women with type 1 diabetes that need to be addressed, or if more aggressive disease management is needed.

Urologic Health

Specialized Bladder Tests Before Urinary Incontinence Surgery in Women May Be Unnecessary

Results from a recent clinical trial suggest that invasive and costly tests commonly performed in women before surgery for stress urinary incontinence (SUI) may not be necessary in many cases. Millions of American women suffer from SUI, in which urine leaks from the bladder through the urethra during a physical stress, such as coughing, laughing, sneezing, or exercise. Treatment for SUI includes surgical procedures to support and compress the urethra to stop urine from leaking. Prior to surgery, many women not only receive an in-office evaluation to diagnose their incontinence, but also undergo specialized bladder function tests called urodynamic studies. These tests help assess how well the bladder, urethra, and muscles that support and compress the urethra work together to store and release urine. Similar to other in-office bladder procedures, the urodynamic tests can be uncomfortable or painful, and they can increase risk for UTI; however, they have not been proven to guide decisions about treatments or improve surgical outcomes. To test whether urodynamic studies influenced the likelihood of treatment success, researchers conducted a study in 630 women who were planning to have surgery for SUI. Women with uncomplicated urinary incontinence that was predominantly SUI were randomly assigned to receive either (1) both a preoperative evaluation in a doctor's office and urodynamic tests, or (2) the office evaluation only. One year after the surgical procedure, the researchers assessed treatment success, defined as a participant's reporting on a questionnaire that her urinary distress had been reduced by 70 percent or more, as well as reporting that her urinary tract condition had improved "much" or "very much." The researchers found that the proportion of women in whom treatment was successful was similar in the two groups (about 77 percent), with no significant differences in quality of life, patient satisfaction, or problems in voiding. While urodynamic testing did lead to changes in diagnoses for some of the women, the researchers observed that this did not lead to significant differences between the two groups in either the selection of surgical treatments or the 1-year outcomes. These results indicate that, for women with uncomplicated SUI who are receiving care from urologists and gynecologists with advanced training in bladder problems, specialized bladder function tests are not necessary to achieve surgical treatment success—information that women and their physicians can consider in planning treatment.

Cohort Studies Yield Insights into Risk for Onset and Progression of Urinary Incontinence

Although lower urinary tract dysfunction and urinary incontinence are major health concerns for women, there has been limited research on the underlying molecular mechanisms of these conditions, their epidemiology, and the clinical outcomes of treatment. For example, while an association between childbirth/delivery and risk for urinary incontinence has long been recognized, identifying whether there are specific and, in some cases, potentially modifiable parturition events (e.g., induction of labor, augmentation of labor, instrumental vaginal delivery, episiotomy, and type of anesthesia) that increase risk in later life is important for developing strategies to prevent incontinence. Investigators at a SCOR at the University of California, San Francisco, cosupported by

NIDDK and ORWH, found through a large, retrospective study that younger age at first birth, greatest birth weight (i.e., having a baby over a certain weight), and induction of labor were associated with an increased risk of urinary incontinence in later life. Another study focused on factors affecting both progression (worsening) and new onset of urinary incontinence. Through a prospective study of an ethnically diverse cohort of middle-aged and older women, investigators were able to ascertain that higher body mass index (BMI) at the beginning of the study or increased BMI at the end of the study (5 years) were significant risk factors for new onset of urinary incontinence. Regarding progression, Black women were less likely than non-Hispanic White women to experience progression of urinary incontinence, and women with chronic obstructive pulmonary disease at baseline were more likely to experience progression. Insights such as these may inform new intervention strategies to help prevent or reduce urinary incontinence in women.

Prevalence of Interstitial Cystitis/ Painful Bladder Syndrome Among Women in the United States

A large national study has provided new estimates of the burden of IC/PBS among U.S. women. IC/PBS is challenging to diagnose, and no fully effective treatment exists. In addition, robust estimates of prevalence and impact in the U.S. population have been elusive. Researchers in the Rand Interstitial Cystitis Epidemiology (RICE) study conducted a two-phase phone interview survey that involved contacting more than 146,000 randomly chosen U.S. households. An initial phone screening identified households with an adult female member reporting bladder symptoms or an actual diagnosis; this was followed by a phone questionnaire to determine whether women identified this way met study criteria for IC/PBS and, if so, to collect demographic information and determine the severity and personal impact of this condition. The criteria included both a "high-sensitivity" definition and a "high-specificity" definition of IC/PBS. The "high sensitivity" definition enabled the researchers to capture the largest number of possible cases in the survey, but it was less effective at excluding cases of pelvic pain not due to IC/PBS, whereas the "high specificity" definition could better distinguish IC/PBS from other bladder and pelvic pain conditions, but was more likely to miss some cases of IC/PBS. When the researchers applied the high specificity definition of IC/PBS to the group initially identified with the high-sensitivity definition, they estimated from their results that about 2.7 percent of adult U.S. women have symptoms consistent with IC/PBS; calculations based on the high sensitivity definition alone increased the estimate to about 6.5 percent. The researchers noted that the severity of IC/PBS among the women who met the high specificity definition was similar to that seen in women selected from urology practices to participate in clinical studies, and yet only about one in 10 of the former reported having been diagnosed with IC/PBS—suggesting that the condition may be underdiagnosed. This information provides new insight into the U.S. burden of IC/PBS and will help researchers in the design of future studies to better understand and improve treatment options for people suffering with this condition.

Insights into Interstitial Cystitis/ Painful Bladder Syndrome Emerging from Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network

The ongoing multicenter MAPP Research Network is conducting innovative, collaborative studies of the two most common urologic chronic pelvic pain syndromes: IC/PBS (in women and men) and chronic prostatitis/chronic pelvic pain syndrome (in men). Since its inception, the Network's unique approach has entailed searching "beyond the bladder/prostate" to find the causes of these conditions, including studying the possible relationships between these conditions and other chronic pain disorders, such as IBS, fibromyalgia, and chronic fatigue syndrome. Groups of patients displaying these comorbid disorders are being recruited and characterized within the current, ongoing efforts of the Network. At the same time, NIDDK is moving forward with plans for a second phase of the MAPP Research Network

once the current phase is completed. A key insight emerging from the Network thus far is the recognition of symptom "flares" in patients with these urologic pain conditions, similar to what is seen in patients with other chronic pain conditions, such as fibromyalgia. Understanding the nature of these flares and determining how they may influence clinical research studies and trials are both of high importance in future studies of possible treatment or prevention strategies for IC/PBS.

Sex-Specific Differences in Pelvic Pain of Interstitial Cystitis/ Painful Bladder Syndrome

Researchers studying IC/PBS in a rodent model have now found evidence that females experience greater pelvic pain than males, but that this disparity does not correspond to estrogen levels or differences in bladder injury. Some evidence has suggested a role for estrogen in IC/PBS pain symptoms. Researchers investigated this hypothesis in a specific mouse model of IC/PBS. In this model, irritated nerves release a chemical that activates inflammatory cells in the bladder. These inflammatory cells, called mast cells, release histamine and other chemicals that inflame the bladder lining and cause pain. This "neurogenic cystitis" model recapitulates the pelvic pain seen in human patients and is also thought to be one possible pathway for how human IC/PBS develops. Using both female and male mice, the researchers induced nerve irritation with a viral infection and then compared female and male mice for potential sex-specific differences in pelvic pain, and also examined the effects of estrogen levels and genetic background. They found that while one genetic strain of mice experienced more pain than another, female mice from either strain experienced greater pelvic pain than did male mice. However, when the scientists ablated estrogen production in some of the female mice prior to the viral infection, they found no significant differences in pelvic pain between those that had normal levels of estrogen and those that did not. Female and male mice with neurogenic cystitis also sustained similar levels of bladder inflammation and injury, making this a less likely explanation for differences in pelvic pain. These findings suggest that, in this rodent model of neurogenic cystitis, sex differences in pelvic pain exist but are not dictated by estrogen, genetic differences play a role in determining susceptibility to pelvic pain, and the two may be related. Further study of sex differences and the role of genetics in pelvic pain could have important implications for understanding IC/PBS pain in people.

Clinical Trial Shows Benefit of Specialized Physical Therapy Regimen for Women with Interstitial Cystitis/ Painful Bladder Syndrome

Results from a clinical trial suggest that a physical therapy regimen targeting muscle and connective tissue in the pelvic floor, hip, and abdominal areas could help improve symptoms in women with IC/PBS. In addition to symptoms of pelvic pain, urinary frequency, and/or urinary urgency, many women diagnosed with IC/PBS exhibit tenderness and tension in the muscle and connective tissues surrounding the pelvic area. Building on a previous study, researchers recruited 81 women with IC/PBS of less than 3 years' duration for a clinical trial to determine the benefit of specialized pelvic floor myofascial physical therapy (MPT) as compared with whole-body therapeutic massage. Participants were randomly assigned to receive up to 10 1-hour sessions of either treatment from a trained physical therapist over the course of 12 weeks. They were then asked to assess overall symptom improvement. Participants were also asked to rate outcomes for specific symptoms and issues related to their condition. The researchers found that, while the two groups reported similar improvements in bladder pain, urinary urgency and frequency, and quality of life, 59 percent of the women in the pelvic MPT group reported that their overall symptoms had moderately or markedly improved compared with when they began treatment, versus only 26 percent in the whole-body therapeutic massage group. Neither group reported a serious adverse event during treatment. With these encouraging results in hand, researchers can now pursue questions such as the durability of treatment effects and which patients are most likely to benefit from treatment, as well as other questions that can help determine whether pelvic MPT could

become a standard clinical treatment for women with IC/PBS.

Interdisciplinary Research Yields Potential New Treatment for Urinary Tract Infections

Women are especially prone to UTIs, primarily because of differences in female and male anatomy of the urinary tract. UTIs caused by *E. coli* accounted for nearly 7 million doctor visits by women in 2000, and many women suffer from frequent infections. Scientists at a recently renewed SCOR at Washington University in St. Louis, cosupported by ORWH and NIDDK, are continuing to gain insights into host and bacterial factors that contribute to UTIs. These researchers have developed a model for chronic/recurrent UTIs that relies upon the existence of intracellular bacterial communities that can protect uropathogenic *E. coli* from antibiotics, allowing these bacteria to reemerge later and cause recurrent infection. Researchers at this SCOR have reported results promising a potential new approach to antimicrobial therapy for UTIs. Specifically, these scientists have identified orally active mannoside compounds that block uropathogenic *E. coli* from binding to host bladder cells, thereby preventing new UTIs and mitigating chronic infections. Treatment of chronic and recurrent UTIs in women has become more challenging because of antibiotic resistance. This study in animal models demonstrates the potential for an alternative approach to UTI treatment, which can now move toward safety and efficacy studies in women. This study was also supported by the National Institute of Allergy and Infectious Diseases (NIAID) and by a Challenge Grant funded under the American Recovery and Reinvestment Act of 2009.

Sex/Gender Analyses—Plans, Ongoing Efforts

As noted in the Accomplishments section, NIDDK has fostered basic and clinical research that has advanced the understanding of sex/gender differences in disease areas that lie within the Institute's mission. In addition to continued sex/gender analyses in or ancillary to large-scale clinical studies, a number of new efforts will promote analysis of sex/gender differences. For example, NIDDK and ORWH cofunded a study that is using an animal model to determine the mechanisms by which Roux-en-Y gastric bypass surgery regulates intestinal satiation, food intake, and body weight; integral to this study is the testing of physiological sex differences in these three areas. A career development grant funded research to leverage observed sexual dimorphism in acute kidney injury (women are relatively protected versus men) to evaluate mechanisms of estrogen's protective action, with the hope of offering possibilities for treatment. Another career development award is focused on providing new information on sex-specific genetic influences involved in the pathophysiology of IBS pain, with the awardee being mentored by the director of the SCOR at UCLA cosupported by NIDDK and ORWH. NIDDK also plans to participate in an ORWH-led effort to provide administrative supplements for research on sex/gender differences, and it will continue to work with ORWH to identify new opportunities to promote research in this area.

FY 2011–2012 Initiatives

Requests for Applications (RFAs)

Lifestyle Interventions in Overweight and Obese Pregnant Women Consortium (U01) (RFA-DK-10-014). This RFA solicited applications to form the LIFE-Moms (Lifestyle Interventions for Expectant Moms) consortium. RFA sponsors: NIDDK, NHLBI, NICHD, and NCCAM.

Lifestyle Interventions in Overweight and Obese Pregnant Women Consortium Research Coordinating Unit (RCU) (U01) (RFA-DK-10-015). This RFA solicited applications for the Research Coordinating Unit for the LIFE-Moms consortium. RFA sponsors: NIDDK, NHLBI, NICHD, and NCCAM.

Fostering the Development of Interdisciplinary Team Science for the Study of Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) (R24) (RFA-DK-10-016). This initiative solicited interdisciplinary research teams to address critical research questions focused on IC/PBS that have translational or clinical relevance. One team supported by this initiative is exploring the

possible role of the gastrointestinal and/or reproductive tract microbiomes in IC/PBS, while the other is studying whether women with IC/PBS have global pain hypersensitivity. RFA sponsors: NIDDK and ORWH.

Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) (U01) (RFA-DK-11-026). The goal of this funding opportunity was to support the development of a cooperative research network to develop and qualify symptom-based instruments to measure early, late, transient, and persistent symptoms in both females and males, and to better define the phenotypes of women and men with symptoms of lower urinary tract dysfunction. The goals outlined in this funding initiative were developed, in part, based on discussions at the 2011 NIDDK Meeting on Measurement of Urinary Symptoms (MOMUS) that was co-led by ORWH. RFA sponsor: NIDDK.

Expansion of Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) (U01) (RFA-DK-12-017). This RFA solicits additional sites to join the LURN Research Network investigators to expand on its efforts. The key responsibilities of the added research sites and of the expanded data coordinating center will be to adopt the study protocols developed by the LURN investigators, validate the developed patient-reported outcome measures, recruit study participants, and conduct extensive characterization (phenotyping) of these persons. RFA sponsor: NIDDK.

Planning Centers for Interdisciplinary Research in Benign Urology (IR-BU) (P20) (RFA-DK-12-003). The intent of this solicitation is to encourage studies that take an integrative approach in addressing basic problems in benign urology in order to advance understanding of symptomatic benign urological disorders. Urological disorders of specific interest are those that produce lower urinary tract symptoms, including lower urinary tract symptoms associated with benign prostate hyperplasia, urinary incontinence, overactive bladder, urinary tract infection, vesicoureteral reflux, and neurogenic bladder. RFA sponsor: NIDDK.

Limited Competition for the Continuation of Look AHEAD (Action for Health in Diabetes) Consortium (U01) (RFA-DK-12-502). This RFA invited cooperative agreement (U01) applications from investigators currently participating in the Look AHEAD Consortium to allow an additional 2-year follow-up period of all currently enrolled participants. RFA sponsors: NIDDK and NHLBI.

Program Announcements (PAs)

Translational Research to Improve Obesity and Diabetes Outcomes (R18) (PAR-12-172). This PA encourages NIH Research Demonstration and Dissemination Project grant (R18) applications to test practical, sustainable, acceptable, and cost-efficient adaptations of efficacious strategies or approaches to prevent and treat diabetes and/or obesity. Research must target the prevention or reversal of obesity, prevention of type 2 diabetes, improved care of type 1 and type 2 diabetes, or the prevention or delay of the complications of these conditions. The approaches tested should have the potential to be widely disseminated to clinical practice and to individuals and communities at risk. PA sponsor: NIDDK.

NIDDK also participated in:

- Role of Environmental Chemical Exposures in the Development of Obesity, Type 2 Diabetes and Metabolic Syndrome (R01) (PAR-11-170)
- Role of Environmental Chemical Exposures in the Development of Obesity, Type 2 Diabetes and Metabolic Syndrome (R01) (PA-12-185)
- Specialized Centers of Research (SCOR) on Sex Differences (P50) (RFA-OD-11-003)
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment (R01) (PAR-12-032)
- Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers (Administrative Supplement) (PA-12-150)

Conferences and Workshops

Meeting on Measurement of Urinary Symptoms (MOMUS), November 14–15, 2011. Symptoms of lower urinary tract dysfunction (LUTD) are common in women and men. Both incidence and prevalence rates increase with age; consequently, treatment costs pose a major financial challenge in the United States. There is a need for a symptom measurement tool, better than what is currently available, that would focus on patient-reported outcomes to quantify early, late, transient, and persistent symptoms of LUTD in both women and men. The goal of this meeting was to increase discussion about this topic among various populations with different expertise: urologists, patients, other clinicians, researchers, industry, advocacy groups, and government agencies such as the U.S. Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Agency for Health Care Research and Quality. ORWH co-led this meeting. The report is available at *http://www3.niddk.nih.gov/fund/other/MOMUS.pdf*.

Strategic Planning

Diabetes Research Strategic Plan. A new strategic plan for diabetes research, "Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee (DMICC)," was released in February 2011. NIDDK spearheaded the development of this plan in its role as chair of the statutory DMICC. The plan was developed through a collaborative process involving multiple Federal agencies and the external research and patient advocacy communities, as well as past and current members of NIDDK's Advisory Council. A broad array of research opportunities was identified, spanning basic, clinical, and translational research. Research opportunities related to women's health are highlighted throughout the plan, including research on hyperglycemia and diabetes during pregnancy and research to understand sex/gender differences in fat patterning and its effect on diabetes risk. The Strategic Plan is meant to serve as a guidepost for federally supported diabetes research at NIH and other agencies for the next decade. The plan is available at *http://diabetesplan.niddk.nih.gov*.

Obesity Research Strategic Plan. The NIH released its second Strategic Plan for NIH Obesity Research in March 2011. The plan was developed by the NIH Obesity Research Task Force, on which NIDDK plays a leadership role. Highlighting the crucial role of research in efforts to reduce obesity, the plan, which had input from internal and external researchers, health care professionals, and the public during its creation, emphasizes moving science from the laboratory to clinical trials to practical solutions, and is designed to help target efforts and resources in areas most likely to help. Several research opportunities cited in the plan are especially relevant to women, including investigation of factors related to excess weight gain associated with critical periods and life events, such as fetal exposures in utero, infancy, childhood, puberty, adolescence, young adulthood, pregnancy/postpartum period, entry into the workforce, marriage, parenting, menopause, older age, and retirement; identifying factors that may be unique to a specific point in the lifespan could provide important insights for the development of interventions. The plan is available at *http://obesityresearch.nih.gov/about/strategic-plan.aspx*.

Information and Education Initiatives

NIDDK continues to support a number of education and awareness campaigns that are important to women's health, including the following efforts:

The NDEP Post-GDM Awareness Campaign, part of the "Small Steps, Big Rewards. Prevent Type 2 Diabetes" Campaign. The National Diabetes Education Program (NDEP) has been working with partner organizations and leveraging social media tools such as Facebook and Twitter and media outlets such as mommy/parenting blogs and publications to provide messages, tools, and educational materials to raise awareness of the lasting impact of GDM on the health of women with a history of GDM and their children, and steps mothers can take to help lower health risks for themselves and their

children. In observance of Mother's Day and National Women's Health Week, in May 2012, NDEP also coordinated and executed a webinar titled "Promoting Health After Gestational Diabetes." This webinar featured the Chief Scientific and Medical Officer for the American Diabetes Association, which helped to promote the webinar (*http://ndep.nih.gov/am-i-at-risk/gdm*).

The Weight-control Information Network (WIN) program "Sisters Together: Move More, Eat Better." In FY 2011–2012, the Sisters Together program continued its efforts to develop and promote relevant tools and tips that help African-American women and their families get more physical activity and select healthier foods. For example, Sisters Together partnered with more than 1,000 hair salons in Washington, D.C., Illinois, New York, and Pennsylvania to distribute the program's brochure series and salon flyer, and developed and sent out 100 "Get Fit by Faith" church tip sheets to African-American churches in Washington, D.C., Florida, Georgia, Virginia, and Tennessee. The program also worked with "Urban Housecall" magazine, "BlackDoctor.org," "Black Health," and "Upscale" magazine to promote core messages; in December 2011, "Urban Housecall" published a feature article from Sisters Together on its Web site and in its magazine. Sisters Together conducted additional media outreach with the North American Précis Syndicate, which featured an article from the program encouraging older African-American women to practice better health habits during spring 2011. Sisters Together also continued to work with its core partners to promote program messages (*http://win.niddk.nih.gov/sisters/index.htm*).

New information and education initiatives and related efforts include the following:

NIDDK Bowel Control Awareness Campaign. In June 2011, NIDDK launched the Bowel Control Awareness Campaign. This campaign is based on recommendations of the panel of experts convened for the NIH State-of-the-Science Conference on Prevention of Fecal and Urinary Incontinence in Adults held in December 2007 to raise public awareness of incontinence and the benefits of prevention and management. Through its resources (available at *http://www.bowelcontrol.nih.gov*), the campaign continues to raise awareness, with the aim of improving the lives of women and men living with this condition.

Weight of the Nation: To help address questions surrounding the obesity epidemic in the United States, to review possible strategies for reversing this national health problem, and to present the science of obesity and NIH's efforts to combat the obesity epidemic, NIDDK, other NIH Institutes, and NIH leadership collaborated with HBO (Home Box Office) and major research and health organizations to develop "The Weight of the Nation," a documentary series and public education initiative that spotlights this urgent public health problem. The project consists of four documentary films that originally aired on HBO in May 2012; a 3-part series for families; 12 short films, including one about NIH; and a nationwide community-based outreach campaign. For more information, visit the HBO Web site (*http://theweightofthenation.hbo.com*) and the NIH project Web site (*http://www.nih.gov/health/NIHandweightofthenation*).

Health Disparities/Special Populations (Research or Other Efforts)

Several of the diseases that disproportionately affect racial and ethnic minority populations in the United States are high priority research areas for NIDDK. Some of these diseases, such as obesity and gallbladder disease, also affect women and men differently within these disproportionately affected groups. The NIDDK Office of Minority Health Research Coordination (OMHRC) oversees the Institute's efforts to address these disparities. In addition to developing and overseeing an NIDDK Strategic Plan on Minority Health Disparities, OHMRC has established and supports the Network of Minority Health Research Investigators (NMRI), a communication network of biomedical research investigators and technical personnel from traditionally underserved communities: African-Americans, Hispanic Americans, American Indians, Alaska Natives, Native Hawaiians, and other Pacific Islanders.

OHMRC also promotes NIDDK and NIH research training programs that help promote diversity in the biomedical research community. OHMRC held the 9th and 10th annual NIDDK NMRI Workshops in 2011 and 2012, respectively. For more information, visit the OHMRC Web site at *http://www2.niddk.nih.gov/OMHRC/OMHRCHome/OMHRCHome.htm.*

Several major NIDDK-supported research efforts pertain to health disparities in women. For example, the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (DPP/DPPOS) and TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study cohorts, which have more females than males, are highly ethnically and racially diverse, reflecting the disproportionate burden of diabetes in racial and ethnic minority girls and women. The composition of study populations in the new LIFE-Moms consortium also reflects the burden of obesity/postpartum weight retention in women from racial and ethnic minority populations in the United States. Historically, NIDDK has also supported numerous individual studies addressing health disparities in women and girls of color. New studies include a study to develop and test the long-term efficacy of an Internet-based weight control program tailored for a multiethnic population of low-income postpartum mothers enrolled in the Women, Infants, and Children (WIC) program; a study investigating whether there are inherent differences in skeletal muscle in African-American women compared with Caucasian women that result in impaired fat oxidation and accumulation of lipid and lipid metabolites within the skeletal muscle of African-American women, contributing to the development of obesity, insulin resistance, and type 2 diabetes in African-American women; and a study to explore racial/ethnic, socioeconomic, and educational-level disparities in treatment-seeking behavior for urinary incontinence over time using 10 years of annual questionnaire and physical measures data from the Study of Women's Health Across the Nation (SWAN), a multiracial/multiethnic, community-based, prospective cohort study of women transitioning through menopause. NIDDK's intramural research program (IRP) also supports projects highly relevant to health disparities in women, such as a study of differences in fat metabolism between African-American and Caucasian women that could explain differences in vascular disease and other health issues, and studies of obesity and GDM in Pima Indian women conducted through IRP participation in DPPOS, Look AHEAD, and LIFE-Moms and through other efforts.

In addition to support for pertinent "Information and Education Activities" described previously, the communications activities of NIDDK that are important to health disparities in women include providing many of its health information publications in Spanish, and some in multiple languages, and having bilingual staff at the information clearinghouses to assist with telephone orders from Spanish-speaking requestors. New publications in the Institute's "Awareness and Prevention" series, which are distributed as one-sheet flyers in English on one side and Spanish on the other, include "Bowel Control Problems: What You Need to Know"; "Overactive Thyroid: What You Need to Know"; and "Underactive Thyroid: What You Need to Know."

Career Development

NIDDK cosponsors the initiative spearheaded by ORWH to support the re-entry of women and men into biomedical and behavioral research careers after a hiatus due to life events such as child rearing and family caregiving. The NIDDK Director is also a member of the NIH Working Group on Women in Biomedical Careers.

Supporting Implementation of the NIH Strategic Plan for Women's Health Research

(1) **Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Follow-up Study (FUS)**

Participating Institutes: NIDDK and NICHD

Strategic Plan Goals and Objectives:

Goal 3—Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women

Top objective:

- 3.4. Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

Other objectives:

- 3.2. Study sex/gender differences in embryonic development, including epigenetic changes.
- 3.5. Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

(2) **LIFE-Moms (Lifestyle Interventions for Expectant Moms)**

Participating Institutes/Offices: NIDDK (lead), NHLBI, NICHD, NCCAM, ORWH, and OBSSR

Strategic Plan Goals and Objectives:

Goal 3—Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls And Women

Top objective:

- 3.3. Encourage research on safe and effective interventions for conditions affecting pregnant women.

Other objectives:

- 3.4. Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

(3) **Sex-Specific Differences in Pelvic Pain of Interstitial Cystitis/Painful Bladder Syndrome**

Participating Institute: NIDDK

Strategic Plan Goals and Objectives:

Goal 1—Increase Sex Differences Research in Basic Science Studies

Top objective:

- 1.4. Include sex parameters in the design of experiments using animal models.

(4) **Interdisciplinary Research Yields Potential New Treatment for Urinary Tract Infections**

Participating Institutes: NIDDK, ORWH, NIAID

Strategic Plan Goals and Objectives

Goal 2—Incorporate Findings of Sex/Gender Differences in the Design and Application of New Technologies, Medical Devices, and Therapeutic Drugs

Top objective:

- 2.7. Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

National Institute on Drug Abuse

Executive Summary

As the foremost authority on drug abuse and addiction, sponsoring the vast majority of the world's research on the subject, the National Institute on Drug Abuse (NIDA) supports science that addresses the most fundamental and essential questions about drug abuse. We do this by monitoring emerging trends, identifying and studying underlying biological and social factors and consequences, and by determining how best to use this knowledge to develop, test, and implement prevention and treatment programs.

Within NIDA's mission is a focus on studying issues specific to women and identifying and studying sex/gender differences. Over the past two decades, research has shown that there are male-female differences in the initiation and progression of drug use and addiction as well as in the risk and protective factors and the consequences of drug abuse; similarly, research has shown that intervention outcomes may be enhanced by sex/gender-specific considerations. In recognition of the important role of sex/gender differences in drug abuse, NIDA continues its commitment to support research to identify sex/gender-specific aspects of drug abuse and addiction across the lifespan and apply these findings to improve outcomes for both males and females.

This FY 2011–FY 2012 biennial report describes NIDA's organizational leadership on women and sex/gender differences research and provides highlights of our research advances and activities to promote further research in this area. Among the research advances are basic and clinical neuroscience studies that have shed light on sex differences in biological and behavioral mechanisms and the consequences of addiction. A recurring theme in both our preclinical and clinical studies is research aimed at gender-based treatments for addictions, both behavioral and pharmacologic. Gender-based treatment discovery and development is the major emphasis in NIDA's three newly funded grants in ORWH's third round of funding of its Specialized Center of Research (SCOR) on Sex Differences program. Another recurring theme in our research advances is the use of brain-imaging techniques that are revealing sex differences in both clinical and preclinical studies and are revealing sex differences in basic mechanisms of addiction and providing clues on treatment strategies.

An area in which significant and much-needed progress has been made is research on drug use in pregnancy. Research continues to reveal consequences of prenatal drug exposure on the child, consequences that often vary by gender. Preclinical data has shown that paternal drug use also has consequences for the offspring in the absence of any direct fetal exposure. This emerging area of research suggests that exposure to drugs of abuse produces transmissible epigenetic effects (i.e., modifications in gene expression) that result in profound changes in the physiology and behavior of offspring. On the positive side, researchers are finding effective behavioral and pharmacologic treatments for drug-addicted pregnant women, treatments that also produce positive outcomes for their babies. And studies are also showing how to improve screening in the doctor's office for prenatal substance use.

For premenopausal women, progress has been made in identifying the best phase of the menstrual cycle in which to initiate smoking cessation. Female-specific studies have also identified health consequences of drug addiction in adolescent girls. And NIDA's HIV/AIDS research has identified important male-female differences among drug users who are HIV+ as well as effective gender-based interventions to reduce HIV risk behavior.

Collectively, these and other research advances described in the following pages continue to provide evidence for the importance of research that is specific to women and the importance of taking a sex/gender-based research approach and analyzing data separately for males and females. Ultimately, identification and understanding of sex/gender differences can have implications for tailoring prevention and treatment interventions that will optimize outcomes for both males and females.

Almost all of NIDA's scientific advances highlighted in this report reflect the goals of the NIH Strategic Plan for Women's Health Research (*http://orwh.od.nih.gov/research/strategicplan/index.asp*). The advances largely fall under Goal 1: Increase Sex Differences Research in Basic Science Studies, or Goal 3: Actualize Personalized Prevention, Diagnostics, and Therapeutics for Girls and Women.

Women & Sex/Gender Differences Research Program

NIDA's Women and Sex/Gender Differences Research Program coordinator and deputy coordinator, along with NIDA's Women & Sex/Gender Research Group (WGRG), lead the scientific effort at NIDA to promote research that is specific to women and that investigates sex/gender differences in drug abuse. The WGRG has members from all of NIDA's divisions and offices, representing research areas that span from molecular biology and genetics to risk and protective factors, prevention, consequences, and treatment and services for drug abuse; members are also involved in the dissemination of research findings. The overarching goal of NIDA's Women and Sex/Gender Differences Research Program, which has been going on for over two decades, is to infuse the study of sex/gender differences and female-specific issues into all areas of drug abuse research and to disseminate resultant findings.

NIDA's Women and Sex/Gender Differences Research Program coordinator and deputy coordinator represent NIDA on the ORWH Coordinating Committee on Research on Women's Health and partner with ORWH in various ORWH programs. They also serve as liaisons and committee members in activities with NIH ICs, the HHS Office on Women's Health and other HHS agencies, and the White House as well as scientific organizations.

Accomplishments

Basic Neuroscience

Sophisticated behavioral and neurobiological animal models of addiction are helping researchers to better understand the nature of the addiction process, the factors that affect it, and the consequences of drug exposure and drug addiction. For over two decades these models have provided a growing body of research revealing sex differences in drug abuse. In cocaine self-administration studies, for example, a greater percentage of females than males acquire intravenous self-administration, they acquire it more rapidly and escalate more quickly to high levels of intake, and they exhibit greater motivation for cocaine. In an animal model of relapse, sex differences also are seen that depend upon the stimuli that induce relapse. Illustrative recent findings of sex differences are described below.

Differences in the Relationship Between Cocaine Reinforcement and Dopamine D2/D3 Receptor Function in Female and Male Monkeys. As was previously observed in a study with male monkeys, the availability of dopamine D2/D3 receptors, measured via PET (positron emission tomography) imaging, significantly increased in female monkeys that became dominant in a comparison with those who became subordinate. In contrast to what was previously found in males, the dominant female monkeys, those with the higher D2/D3 receptor levels, were more vulnerable to cocaine reinforcement than were the subordinate monkeys. These data indicate that the social environment profoundly affects the dopamine system, but it does so in a manner that has opposite effects on cocaine reinforcement for females and males. (Goal 1, Objectives 1.4, 1.5, 1.8; Goal 2, Objective 2.6.)

Females Are More Sensitive than Males to Stress-Activated Relapse to Cocaine Seeking Produced by Cocaine-Paired Cues. Stress and environmental cues play powerful roles in triggering relapse in cocaine addiction. Biological differences in the brain reward and stress pathways can lead to different patterns of relapse in males and females. Further, data suggest that females may be more prone to relapse during specific phases of the ovarian hormone cycle. In an animal model of cocaine addiction and relapse, researchers examined in male and female rats their risk of relapse produced by cocaine-paired cues or the stress-activating drug yohimbine, or a combination of the cues and the drug. Females showed greater cocaine seeking than did males when stress and cues were combined, with the highest level of response seen during the proestrus phase of the estrous cycle. This cycle-dependent sensitivity to stress enhancement of cocaine-paired cues suggests that women may be more vulnerable to relapse trigger factors during certain phases of their menstrual cycle. (Goal 1, Objectives 1.4, 1.5; Goal 3, Objective 3.1.)

Social Stress Produces Greater Behavioral and Neural Responses to Cocaine in Female as Compared to Male Rats. Clinical research has found gender differences in the effects of stress on various aspects of drug dependence, with effects generally stronger in women than in men. In a preclinical model of social stress in rodents, researchers examined sex and estrous cycle differences in rats exposed to episodic social defeat stress and their relationship to behavioral and neural responses to cocaine. Social defeat stress resulted in behavioral and dopaminergic increases in both sexes, but the effect was larger and longer lasting in stressed females. Furthermore, while stress engendered a longer cocaine "binge" in both sexes, females had significantly longer binges than males. These data suggest that socially stressed females exhibit larger and longer increased sensitivity to the behavioral and neural effects of cocaine, and a more dysregulated cocaine taking, than males. The results also suggest that estrogens play a facilitatory role in both behavioral

and dopaminergic sensitization. (Goal 1, Objectives 1.4, 1.5; Goal 3, Objective 3.1)

The Sons, But Not the Daughters, of Rat Fathers Exposed to Cocaine Inherit Resistance to Cocaine. There is a large body of preclinical research on maternal exposure to drugs during pregnancy and effects on the offspring, whereas little research attention has been paid to the role of paternal drug abuse. In a recent study, investigators trained male rats to self-administer cocaine for 2 months. Afterwards, the males were mated to cocaine-naïve females, and the offspring were tested for their willingness to self-administer cocaine. The male offspring took less cocaine than did the female offspring and were less willing to work hard for the cocaine. To determine possible mechanisms for the sex difference in this transgenerational effect, the researchers looked for epigenetic changes. Epigenetic changes alter the ability of specific genes to be transcribed while leaving the underlying genetic code intact, and in some cases they can be inherited across generations. The researchers found epigenetic changes in the brains of the male, but not the female, offspring that increased the level of brain-derived neurotrophic factor (BDNF) in the prefrontal cortex (PFC). These same epigenetic changes were observed in the sperm of cocaine-exposed fathers, and they were apparently passed on to their sons. In an earlier study, the investigators had shown that BDNF in the PFC blunts the effects of cocaine, which can explain why the males were resistant to cocaine, although further studies will be needed to understand why the females did not inherit these same epigenetic alterations. The study of epigenetics is very new, but it is already promising to reveal new mechanisms by which males and females can be affected differently by similar environmental exposures or can inherit different traits from their parents. (Goal 1, Objectives 1.4, 1.5; Goal 3, Objective 3.2)

Basic Neuroscience: Sexual Dimorphism in Responses to Opioids

NIDA is the second largest funder of pain research at NIH and supports a large portfolio of grants studying opioids and the opioid system. It is becoming increasingly clear from both clinical and preclinical research that males and females do not respond similarly to opioids and that studying only males and extrapolating the results to females can be very misleading and is no longer adequate. During FY 2011 and FY 2012, important preclinical advances in understanding molecular determinants of sexual dimorphism in nociception, opioid antinociception, and opioid tolerance and dependence were made by Dr. Alan Gintzler and his collaborators at SUNY Downstate Medical Center (Brooklyn, NY) using an animal model. Together these studies, which are described below, emphasize the importance of including both males and females in animal models and point to possible sex-based approaches to pain management.

One study conducted by Gintzler and associates investigated the importance of estrogen and rapid signaling by membrane estrogen receptors to the heterodimerization of kappa-opioid receptors (KOR) and mu-opioid receptors (MOR). These heterodimers (KOR/MOR) are 4 to 5 times as prevalent in the spinal cord of proestrus females as in diestrus females or males. The researchers identified two critical molecular determinants of spinal KOR/MOR, spinally synthesized estrogen (via aromatase), and the activity of all three major types of membrane estrogen receptors (a, b, GPR30). This study suggests that KOR/MOR is a molecular switch that shifts the function of KOR and thereby endogenous dynorphin from pronociceptive (mediated by monomeric KOR) to antinociceptive (mediated by KOR/MOR). Pharmacological interventions that promote KOR/MOR formation could be a novel approach for pain management in women. (Goal 1, Objectives 1.4, 1.5; Goal 3, Objective 3.1)

A second study by these investigators demonstrates that it is not only imperative to include females in all studies of KOR antinociception but also critical to study multiple nociceptive modalities, as sex differences can be modality specific. In one pain test (intraperitoneal acetic acid-induced writhing test), release of spinal dynorphin and KOR activation produced antinociception only in females. In contrast, in the intraplantar formalin-induced paw flinch test, dynorphin

and KOR antinociception occurred only in males. These findings emphasize the importance of using both sexes and multiple pain models when investigating dynorphin/KOR antinociception. (Goal 1, Objectives 1.4, 1.5)

A third study by Gintzler and colleagues at SUNY Downstate showed that sexual dimorphism also extends to mechanisms underlying opioid tolerance and opioid withdrawal. Males and females differentially use spinal endomorphin 2 to cope with opioid withdrawal. In spinal cord tissue of male rats withdrawn from opioids, MOR signaling via stimulatory G protein (Gs) is augmented. This is causally associated with increased release of endomorphin 2, which enables endomorphin 2 to substitute for morphine following its precipitous removal. Strikingly, in the spinal cord of females, this adaptation is missing. Females use alternative spinal coping strategies that are yet to be determined. The predominance of MOR Gs-coupled facilitative modulation of endomorphin 2 release from withdrawn spinal tissue of males, but not females, suggests that the clinical management of opioid dependence in women would benefit (more than it would in men) from adjunctive pharmacotherapies that enhance the release of spinal endomorphin 2. (Goal 1, Objectives 1.4, 1.5, 1.7)

Clinical Neuroscience

NIDA's clinical neuroscience program is shedding light on the understanding of male-female differences in the response to abused drugs and the etiology and consequences of drug use and addiction, work that can potentially lead to gender-based prevention and treatment strategies. Highlighted below are studies on biological and behavioral mechanisms of male-female differences in smoking, a cocaine study suggesting that differential treatment approaches may work best for males and females, and a study of differential brain changes in male and female adolescent marijuana users.

Brain-Imaging Studies Reveal Sex Differences in Neurotransmitter Function in Tobacco Smokers. Sex differences have been reported in the reinforcing effects of nicotine, smoking cessation rates, and response to nicotine therapies. Possible neurobiological contributions to these and other sex differences in smoking are suggested by two recent studies that found sex-specific effects in brain neurotransmitter systems involved in smoking.

In the first study, researchers used PET imaging to examine brain receptors for dopamine (D), which is a key neurotransmitter involved in drugs of abuse. These investigators compared D2/D3 dopamine-receptor availability in light smokers and nonsmokers in brain regions associated with addictive aspects of drugs of abuse. Male smokers had significantly lower D2/D3 dopamine-receptor availability than female smokers and male nonsmokers, whereas female smokers did not differ from nonsmokers. These sex-related differences in dopamine-system function may play a role in observed clinical differences in smoking outcomes in males and females. (Goal 1, Objective 1.5; Goal 2, Objective 2.6)

In the second study, using magnetic resonance imaging, sex differences were observed in the availability of nicotinic acetylcholine receptors containing the β(2) subunit (β(2)*-nAChRs) in recently abstinent smokers. β(2)*-nAChRs mediate the primary reinforcing effects of nicotine. The researchers found that β(2)*-nAChR availability was significantly higher in male smokers than in male nonsmokers in specific brain areas; this difference was not found in females in any region. In females, β(2)*-nAChR availability in certain brain areas was negatively and significantly correlated with the level of progesterone. In female smokers, the progesterone level was positively and significantly correlated with depressive symptoms, craving for a cigarette, and nicotine withdrawal. These findings suggest an underlying neurochemical mechanism for the reported behavioral sex differences in smoking, with female sex steroid hormones likely playing a role, and also suggest that effective treatment of female smokers may need to involve non-nicotinic-mediated medications. (Goal 1, Objective 1.5; Goal 2, Objective 2.6; Goal 3, Objective 3.1)

Gender Differences in Craving and Reactivity to Smoking Cues and Negative Affect/Stress Cues. A potential contributory

factor in the lower smoking cessation rates seen in women compared with men may be male-female differences in craving and stress reactivity to smoking-related cues and negative affect/stress-related cues. This possibility was investigated in a study of the effects of gender on reactivity to smoking cues and negative affect/stress cues by exposing nicotine-dependent smokers to those two cue types, after which participants provided subjective reports of smoking-related craving and affective reactions. Women reported greater craving, gave higher stress and arousal ratings, and reported greater negative emotion in response to the negative affect/stressful cues. There were no gender differences in responses to smoking cues. These findings suggest that smoking cessation strategies that include stress reduction strategies may be particularly helpful for women. (Goal 1, Objective 1.5)

Stress and Drug Cues Affect Brains Differently in Men and Women Cocaine Users. A neuroimaging study of cocaine-dependent individuals found male-female differences in response to cues for stress and cues for drugs. As cues, researchers used recordings in which the participant had previously described memories involving stress, drugs, or relaxation. Among women, in response to stress cues but not drug cues, those with cocaine dependence had a greater increase in activity in the brain's reward pathway and emotion circuits than those in a comparison group who reported recreational drinking but no illicit drug use. In contrast, for men in the cocaine dependence group but not in the comparison group, drug cues but not stress cues elicited hyperactivity in these areas. There was no difference between men and women in response to a cue describing a relaxing experience. Both men and women with cocaine dependence demonstrated greater activation of the brain regions than participants in the comparison group. Among all the participants with cocaine dependence, measures of drug-induced craving correlated with activation of the reward pathway and emotion circuits. These findings suggest that therapies that emphasize stress reduction, such as mindfulness-based stress reduction approaches, might be particularly beneficial for women, whereas behavioral therapies focusing on responses to drug cues may be particularly beneficial for men. (Goal 1, Objective 1.5; Goal 2, Objective 2.6)

Sex Differences in Amygdala Morphometry in Adolescent Marijuana Users. NIDA's annual Monitoring the Future Survey found that marijuana use among 12th-graders has been on the rise over the past several years. Beginning in 2010, marijuana use has been higher than cigarette use among 12th-graders. Research is showing that adolescence represents a period of increased vulnerability to the neurobehavioral consequences of marijuana use and that the amygdala may be a brain site that is particularly sensitive to marijuana exposure. In a recent NIDA study, the relationship between amygdala volume and internalizing symptoms was examined in male and female teenage chronic marijuana users and nonmarijuana user controls ages 16–19 years, excluding those with psychiatric or neurologic disorders. Substance use, internalizing (anxiety/depression) symptoms, and brain scans were collected after 28 days of monitored abstinence. Female marijuana users had larger right amygdala volumes and more internalizing symptoms than female controls, an outcome unrelated to head size, alcohol, or nicotine and other substance use, whereas male users had similar volumes as male controls. These sex-based outcomes may reflect marijuana-related interruptions to sex-specific neuromaturational processes and staging and suggest that subtle amygdala development abnormalities may underlie particular vulnerabilities to subdiagnostic depression and anxiety in teenage female marijuana users. (Goal 1, Objective 1.5; Goal 2, Objective 2.6)

Drug Abuse Risk Factors: Variability by Gender

NIDA's research has shown that drug use by males and females may begin and progress differently in the two genders and is often characterized by different risk and protective factors. Identifying these gender-based factors is important for designing tailored prevention programs for males and females and could have treatment implications as well. Selected recent advances described below point to risk factors for drug abuse that

operate differently for males and females, including childhood abuse, lifetime adversity, behavioral inhibition, and perceived racial discrimination.

Sex Differences in Disinhibition and Its Relationship to Physical Abuse in a Sample of Stimulant-Dependent Patients. Research suggests that childhood abuse increases impulsivity and that impulsivity increases vulnerability to developing stimulant dependence. Behavioral disinhibition, which is an aspect of impulsivity, has been found in prospective studies to predict substance use. Using data from NIDA's Clinical Trial Network, researchers examined the relationship between disinhibition and stimulant abuse and the role of childhood abuse in both males and females. They used the Frontal Systems Behavior Scale to assess disinhibition and the Addiction Severity Index to define lifetime physical abuse. A significantly greater proportion of women than men reported clinically significant disinhibition prior to initiation of stimulant abuse. Physical abuse in women, but not men, was associated with worse functioning, and a greater proportion of physically abused (relative to nonabused) women showed clinically significant disinhibition. These findings suggest that women may have significantly greater disinhibition than men prior to initiation of stimulant abuse and that physical abuse in women is associated with greater disinhibition. These data have implications for identifying targets for drug abuse prevention and interventions, especially for women. (Goal 1, Objective 1.5)

Association Between Adverse Life Events and Addictive Behaviors Among Urban Male and Female Adolescents, Primarily African-American. Adverse life events have been associated with addictive behaviors, both substance use and gambling. A recent study explored potential male-female differences in the association between self-report of addictive behavior and adverse life events among 515 urban, primarily African-American, adolescents. Adverse life events were classified in three categories:

(1) Relationship life events (e.g., family death, the loss of a friend);

(2) Violence life events (e.g., seeing someone stabbed, being beaten up); and

(3) Instability life events (e.g., getting evicted from home, parent losing a job).

For both males and females, adverse life events and engaging in at least one addictive behavior were common. Substance users and gamblers had more than twice the likelihood of nonsubstance users and nongamblers of experiencing any adverse life event as well as events in each of the three categories. Females exposed to violence events were significantly more likely than similarly exposed males to report the cooccurrence of substance use and gambling. Although the study could not determine which came first, the violence or the addictive behaviors, these results emphasize the need to focus more attention on the development of effective programs that teach adaptive coping strategies to adolescents, particularly females, upon exposure to violence. (Goal 1, Objective 1.5)

Perceived Discrimination and Longitudinal Increases in Substance Use Among Rural African-American Adolescents: Gender Differences and Mediational Pathways. Recent epidemiologic data indicate that African-American adolescents in rural areas are engaging in substance use at rates equal to or exceeding those of youth who live in densely populated inner cities. In a recent prospective study of African-American youth in rural Georgia, researchers found that for male but not female youth, perceived discrimination was significantly related to increases in substance use. This association was mediated by the contribution of perceived discrimination to both decreases in school engagement and increases in affiliations with substance-using peers. Importantly, results indicated that discrimination influenced substance use rather than vice versa. This study highlights the need to tackle discrimination issues in conjunction with robust substance-use prevention initiatives, as well as the importance of having gender-based public health campaigns that address risk factors for substance use. (Goal 1, Objective 1.5)

Drug Abuse and Health Among Adolescents: Gender Matters

Drug use is associated with untoward outcomes for adolescent users in many aspects of their life: academically, emotionally, relationally, legally, professionally, and elsewhere. Drug use also is often associated with negative health outcomes. Selected recent examples described below report relationships between drug use and sexually transmitted diseases, bone health, and mental health.

Drugs Contribute to High Rates of Sexually Transmitted Diseases Among Juvenile Offenders. In a study of 948 newly arrested youth undergoing criminal justice intake processing in Tampa, FL, more than 19 percent of girls and 11 percent of boys tested positive for chlamydia, gonorrhea, or both infections. Correlations were found between the youth's prevalence of these sexually transmitted diseases (STDs) and their cocaine and marijuana use, as confirmed by urine tests. Responses of the youth to a survey provided additional evidence of a prominent role for drug abuse as a risk factor for STDs. Sexual activity while using noninjected drugs was, at 8 percent, the second most commonly reported risk factor among boys and, at 9 percent, the third most common among girls. The primary STD risk factor for both sexes, at 21 percent for boys and 24 percent for girls, was heterosexual intercourse without a condom; the second most common for girls, at 10 percent, was sexual assault. Among youth who tested positive for an STD, 66 percent of the girls and 57 percent of the boys were released back into the community after arrest. Overall, these findings raise serious public health and social welfare concerns for both the youth and the community. The researchers concluded that universal, voluntary STD testing for newly arrested juveniles, with treatment follow-up for STD-positive cases, seems to be seriously needed, especially for youth released to the community. (Goal 1, Objectives 1.5, 1.6)

Smoking Affects Bone Health in Adolescent Girls. Osteoporosis is primarily evident in postmenopausal women, but its roots are traceable to periods of growth, including during adolescence. In adults, lower bone mineral density (BMD) is associated with smoking, depression, and anxiety. Recently these associations were studied longitudinally in girls across adolescence, the period in which more than 50 percent of bone accrual occurs. Bone accrual was examined in 262 healthy girls who were enrolled in age cohorts of 11, 13, 15, and 17 years. Higher-frequency smoking was associated with a lower rate of lumbar spine and total hip BMD accrual from age 13 to 19. Higher depressive symptoms were associated with lower lumbar spine BMD across the span of 11 to 19 years of age. There was no effect of depressive symptoms on total body bone mineral content, and there was no effect of alcohol intake on any bone outcome. These findings highlight the importance of targeting females for smoking interventions, both prevention and treatment. (Goal 3, Objective 3.1)

Associations Between First Use of a Substance and Change in Internalizing Symptoms Among Girls. Among girls, is initial use of alcohol, cigarettes, and marijuana related to changes in depressive, generalized anxiety, and social anxiety symptoms? Do these substances "medicate" these symptoms or do they exacerbate them? These questions were addressed in the Pittsburgh Girls Study, a community-based study of girls (52 percent African-American, 41 percent Caucasian) who were assessed at ages 5 to 8 and followed for 6 years. The study found that for girls on a "high-depressive symptom" trajectory, initial use of marijuana was related to further increases in depressive symptoms. Initial use of alcohol was related to increases in social anxiety among girls experiencing increasing levels of social anxiety, but it was related to decreasing levels of social anxiety among girls experiencing decreasing levels of social anxiety. Initial use of cigarettes was related to increases in social anxiety among girls experiencing decreasing social anxiety, but it was related to decreases in social anxiety among girls experiencing increasing levels of social anxiety. These findings and this line of research have important implications for identifying girls at risk based on symptoms of depression, anxiety, and social anxiety and the use of specific substances and point to the need for further research aimed at understanding the factors that mediate or moderate these complex relationships.

Drug Use in Pregnancy: Stopping Is Good for Mother and Child

All drugs of abuse cross the placenta to expose the fetus. Therefore, prenatal drug exposure is an important consequence of drug use and remains a public health concern. Despite the well-established dangers of using either licit or illicit drugs during pregnancy, pregnant women continue to use these substances. As described in the next three sections of this report, NIDA researchers continue to make advances in three aspects of drug use in pregnancy:

(1) Longitudinal outcome studies continue to identify specific, often subtle, differences in development between drug-exposed and nonexposed children and are finding that outcomes often vary by gender.

(2) The research is identifying how best to provide treatment for pregnant and postpartum women, both for their drug addiction as well as for the well-being of their babies.

(3) Finally, the research is addressing how to increase screening efforts in primary care settings.

The importance of NIDA's continued research on drug use in pregnancy is poignantly illustrated by the two NIDA studies below, showing first that substance use can affect the mortality risk of pregnant and parenting women and perhaps the well-being of the children they leave behind, and second that treatment, in this case for smoking, can produce positive outcomes for both mother and baby.

Mortality Rate Increased 8-Fold Among Substance-Using Pregnant and Parenting Women in California: A 10-Year Prospective Study. In a study of mortality rates, causes of death, and mortality risk factors among a cohort of substance-using mothers, researchers found that substance-using mothers had 8.4 times the mortality rate of that observed among U.S. women of similar age in the general population. The researchers prospectively studied a cohort of 4,447 substance-using mothers (pregnant or parenting) who were enrolled during 2000–2002 in 40 drug abuse treatment programs across California. All mothers were assessed at baseline using the Addiction Severity Index. Mortality data were obtained from the National Death Index, and causes of death were coded using ICD-10. Standardized mortality ratios (SMRs) were calculated relative to women in the general population adjusted for age. At the end of 2010, 194 deaths were confirmed, corresponding to a crude mortality rate of 4.47 per 1,000 person-years and an SMR of 8.4. Drug overdose (28.8 percent), cardiovascular disease (10 percent), and alcohol or drug disorders (8.9 percent) were the leading causes of death. Baseline factors associated with higher mortality included being White (relative to being African American or Hispanic) and having heroin, alcohol, cocaine, or marijuana (relative to methamphetamine) as the primary drug problem; other factors were drug injection, severity of employment problem, medical/health and psychiatric symptoms, and having never been married. The mean age for the deceased women at baseline was 37.2 years, and thus their premature death could have had adverse consequences for the welfare of their minor children. (Goal 3, Objective 3.1)

Vouchers Improve Mothers' Smoking Abstinence and Outcomes for Baby. Smoking during pregnancy is the leading preventable cause of poor pregnancy outcomes. Analysis of data from three controlled clinical trials conducted by University of Vermont researchers indicate that voucher-based reinforcement therapy (VBRT) helps women to stop using tobacco during pregnancy and improves outcomes for their babies. In these trials, women could earn vouchers exchangeable for retail items contingent on biochemically verified abstinence from recent smoking. An estimated 34 percent of 85 women who received VBRT were abstinent during late pregnancy, compared with only 7 percent of 81 women in the comparison group, who received vouchers simply for attending assessments regardless of abstinence. Women receiving VBRT maintained an advantage 3 months after giving birth: 24 percent were abstinent at this point, compared with only 3 percent of the control group. An estimated 6 percent of women in the VBRT group had a baby categorized as

low birth weight—less than 2,500 grams—compared with 19 percent of those in the control group. Additionally, mothers who received VBRT engaged in breastfeeding longer than the control-group mothers. The participants, most of whom had low incomes, each received, in total, vouchers worth about $450, which is a relatively small investment for the benefits to both the health of the mother, the baby, and the health care system. (Goal 3, Objectives 3.3, 3.4)

Drug Use in Pregnancy: Gender-Specific Effects on the Child

Drug use during pregnancy, including the use of legal drugs such as nicotine and alcohol, has been associated with potentially deleterious long-term effects on the child. NIDA's longitudinal cohort studies of children followed since birth continue to identify outcomes associated with prenatal drug exposure. These studies frequently find that outcomes are gender specific, as seen in the two examples below.

Gender-Specific Effects of Prenatal Cocaine Exposure on Attention and Inhibitory Control. There is growing evidence that males may be more adversely affected than females by prenatal drug exposure. Support for this conclusion comes, for example, from a recent report of the effects of prenatal cocaine exposure and gender on attention and inhibitory control, as measured by laboratory tasks, in 203 low-income, urban, predominately African-American children at ages 6, 9, and 11 years. The researchers controlled for medical complications in the perinatal period, environmental risk, and prenatal polydrug exposure (alcohol, tobacco, and marijuana). They found that cocaine exposure affected the performance of males, but not females. Heavily exposed males showed deficits in the attention and the inhibition tasks. In addition, a significantly greater proportion of heavily exposed males than unexposed males or heavily exposed females failed to complete the tasks. Even without those poorest-performing subjects, the overall accuracy for heavily exposed males was significantly reduced compared with lightly exposed males and unexposed males. The findings highlight the importance of considering gender specificity in cocaine exposure effects. (Goal 1, Objective 1.5; Goal 3, Objective 3.4)

Gene Influence on the Impact of Maternal Smoking on Children's Behavioral Problems Is Opposite in Boys from Girls. Maternal smoking during pregnancy has been linked with antisocial behavior in offspring. The MAOA gene encodes an enzyme, monoamine oxidase A, which influences fetal brain development and regulates communication in brain circuits throughout life. NIDA-funded researchers found that the combination of prenatal smoking exposure and specific MAOA genotypes increases children's and adolescents' risk for antisocial behavior in a sex-dependent fashion. Prior research had shown that among males who experienced maltreatment as children, those with the low-activity (MAOA-L) genotype were more likely to develop antisocial behavior than those with the high-activity (MAOA-H) genotype. In the recent NIDA study, consistent with the pattern found among maltreated males, prenatal smoking exposure increased risk of conduct symptoms for boys with MAOA-L variants but not for those with MAOA-H variants. Among girls, the reverse was true; smoking exposure increased the risk of conduct symptoms only for those with MAOA-H variants. These relationships remained after researchers took into account harsh parenting, parents' antisocial behavior, mothers' genotypes, and other potentially influential factors. (Goal 1, Objective 1.5; Goal 3, Objectives 3.4, 3.5)

Drug Use in Pregnancy: Treatment of Opiate Addiction Is Critical for Both Mother and Child

Use of opiates during pregnancy can result in a drug withdrawal syndrome in newborns called neonatal abstinence syndrome (NAS). A study supported by the Robert Wood Johnson Foundation to determine the extent, context, and costs of NAS found that the incidence of NAS is rising in the United States. The proportion of babies born with NAS tripled from 2000 to 2009, a year in which an estimated 13,539 infants were born with NAS, equivalent to 1 baby suffering from opiate withdrawal born every hour. Newborns

with NAS were more likely than other babies to have low birth weight and respiratory complications. The number of delivering mothers either using or dependent on opiates rose even more—nearly fivefold—from 2000 to 2009, to an estimated 23,009. In 2009, newborns with NAS stayed in the hospital an average of 16.4 days (compared with 3.3. days for other newborns), costing hospitals an estimated $720 million; the majority of these charges (77.6 percent) were paid by state Medicaid programs, reflecting the greater tendency of opiate-abusing mothers to be from lower-income communities. The hospital costs for newborns with NAS were $53,400 on average, versus $9,500 for those without NAS. The studies summarized below describe recent NIDA research investigating the use of buprenorphine as a medication to treat opioid-dependent pregnant women, reduce NAS, improve fetal and neonatal well-being, and reduce hospital costs.

Buprenorphine Treatment for Opioid-Dependent Pregnant Women: Less Withdrawal Distress and Shorter Hospital Stay for Babies. Although methadone has been used for the treatment of opioid dependency in pregnant women, recent NIDA research has focused on finding other medications that might be more beneficial to both the mother and infant. In a comparative effectiveness eight-site trial conducted by a multidisciplinary team of researchers from North America and Europe, buprenorphine was found to be superior to methadone in reducing neonatal abstinence withdrawal symptoms, with newborns requiring less morphine medication and less time in the hospital after birth. The research project, called Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study, gives health care providers and their opiate-dependent patients vital information to help them choose the treatment that offers the greatest benefits. If buprenorphine is adopted in the future as the standard of care for women of childbearing age, not only would that dramatically improve clinical outcomes, but it also could result in a savings of nearly $260 million per year. In the MOTHER Study, buprenorphine and methadone had equal efficacy for the treatment of maternal opioid dependency. Results of the study are being used to support a request for an FDA review of labeling changes for both medications. (Goal 3, Objectives 3.3, 3.4)

Fetal Neurobehavioral Effects of Exposure to Methadone or Buprenorphine. As part of the MOTHER Study, a subset of opioid-dependent women underwent fetal monitoring at 24, 28, 32, and 36 weeks of gestation. Results indicated better fetal well-being among women maintained on buprenorphine compared with methadone, including greater variability in fetal heart rate, more accelerations, and better coupling between fetal movements and heart rate. These differences were significant earlier in gestation but not later, suggesting that the developing fetal nervous system is more vulnerable to threats earlier in the second half of gestation than later. In contrast, fetal motor activity was most consistently suppressed in methadone-exposed fetuses in the later gestational period. The effects on the electronic fetal monitoring records were substantial enough that a blinded clinician correctly identified 83 percent of the buprenorphine-exposed cases. (Goal 3, Objective 3.4)

Neonatal Neurobehavior Effects Following Buprenorphine Versus Methadone Exposure. Also as part of the MOTHER Study, 3 sites evaluated the effects of in utero exposure to buprenorphine versus methadone on infant neurobehavior in 39 full-term infants. While neurobehavior measures improved under both medications, infants exposed in utero to buprenorphine exhibited fewer stress-abstinence signs, were less excitable and less overaroused, exhibited less hypertonia, had better self-regulation, and required less handling to maintain a quiet alert state relative to in utero methadone-exposed infants. Thus, buprenorphine exposure resulted in superior neurobehavior scores and less-severe withdrawal than did methadone exposure. These results provide significant information to health care providers and their opioid-dependent patients for choosing the treatment that offers the greatest benefit. (Goal 3, Objective 3.4)

Drug Use in Pregnancy: Improving Prenatal Screening in the Doctor's Office

15 Minutes with a Video Doctor Plus Cueing by the Provider Reduces Smoking Among Pregnant Women. As an aid to making advice more readily available in provider settings, NIDA researchers have developed an intervention that combines a production called Video Doctor with cueing by a provider; this intervention was evaluated in a randomized controlled trial conducted at five community prenatal clinics in the San Francisco Bay area of California. Video Doctor is a multimedia interactive intervention that is delivered on a laptop computer via a secure Internet connection. Video Doctor, through an actor, delivers interactive risk-reduction messages designed to simulate an ideal discussion with a prenatal health care provider, who provides nonjudgmental counseling. Based on the participant's (patient's) input, the program tailors messages to that person's risk profile and intention to change, which results in two automatically printed documents: (1) an educational worksheet for participants with questions for self-reflection, harm reduction tips, and local resources; and (2) for the provider, a cueing sheet with suggested risk-reduction counseling statements. The cueing sheet is placed in the patient's medical record for the provider's use during the prenatal appointment. Researchers found that implementation of two 15-minute automated Video Doctor sessions plus provider cueing prior to routine prenatal visits yielded a significant increase in patients' report of provider advice on tobacco use and a significant reduction in smoking among pregnant smokers at 2 months. (Goal 3, Objectives 3.3, 3.4)

Gender Differences in Provider's Use of a Standardized Screening Tool for Prenatal Substance Use. Given the impact of prenatal substance use on birth outcomes it is critical for medical professionals to receive the appropriate education and for the medical community to actively engage in screening patients. Is it possible that a physician's gender may influence differences in those screening practices? This question was addressed in a study of 131 obstetrics/gynecology physicians in Kentucky using a Web-based survey. Results indicated that female obstetrics/gynecology physicians were more likely to "believe in" the effectiveness of screening, to discuss sensitive topics with patients, and were motivated to screen as a part of comprehensive care or because screening could produce a behavioral change. However, gender differences were not significant when additional variables were considered. Specifically, younger obstetrics/gynecology physicians who frequently discussed mental health issues with female patients of childbearing age, and were motivated to screen because it is part of comprehensive care were significantly more likely to use a standardized substance use screening tool. This suggests additional training is needed to increase the use of substance use screening tools, especially those geared toward pregnant women. It also suggests gender-sensitive approaches could be appropriate in educating health care professionals on screening use. (Goal 3, Objective 3.3)

Substance Abuse Treatment: Gender Matters

NIDA's treatment research is increasingly adopting a gender-based approach. This approach is identifying factors that can potentially lead to better treatment outcomes for both men and women and is also addressing special issues for women. The research described below highlights some recent advances in the understanding of gender differences in treatment-entry profiles of opioid-dependent individuals, the important role of psychiatric comorbidity in substance-dependent women, and factors contributing to smoking cessation in women.

Comparative Profiles of Men and Women with Opioid Dependence: Results from a National Multisite Effectiveness Trial. Despite the growing body of evidence indicating important gender differences in substance use disorders in general, little research has been reported on gender differences in opioid use disorders specifically. To help fill this gap, researchers compared demographic characteristics, substance use severity, and other associated areas of

functioning among 892 treatment-seeking opioid-dependent men and women who were participating in a multisite effectiveness trial in NIDA's Clinical Trial Network. Women comprised approximately one-third of the sample. The majority of men and women tested positive for oxycodone and morphine. Craving for opioids was significantly higher among women, and more women than men tested positive for amphetamines, methamphetamine, and phencyclidine. In contrast, more men than women tested positive for methadone and marijuana. Compared with men, women presented with a broader range of collateral symptomatology such as greater psychiatric comorbidity, medical problems, employment problems, and family/social impairment. These data point to the need for integrated treatments for opioid dependence and cooccurring psychiatric conditions, as many opiate-dependent individuals, women in particular, likely use opiates as a means of coping with psychiatric symptoms. As rates of opioid misuse and dependence continue to rise, it will become increasingly important for researchers to use data from multisite effectiveness trials, such as this study, to better understand clinically relevant gender differences. (Goal 1, Objective 1.5)

Alleviation of Posttraumatic Stress Disorder May Improve Addiction Treatment of Women. NIDA researchers found that women responded better to substance abuse treatment after their symptoms of posttraumatic stress disorder (PTSD) improved, but reductions in substance abuse did not ease PTSD severity. The 353 participants in the 6-week treatment were patients in 7 community-based substance abuse treatment programs in NIDA's Clinical Trial Network. The women received their programs' standard drug treatments plus 12 group sessions of either Seeking Safety, a cognitive-behavioral therapy with components addressing both trauma and substance abuse, or Women's Health Education, which does not specifically address either problem. The study found that the two additional therapies had similar effects. When the data from the two treatment arms were combined in a secondary study, reductions in the severity of PTSD tended to presage improvements in substance abuse disorder, but there was minimal evidence that reducing substance use improved PTSD symptoms. The findings indicate that people with trauma may self-medicate with substances of abuse, and they suggest that clinicians reconsider the common practice of requiring patients to attain abstinence before treating their trauma symptoms. (Goal 1, Objective 1.5)

A Review of Two Decades of Smoking Cessation Treatment Research on Smokers with Depression (1990–2010) Finds that Only 10 Percent of Studies Reported Outcomes by Gender. Adults with depression smoke at higher rates than other adults. Women are more likely than men to meet criteria for major depression, and they exhibit stronger relationships between smoking and depressive disorders. Women are also more likely than men to report smoking to manage negative affect, to believe that smoking will reduce negative affect, and to be concerned about managing negative affect after quitting. In view of this research base, in a recent review paper, researchers examined the clinical trials research on the relationship of depression to smoking cessation outcomes over a 20-year period in order to determine the gender composition of these studies. A total of 68 eligible studies published between 1990 and 2010 were identified, and among them, only 10 percent examined smoking cessation outcomes in smokers with depression by gender. Importantly, these few studies found that depression had a greater negative impact on the outcomes of smoking cessation treatments for women than for men. These findings highlight the need for research on smoking cessation to routinely consider the impact of depression on treatment outcomes for women in order to develop treatments that will be effective for them. (Goal 1, Objective 1.5)

Menstrual Cycle Phase at Quit Date and Smoking Abstinence at 6 Weeks in an Open-Label Trial of Bupropion. Studies show that women have more difficulty quitting smoking than men, whether quitting without assistance, with behavioral interventions, or with nicotine replacement therapy. Possible involvement of the menstrual cycle in this outcome is suggested by

studies showing higher rates of smoking during menses, greater desire to smoke and reduce negative affect in luteal versus follicular phases, and more intense cue-induced craving in luteal versus follicular phases or in comparisons with males. Bupropion, an FDA-approved medication for smoking cessation, has been shown to be effective for women. In a recent preliminary investigation, NIDA researchers examined whether success in smoking cessation varies by the menstrual cycle phase of the smoking quit date in women receiving bupropion. They found that women whose self-selected quit date occurred in the luteal phase (between ovulation and menses) had significantly higher rates of point prevalence abstinence during the final week of a 6-week post-quit treatment period than women quitting in the follicular phase (62.5 percent versus 29.4 percent). This outcome is consistent with findings related to cycle phase at quit date in the absence of pharmacotherapy, and it differs from studies using nicotine replacement, which have reported better cessation outcomes with quit dates in the follicular phase. These bupropion results add to emerging data suggesting that smoking cessation interventions with varying mechanisms of action may result in different outcomes for premenopausal women based on gonadal hormones at quit date. (Goal 3, Objective 3.1)

HIV/AIDS: Risks and Intervention

Among both males and females, few drug abuse consequences are more severe than HIV infection. Drug abuse heightens the risk of contracting HIV through shared injection equipment, and it alters decision making, resulting in increased sexual risk-taking behaviors. To address issues at the intersection of HIV/AIDS and drug abuse, NIDA's HIV/AIDS research portfolio includes studies of gender-related differences in factors that contribute to and protect from HIV risk, studies of characteristics of male versus female HIV+ substance-dependent individuals, and HIV treatment concerns in males versus females. Other studies are pursuing gender-specific strategies to decrease injection drug use and high-risk sexual behaviors among women and men. Highlights of selected research findings are summarized below, each pointing to the importance of taking a gender-based approach when studying drug abuse and HIV/AIDS.

HIV+ Men and Women Show Different Performance Patterns on Procedural Learning Tasks. Research suggests that nondeclarative, or nonconscious, learning might be impaired among HIV+ individuals compared with HIV- matched control groups, but these studies have included relatively few women. In a recent study of men and women with a history of substance dependence, some of whom were HIV+, researchers administered measures of motor skill and probabilistic learning tasks with a nondeclarative or procedural learning component that depends on the integrity of prefrontal-striatal brain systems. All participants were abstinent at the time of testing. Compared with HIV- women, HIV+ women performed significantly more poorly on both tasks, but HIV+ men's performance did not differ significantly from that of HIV- men on either task. These sex-specific patterns of performance indicate that features of HIV-associated neurocognitive disorder (HAND) cannot always be generalized from men to women. Additional studies are needed to address directly the possibility of sex differences in HAND and the possibility that women might be more vulnerable than men to the effects of HIV and substance dependence on some neurocognitive functions. (Goal 1, Objectives 1.5, 1.6)

Female Gender Predicts Lower Access and Adherence to Antiretroviral Therapy in a Setting of Free Health Care. Barriers to HIV treatment among injection drug users (IDUs) are a major public health concern. However, there are few long-term studies investigating key factors—gender differences in particular—that may pose barriers to antiretroviral therapy (ART), especially in settings with universal health care. To help fill this research gap, researchers evaluated access and long-term adherence to ART in a cohort of Canadian HIV+ IDUs in a setting where medical care and ART are provided free of charge through a universal health care system. The study found that despite universal access to free HIV treatment and medical care, female IDUs were less likely to access

ART and adhere to this treatment. This finding suggests that interventions to improve access to HIV treatment among IDUs should be tailored to address unique barriers to ART faced by female IDUs. Effective management of HIV disease requires high levels of ART adherence, as incomplete adherence can detrimentally affect virological control and subsequently disease progression, and it can contribute to elevated rates of antiretroviral resistance. Therefore, ensuring that HIV+ persons maintain high levels of ART adherence is of critical clinical and public health importance. (Goal 1, Objective 1.6)

Gender-Specific Intensive Interventions Reduce Risky Sexual Behaviors. Prevention of sexual transmission of HIV, especially among drug-abusing populations, is a critical priority for curbing the AIDS epidemic. Researchers in NIDA's Clinical Trial Network have shown that multisession motivational and behavioral training targeted specifically to men or women can cut substance abusers' high-risk sexual behaviors more effectively and enduringly than a typical single preventive educational intervention. In a large-scale test of gender-specific interventions, male participants in Real Men Are Safe (REMAS) and female participants in Safer Sex Skills Building (SSB) workshops made greater reductions in high-risk sexual behavior for a longer period than comparison groups who were provided a standardized single-session HIV educational intervention designed to mimic those provided in many substance abuse clinics. Moreover, at the 3-month follow-up, men who received the training were less likely than the comparison group to have been under the influence of drugs during their most recent sexual experience. CDC has placed both REMAS and SSB in its database of interventions that have been established by scientifically rigorous studies as highly effective. Placement in that CDC database means that these interventions will be disseminated on a much larger scale than if they were only published in a scientific journal. For detailed descriptions of the interventions and free manuals and implementation aids regarding REMAS, see *http://ctndisseminationlibrary.org/display/397.htm; for SSB, see http://ctndisseminationlibrary.org/display/398.htm.* (Goal 1, Objective 1.6)

NIDA's Clinical Trial Network

NIDA's Clinical Trials Network (CTN), *http://www.nida.nih.gov/CTN*, is a national consortium of drug abuse investigators and community treatment providers that cooperatively develop, validate, refine, and deliver new treatment options to patients in community-level clinical practice. Currently, CTN consists of 13 regional centers at academic medical centers affiliated with 57 academic institutions and more than 240 community treatment providers throughout the United States and Puerto Rico. It has conducted 4 gender-specific multisite clinical trials as well as several analyses of gender differences in multiple trials, publishing more than 40 manuscripts from this work. The gender-specific studies focused on (1) treatment outcomes or services for special populations of women with substance use disorders, including pregnant women and women with cooccurring disorders (e.g., PTSD and eating disorders); and (2) gender differences in HIV risk behaviors and outcomes of gender-specific protocols for HIV risk reduction. In addition, CTN has conducted three secondary analyses across multiple studies examining specific gender differences. It established a Gender Special Interest Group, which has played a key role in overall gender research across CTN studies and in identifying substance abuse research areas that could benefit from additional attention to gender-related outcomes. Currently, data for 27 multisite studies are available for secondary analyses at *http://www.ctndatashare.org*. NIDA encourages investigators to take advantage of these data for addressing gender-specific questions. In addition, as new trials are planned, NIDA invites scientists to work with the trial investigators to plan ancillary or platform studies that can provide needed information on issues that can affect women in drug abuse treatment.

ORWH/NIDA Special Centers of Research on Sex/Gender Differences

NIDA is pleased to participate in ORWH's third cycle of funding of its signature program, Specialized Centers of Research (SCOR) on Sex Differences (RFA-OD-11-003) by cofunding and administering 3 of the 11 grants issued in that program. NIDA

also participated in the first two cycles of this program, again cofunding three of the SCORs. As described below, each of the three NIDA SCORs funded in the 2012 cycle has a translational focus, taking a sex/gender-based approach to the development of medications to treat nicotine and cocaine addictions.

The SCOR at the Yale University School of Medicine, led by Dr. Sherry McKee, is aimed at developing effective smoking cessation treatments, especially for women. Compared with men, women have poorer rates of smoking cessation and exacerbated health risks, and yet there is a lack of gender-sensitive smoking cessation treatments. There is a considerable body of data suggesting that women are more likely than men to smoke to regulate negative affect and stress, while men are more likely to smoke for the reinforcing properties of nicotine. In her preliminary human laboratory studies and a small smoking-cessation efficacy trial, Dr. McKee has demonstrated that the drug guanfacine can effectively reduce smoking rates in both men and women, but via different mechanisms. In males, guanfacine appears to modulate nicotine reinforcement, whereas in females the drug appears to mitigate negative affect and stress. Going forward, the Yale SCOR will study sex differences in the drivers of smoking and relapse, both behavioral and neurobiological, via an animal model project and a human brain-imaging project linked to a human laboratory project and larger Phase 2 smoking cessation trial with guanfacine. Together, these projects will probe the noradrenergic system's effects on stress reactivity and nicotine reinforcement, testing the hypotheses that different brain systems modulated by noradrenergic activity are activated by smoking in women and men, and that guanfacine, an α-2a noradrenergic agonist, can preferentially target these gender-sensitive systems to improve smoking cessation outcomes. (Goal 1, Objectives 1.4, 1.5; Goal 2, Objective 2.6)

The SCOR at the Medical University of South Carolina, led by Dr. Kathleen Brady, focuses on three neuropeptides (oxytocin, orexin, and corticotrophin-releasing factor) as potential mechanisms underlying the stress response in cocaine-dependent men and women and as potential targets for gender-based medications for the treatment of cocaine dependence and nicotine dependence. Currently, there are no FDA-approved medications for the treatment of cocaine addiction. The SCOR contains two clinical projects and two animal model projects. One set of clinical studies will investigate the use of oxytocin as a potential cocaine medication for stress-based relapse. Oxytocin is a hypothalamic neuropeptide that has been shown to mediate behavioral responses to stress and to play a role in neuroadaptations that occur following long-term drug use. Other clinical studies will examine the influences of sex hormone and oxytocin administration on the relationships among stress, craving, and smoking resistance. One set of preclinical studies will examine orexin and oxytocin as neuropeptide substrates that may underlie sex and estrous cycle-dependent differences in cocaine taking and reinstatement of cocaine seeking. The other will use a model of cocaine addiction focused on the role of norepinephrine and corticotrophin-releasing factor in the involvement of stress reactivity in cocaine self-administration. The gender-based and stress-based focus of this SCOR has the potential for leading to gender-based treatments for nicotine and cocaine addictions. (Goal 1, Objectives 1.4, 1.5)

The SCOR at the University of Minnesota, led by Dr. Marilyn Carroll, focuses on interactions among sex differences, hormonal status, impulsivity, and drug-motivated behavior to identify medications to assist in the treatment of nicotine and cocaine addiction. Three medications that have been shown to reduce impulsivity will be examined: progesterone, atomoxetine, and varenicline. A preclinical project will study sex differences in an animal model of nicotine and cocaine relapse and a different animal model of impulsivity for nicotine or cocaine in rats treated with progesterone alone and in combination with atomoxetine or with varenicline, which is FDA approved for nicotine cessation. This preclinical project will determine whether medications that reduce impulsivity will also reduce drug seeking and will also consider hormonal factors, including naturally occurring hormonal fluctuations in pregnancy

and the postpartum period. Two sets of clinical studies will be conducted. The first will investigate sex differences in the effect of exogenous progesterone on impulsivity and smoking cessation, and the second will investigate sex differences in the effect of exogenous progesterone combined with atomoxetine on impulsivity and on preventing relapse to cocaine abuse. Goal 1, Objectives 1.4, 1.5; Goal 3, Objectives 3.1, 3.4)

Initiatives

NIDA's Women and Sex/Gender Differences Research Program seeks to promote and facilitate drug abuse research on sex/gender differences and issues specific to women by using a variety of strategies, some of which are listed below. These include funding opportunity announcements (FOAs), travel awards, development and sponsorship of symposia and meetings, scientific presentations, and publications.

NIDA-Issued Funding Opportunity Announcements

The following are NIDA-issued FOAs, including requests for applications (RFAs), program announcements (PAs), and notices (NOT) in effect during FYs 2011 and 2012 that seek to promote research on sex/gender differences and issues specific to females.

NIDA-issued FOAs specific to women and sex/gender differences:

- PA-11-047 (R01), PA-11-048 (R21), PA-11-049 (R03), Women and Sex/Gender Differences in Drug and Alcohol Abuse/Dependence, rereleased November 5, 2011.
- PAR-10-020 (R36), Drug Abuse Dissertation Research: Epidemiology, Prevention, Treatment, Services, and Women and Sex/Gender Differences, rereleased January 16, 2010.

Other NIDA-issued FOAs with an emphasis on women and sex/gender differences:

- PA-09-106 (R01), PA-09-107 (R21). Medications Development for the Treatment of Pregnant/Postpartum Women with Substance Related Disorders and/or In Utero Substance Exposed Neonates, rereleased March 3, 2009.
- PAR-10-018 (R01), Accelerating the Pace of Drug Abuse Research Using Existing Epidemiology, Prevention, and Treatment Research Data, released October 2009.
- RFA-DA-10-017 (R01), Seek, Test, and Treat: Addressing HIV in the Criminal Justice System, released November 24, 2009.

Other FOAs in Which NIDA Participates

In addition to the above NIDA-issued FOAs, NIDA participates with other ICs in the following announcements that seek to promote research on sex/gender differences and issues specific to females:

- PAS-10-226 (R21), ORWH-led, Advancing Novel Science in Women's Health Research (ANSWHR), rereleased July 1, 2010.
- PA-12-215 (R21) NIMH-led, Women's Mental Health in Pregnancy and the Postpartum Period, rereleased June 21, 2012.
- PA-12-150 (Administrative Supplement), ORWH-led, Research Supplements To Promote Reentry into Biomedical and Behavioral Research Careers, rereleased April 6, 2012.

Nurturing the Next Generation of Researchers: NIDA-Sponsored Travel Awards

Women & Sex/Gender Junior Investigator Travel Award Program for the Annual Meeting of the College on Problems of Drug Dependence. These $750 travel awards have been made annually since 2000 and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. At the 2011 meeting, June 18–23 in Hollywood, FL, there were 27 awardees. At the 2012 meeting, June 9–14 in Palm Springs, CA, there were also 27 awardees.

NIDA Staff—Invited Presentations

- Discussant presentation for the symposium, "Milestones in the Development of Sex Differences in the Biological Actions of Drugs of Abuse," Organization for the Study of Sex Differences, Oklahoma City, OK, June 2–4, 2011.

- Presentation, "NIDA's Women & Sex/Gender Differences Research Program," NIDA Mentored K Awardees Meeting: Nuts and Bolts of Developing Independence in a Research Career, Rockville, MD, July 25–26, 2011.
- Presentation, "Sex/Gender Differences in Drug Abuse: The Importance of Conducting a Sex/Gender Analysis of Data," NIDA Prevention Research Branch, July 27, 2011.
- Lecture, "The Ubiquity of Sex/Gender Differences in Drug Abuse," part of the Addiction Course held at the Institute of Drug Abuse, Toxicology and Pharmaceutical Science, Ege University, Izmir, Turkey, August 21–22, 2011.
- Lecture, "Techniques and Best Practices of Treatment in Women," International Seminar on Women and Addiction, Santiago, Chile, August 24–25, 2011.
- Presentation, "Sex Differences in Drug Abuse," National Institute of Mental Health Women's Team, Neuroscience Center, Rockville, MD, October 31, 2011.
- Presentation, "The Ubiquity of Sex/Gender Differences in Drug Abuse," Johns Hopkins University, February 27, 2012.
- Keynote address, "The Ubiquity of Sex/Gender Differences in Drug Abuse," annual Women's Health Research Day, University of Illinois at Chicago, IL, March 29, 2012.
- Breakfast briefing, "Women and Addiction: Why Is It More Difficult for Women to Quit Smoking?," meeting of Legacy® and Women's Policy, Inc., Washington, DC, June 8, 2012.
- Luncheon address, "Sex/Gender Differences in Drug Abuse & Implications for Gender-Focused Treatment," 2012 International Women's Fifth Meeting and Conference, Palm Springs, CA, June 8, 2012.
- Breakout session, "Women's Health Research at the National Institutes of Health," SAMHSA 5th National Conference on Behavioral Health for Women and Girls: Health, Empowerment, Resilience and Recovery, San Diego, CA, July 17–19, 2012.
- Panel, "Federal Initiatives, Funding & Priorities," 17th International Conference on Violence, Abuse and Trauma, San Diego, CA, September 9–12, 2012.
- Talk, "Gender Differences in Substance Abuse: Are Females More Vulnerable to Drug Abuse Than Males?," 17th International Conference on Violence, Abuse and Trauma, San Diego, CA, September 9–12, 2012.
- Presentation, "NIDA Funding Opportunities Examining Sex Differences," miniconference "Sex Differences in Stress, Eating, and Addiction, a satellite to the annual International Society for Psychoneuroendocrinology, New York Academy of Sciences, New York, NY, September 10–14, 2012.
- Presentation, "Sex Differences in Pain: Progress & Promise," ORWH symposium, Beyond the Fig Leaf: The Science of Sex and Gender Differences, Bethesda, MD, October 9, 2012.

NIDA-Organized Symposia at National and International Conferences

- Symposium, Prenatal Cocaine Exposure in Animals and Humans: Sex Differences Across the Lifespan, College on Problems of Drug Dependence, Hollywood, FL, June 18–23, 2011.
- Symposium, Sex Differences in Pain and Opioid Analgesia, International Narcotics Research Conference, Hollywood, FL, June 21–25, 2011.
- Symposium, Prenatal Cocaine Exposure in Animals and Humans: Sex Differences in Effects on Behavior and Brain in Offspring Across the Lifespan, American Psychological Association 119th Annual Convention, Washington, DC, August 4–7, 2011.
- Symposium, Sex Differences, Women and Smoking: Biobehavioral, Developmental and Translational Perspectives, Annual Meeting of the Society for Research on Nicotine and Tobacco—Europe, Antalyla, Turkey, September 8–11, 2011.

- Symposium, Social Stress and Drug Addiction in Preclinical & Clinical Studies: Sex/Gender Matters in Effects on Brain and Behavior and Treatment Implications, American Psychiatric Association Annual Meeting, Philadelphia, PA, May 5–9, 2012.
- Symposium, Triggers, Treatments & Sex Differences in Models of Relapse and Translational Implications, American Psychological Association Convention, Orlando, FL, August 2–5, 2012.

Seminars at NIDA

- Seminar, NIDA Science Becomes Reality (TV): The Science Behind the Substance Abuse Therapy Featured on the Oprah Network Television Series "Breaking Down the Bars," July 20, 2011.
- Seminar, Sex Influences on Substance Abuse and Other Brain Disorders: The Burden of Proof Has Shifted, August 6, 2012.
- Seminar, Are Females Less Vulnerable to Drug Abuse than Males?, September 26, 2012.

NIDA Publications

- Greenfield, S. F., Rosa, C., Putnins, S. I., Green, C. A., Brooks, A. J., Calsyn, D. A., … Winhusen, T. (2011). Gender research in the National Institute on Drug Abuse National Treatment Clinical Trials Network: A summary of findings. *American Journal of Drug and Alcohol Abuse, 37*, 301–312.
- Whitten, L. (2012). "Women and Sex/Gender Differences Research Program," *NIDA Notes, 24*(2). Retrieved from *http://www.drugabuse.gov/news-events/nida-notes/2012/04/women-sexgender-differences-research-program*
- Mini-Program: Focus on Women & Sex/Gender Differences. (2011, June). In *73rd Annual Meeting Program Book.* Meeting of the College on Problems of Drug Dependence, Hollywood, FL; Mini-Program: Focus on Women & Sex/Gender Differences. (2012, June). In *74th Annual Meeting Program Book.* Meeting of the College on Problems of Drug Dependence, Palm Springs, CA. Prepared since 1999, the mini-program contains only those program listings related to women and sex/gender differences. It also contains the CPDD abstracts on women and sex/gender differences, information about the Women & Sex/Gender Junior Investigator Travel Awardees, announcement of the travel award program for the following year's CPDD meeting, and information on current NIDA funding opportunities relative to women and sex/gender differences.
- University of Michigan. (2011; 2012). Monitoring the Future National Results on Adolescent Drug Use [Web page]. Retrieved from *http://www.monitoringthefuture.org.* Updated yearly, this Web site provides a summary of drug use trends from a survey of 8th-, 10th -, and 12th-grade students nationwide, including analysis by gender. It also includes perceived risk, personal disapproval, and perceived availability of each drug by this group.
- National Institute on Drug Abuse. (2012). Women and Sex/Gender Differences Research Program [Web page]. Retrieved from *http://www.drugabuse.gov/about-nida/organization/offices/office-nida-director-od/women-sexgender-differences-research-program*

Research on Special Populations

NIDA-supported research has shown that the causes and consequences of drug abuse and addiction, as well as prevention and treatment needs, often vary among female population groups. Thus, NIDA research continues to explore new approaches to address special populations of women, such as those with children or who are pregnant or postpartum, women with drug-using partners, women experiencing current and past violence and trauma, and adolescent girls. Other special populations of female drug abusers include criminal offenders, the homeless, and those living with or at risk for HIV/AIDS as well as members of particular ethnic or minority groups. Ongoing NIDA-supported research targets these and other subgroups, reflecting the belief that ongoing research into population-specific needs related to preventing and treating drug abuse and addiction will help keep more people from abusing drugs in the first place; and for

those who do use drugs, it will lead to better treatments for them. Findings described throughout this report highlight the need for continuing research focused on special populations at increased or unique risk.

Sex/Gender Analysis: Plans and Implications

For over two decades, NIDA has emphasized sex/gender analysis in all areas of drug abuse research. From basic research on animal models to prevention and treatment, the resultant findings are demonstrating that outcomes are not always the same in males and females, as shown in many of the research advances contained in this report. In many instances, outcomes are observed only in one sex and failure to have detected those cases because of neglect to perform a sex/gender analysis of data would have led to scientific conclusions that are wrong—either wrong for females or wrong for males or wrong for both. Such sex/gender-specific research findings and their scientific and translational implications highlight the need for widespread scientific recognition that sex/gender should be an integral consideration in the design of all drug addiction research in order to achieve optimal scientific and translational value from it—for both males and females.

National Institute of Environmental Health Sciences

Executive Summary

The National Institute of Environmental Health Sciences (NIEHS) works to discover how the environment affects people in order to promote healthier lives. NIEHS investigators conduct studies to better understand how women are affected by environmental exposures, how diseases may affect men and women in the same way or differently, and how gender may influence both susceptibility to disease and the eventual outcome. The scope of women's health research has expanded from a primary focus on reproductive health to become a dynamic, multifaceted area of study. There are striking sex/gender differences in the prevalence, progression, and outcome of numerous conditions, including diabetes, obesity, cardiovascular diseases, substance abuse disorders, depression and brain disorders, infectious diseases, cancer, and autoimmune diseases. These disparities between women and men are influenced by biological sex and gender identity, as well as by developmental, cultural, environmental, and socioeconomic factors. Women's health and sex differences research, therefore, encompasses not only clinical studies but also a full spectrum of scientific investigations, such as molecular, genetic, and other basic and laboratory studies, as well as investigations into healthy lifestyles and behavior, risk reduction, and disease prevention. As results of these studies become available, women can better determine how to alter the lifestyle factors that lead to these diseases, and environmental health regulators can better define standards that protect women from the environmental triggers of these diseases and develop better gender-specific interventions and therapies.

Working Groups Focused on Women's Health

NIEHS has several groups focused entirely or in part on women's health. The work of the Institute's Women's Health Group (WHG) work is focused on fertility, early pregnancy, and the epidemiology of uterine fibroids. WHG uses the tools of reproductive epidemiology to address women's reproductive health issues. The Laboratory of Reproductive and Developmental Toxicology conducts basic research on reproductive and developmental health, including developmental biology, gene regulation, pharmacogenetics, and receptor biology. The Reproductive Endocrinology Group focuses on the role of environmental chemicals in breast developmental timing as it relates to puberty, increased susceptibility to breast cancer, and altered lactational ability. The Reproductive Epidemiology Group investigates environmental substances that affect fertility, conception, and early pregnancy; low birth weight; and teratogenesis. The Reproductive Medicine Group focuses on the basic

reproductive biology of early mammalian embryogenesis, including gametes, fertilization, preimplantation embryo development, and implantation. This group is focused on specific areas that have direct relevance to human reproduction and human infertility and on how the environment influences these areas. NIEHS also supports women's health research through its Division of Extramural Research and Training (DERT). Many of the projects funded by DERT are investigating gender differences in response to exposure to environmental substances. There were many new projects initiated in FYs 2011 and 2012, primarily at institutions of higher learning, that are investigating women's health and gender differences and are educating or training researchers in this field. The Breast Cancer and the Environment Research Program (BCERP) is an example of a DERT program focused on women's health. BCERP supports multidisciplinary scientists, clinicians, and community partners studying environmental exposures that occur throughout a woman's life and that could predispose her to breast cancer. BCERP is also supporting Windows of Susceptibility Studies, which examine how the risk of breast cancer relates to environmental exposures that occur during susceptible times in development, and the BCERP Puberty Study is following more than 1,200 young girls to better understand predictors of early puberty, which is associated with increased risk of breast cancer.

Accomplishments

Reducing Women's Risk and Chemical Exposure

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study has focused on addressing the adverse health effects of disproportionate pesticide and other chemical exposure on the families of farm workers in Salinas Valley, California. Much of the CHAMACOS effort has centered on longitudinal research that recruited and followed primarily low-income, Mexican immigrant farm worker women and their children living in the agricultural Salinas Valley over a span of 12 years, to document the impacts of the exposures on growth, health, and development. One highlight has been the development of the Prenatal Environmental Health Kiosk. This Spanish interactive, self-guided computer program, which is available free online, advises pregnant women on reducing their exposure to chemicals. The program covers topics on exposure through foods, the home, the outside environment, and at work through a series of 60 screens. A survey of 187 pregnant women has revealed a positive response from users. CERCH will continue to update the Kiosk with information on new exposures.

Susceptibility and Breast Cancer over Women's Lifespan

NIEHS and the National Cancer Institute cofund the Breast Cancer and the Environment Research Program, which supports multidisciplinary scientists, clinicians, and community partners studying environmental exposures that occur throughout a woman's life and could predispose her to breast cancer. The program is made up of several complementary components, including a longitudinal cohort of young girls who have been followed since the age of 6 to 8 years, to examine how environmental exposures, lifestyle factors, and genetics affect pubertal development in girls, including their age at breast development, menarche, and other markers of pubertal development (e.g., peak height velocity [the period in which growth in height is most rapid]) that have been associated with future breast cancer risk. Other projects funded through this program include novel experimental and epidemiological studies to examine whether women are more susceptible to environmental exposures at specific developmental times in their lives with respect to breast cancer risk (termed "windows of susceptibility"). All projects include partnerships between researchers and breast cancer advocates and other members of the engaged community to build and promote bidirectional communication regarding environmental exposures of high and relevant importance, assist with retention of participants in epidemiological studies, and develop and implement tools and materials to communicate study findings to the public and to policymakers.

Fertility Drugs and Young-Onset Breast Cancer

The Two Sister Study builds on the work of the Sister Study. The Two Sister Study focuses on women who develop breast cancer at a young age and seeks to determine how environmental exposures as well as genetic factors may trigger breast cancer. An investigation found that among participants in the NIEHS Two Sister Study, funded in part by Susan G. Komen for the Cure, women who had used ovary-stimulating fertility drugs, either clomiphene citrate or follicle-stimulating hormone, without getting pregnant had reduced risk of young-onset breast cancer. Participants in that substudy (as well as in the ongoing Two Sister Study as a whole) were pairs of sisters, one of whom had been diagnosed with breast cancer before the age of 50. They were categorized based on whether they had used ovulation-stimulating fertility drugs and whether pregnancy had resulted. Unlike previous studies, the Two Sister Study distinguishes between fertility treatments that produce pregnancy and those that do not. Moreover, the use of sisters who are well matched for many factors allows for a fair comparison.

National Toxicology Program: Pregnancy Outcomes Following Chemotherapy During Pregnancy

The National Toxicology Program (NTP) recently completed a draft monograph of pregnancy outcomes following chemotherapy treatment for cancer during pregnancy, which was peer-reviewed by an expert panel in a public meeting held in October 2012. The goal of the monograph was to summarize the peer-reviewed literature documenting the effects of gestational exposure to cancer chemotherapy on pregnancy outcomes to serve as a resource for the clinical and patient communities. Of the approximately 110 cancer chemotherapeutic agents currently in use, the NTP monograph includes data on 52 agents that were used in over 1,250 pregnancies for which pregnancy outcomes were documented. The NTP monograph focuses on five health outcomes:

(1) Major congenital malformations;

(2) Spontaneous fetal death, including spontaneous abortion and stillbirth;

(3) Spontaneous preterm birth;

(4) Small for gestational age; and

(5) Adverse health effects at follow-up evaluation.

In addition, the NTP monograph provides background materials on individual cancer chemotherapeutic agents (e.g., evidence for placenta and breast milk transport of agents, developmental toxicity in animals), and a brief review of the prevalence and prognosis of seven frequently diagnosed cancers in women during pregnancy. Finally, the NTP monograph identifies the challenges in interpreting the health outcomes from this observational literature base and discusses possible actions to improve the understanding of the developmental effects of chemotherapy treatment for cancer administered during pregnancy. It is anticipated that the final NTP monograph will be released in late June 2013.

Effects of Prenatal Bisphenol A Exposure and Reproductive Effects

In collaboration with university partners, NIEHS intramural researchers are studying the effects of maternal exposure to bisphenol A (BPA) during pregnancy on the development of animal offspring. The researchers found significant effects on both mammary gland development and ovarian development in the offspring of mothers who had been exposed to BPA during pregnancy. In addition, NIEHS intramural researchers evaluated uterine morphology and gene expression and found subtle differences in gene expression of developmentally important Hox and Wnt genes, but no significant changes in tissue. From this research it seems that maternal BPA exposures cause genetic changes in offspring while not affecting the form or structure of organs.

Estrogenic Chemicals and Endometrial Cancer

In two studies, NIEHS intramural researchers are using genetic tools such as microarrays to better understand how estrogenic chemicals

such as DES (diethylstilbestrol) may have an adverse effect on uterus tissue. In one study, animals exposed as neonates to DES and the phytoestrogen genistein had permanent alterations in genes found in uterine tissue. In another study, researchers have found that human genes, similar to those in the aforementioned animal study, may play a role in the progression of cancer in the lining of the uterus. As a result of these studies, researchers have evidence that early-life exposure to estrogenic chemicals may play a larger role in the progression and severity of human endometrial cancer than previously thought.

Breast Cancer and the Environment: Prioritizing Prevention

The Breast Cancer and Environmental Research Act established the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC), which has examined research on the current state of the relationship between breast cancer and the environment. IBCERCC was charged with making recommendations for eliminating any knowledge gaps in this area. Based on its review of the state of the science, the current programs of Federal agencies and nongovernmental organizations and the investments made by such entities, and relevant communication efforts and policies, the IBCERCC has provided a comprehensive report summarizing its findings and making seven recommendations to highlight the need for coordinated, targeted efforts to identify and mitigate the environmental causes of breast cancer. IBCERCC recently released its report, which is available on the NIEHS Web site (*http://www.niehs.nih.gov/ibcercc*). The seven recommendations are to:

(1) Prioritize prevention;

(2) Transform how research is conducted;

(3) Intensify the study of chemical and physical factors;

(4) Plan strategically across Federal agencies;

(5) Engage public stakeholders;

(6) Train transdisciplinary researchers; and

(7) Translate and communicate science to society.

Autism Risk Linked to Maternal Diabetes and Obesity

Findings from the NIEHS-funded Childhood Autism Risks from Genetics and the Environment (CHARGE) study provide evidence that maternal metabolic conditions can increase the risk for autism as well as for developmental delay without autistic symptoms. The findings suggest that fetal exposure to elevated levels of glucose and maternal inflammation adversely affect fetal development. The metabolic conditions studied included obesity or hypertension at the start of pregnancy and diabetes during pregnancy, which were linked with significantly increased risk for having a child with autism or other developmental disorders. In addition, children with autism spectrum disorder and mothers with diabetes had greater deficits in adaptive communication, language comprehension, and language production than did children with autism spectrum disorder who were born to healthy mothers.

Rice Consumption and Arsenic Exposure in Pregnant Women

NIEHS grantees report that urinary arsenic concentrations were higher for pregnant women who had recently consumed rice than for those who had not. These findings highlight the need to monitor arsenic levels in food. The researchers tested for arsenic in the urine of 229 pregnant women in New Hampshire, 73 of whom reported eating rice during the 2 days before urine collection. The arsenic concentration of the tap water in the women's homes was also tested to identify any exposure from drinking water. The women who reported eating rice during the 2 days prior to urine collection had a median total urinary arsenic concentration of 5.27 micrograms (mcg) per liter, which was significantly higher than the median concentration of 3.38 mcg per liter among those who did not consume rice. The researchers noted the need for more research to determine any health impacts of this source of exposure. Any identified health risks will need to be weighed against the nutritional benefits of eating rice.

An Ethanolic Extract of Black Cohosh Causes Hematological Changes But Not Estrogenic Effects in Female Rodents

Black cohosh extract (BCE) is used as a remedy for pain and gynecological ailments, and modern preparations of BCE are commonly sold as ethanolic extracts available as dietary supplements. In the first study of its kind, researchers used rodent models to characterize the general toxicity of BCE and address suspected estrogenic and antiestrogenic activity. BCE induced dose-dependent hematologic changes that were consistent with a nonregenerative macrocytic anemia and increased frequencies of peripheral micronucleated red blood cells. Effects were more severe in mice—at all exposure levels—than in rats. Dose-dependent thymus and liver toxicity was also observed in rats. Apparent effects on puberty were observed but were not associated with alteration in estrogenic and antiestrogenic activity.

Effects of Neonatal Exposure to Estrogenic Chemicals on Female Reproductive Tract Development and Function

Female mice treated neonatally with the phytoestrogen genistein are infertile because of deficiencies in both embryo development in the oviduct and implantation in the uterus. NIEHS intramural researchers performed a series of experiments to characterize the abnormalities in the oviduct and found permanently altered patterns of gene expression of factors known to modulate development of the female reproductive tract. The researchers also found significant alterations in immune-response genes expressed in the oviduct, and they found abnormalities in blastocyst development that are likely a consequence of alterations in the oviduct mucosal immune response to pregnancy.

Association Between BPA Exposure During Pregnancy and Changes in Thyroid Hormone Levels

As part of the CHAMACOS study, a longitudinal birth cohort study of environmental exposures and health among pregnant women and children, investigators found that exposure to BPA is linked to changes in thyroid hormone levels in pregnant women and newborn boys. Participants were primarily young (less than 30 years of age) Latinas born in Mexico who had immigrated to the United States within 10 years of enrollment (74–78 percent), and most women had low socioeconomic status. Although thyroid hormones play a determinant role in human growth and brain development, no studies have investigated relations between exposure to BPA and thyroid function in pregnant women or neonates. This is the first study to show an association between BPA and thyroid hormone in pregnant women and indicates that exposure to BPA during pregnancy may have adverse health effects on fetal and child development.

PDBE Exposure During Pregnancy Affects Child Health

In the largest study conducted to date, NIEHS grantees reported that exposure to flame-retardant compounds (polybrominated diphenyl ethers, or PBDEs) is associated with decreased levels of thyroid-stimulating hormone around the beginning of the third trimester of pregnancy. In addition, the report found that both prenatal and childhood PBDE exposures were associated with poorer attention, diminished fine motor coordination, and reduced cognition. This study contributes to growing evidence suggesting that PBDEs have adverse impacts on child neurobehavioral development.

Moderate Physical Activity Found to Reduce Risk of Breast Cancer

Although physical activity reduces the risk of breast cancer, issues critical to providing clear public health messages in this area remain to be elucidated. These include the minimum duration and intensity necessary for risk reduction and the optimal time period for occurrence, as well as subgroup effects, particularly with regard to tumor heterogeneity and body size. In an NIEHS-funded study, the effects of physical activity, weight gain, and body size on risk of breast cancer were examined. The findings suggest that even a moderate level of physical activity can reduce a woman's risk of breast cancer

as long as there is no significant weight gain after menopause.

Sex/Gender

NIEHS is funding a study to evaluate the association between exposure to individual ambient air pollutants and the risk of stroke. The project will use data on 159,643 post-menopausal women participating in the Women's Health Initiative (WHI) and 45,358 men participating in the Health Professionals Follow-Up Study (HPFS). Specifically, the study will evaluate the effects of long-term (measured in years) and short-term (days) exposure to ambient pollutants on the risk of ischemic and hemorrhagic stroke and whether risk varies by known stroke risk factors, ischemic stroke subtype, or mixtures of pollutants. In addition, the inclusion of both the WHI and HPFS cohorts will allow investigators to examine whether the findings will be generalizable across the population or are gender specific.

In another NIEHS-funded study, this one at the University of California, Irvine, researchers are examining the association between secondary organic aerosols (SOAs), O_3 (ozone), NO_2 (nitrogen dioxide), and other air pollutants on emergency department visits and hospitalizations for pediatric asthma. The researchers will then use this information to predict the impacts of climate change on exposure levels to photochemical oxidant air pollutants and future pediatric asthma morbidity. A primary aim of the study is to examine effect modification of subject and geographic factors that may represent increased vulnerability, including effect modification of differences by gender.

In a different study, NIEHS researchers found that antinuclear antibodies (ANAs) are more prevalent among females than males. The immune system makes antibodies, which recognize and combat infectious organisms in the body, but sometimes these antibodies make a mistake, identifying normal, naturally occurring proteins in the body as being "foreign" and dangerous. The antibodies that target "normal" proteins within the nucleus of a cell are called ANAs. ANAs could signal the body to begin attacking itself, which can lead to autoimmune diseases, including lupus, scleroderma, and many others. The findings from this study suggest that more than 32 million people in the United State have ANAs and that their prevalence is higher among females, older individuals, African-Americans, and those with a normal body weight. For this study, researchers used data that included nearly 5,000 individuals from the National Health and Nutrition Examination Survey. These data will serve as a useful baseline for future investigations of predictors and changes in ANA prevalence over time.

NIEHS grantees are investigating the association between serum levels of perfluoroalkyl chemicals (PFCs) and the risk of developing incident cardiovascular outcomes (cardiovascular disease [CVD], coronary heart disease, and stroke), subclinical measures of atherosclerosis, and chronic kidney disease (CKD) among participants in the Multi-ethnic Study of Atherosclerosis (MESA). Primary aims of this study include determining whether the distribution of serum PFCs levels varies by gender and race/ethnicity and whether associations with risk of CVD and CKD are modified by gender or race/ethnicity.

NIEHS is funding numerous human studies examining the health effects on the developing fetus of prenatal exposures to environmental chemicals. To date, many studies have reported small but significant changes as they relate to reported sexually dimorphic behaviors. In some studies, pregnant women exposed to a specific class of endocrine disruptors have shown changes in their girls but not in their boys as related to risk for depression, but changes in play behavior have been reported in boys but not girls. Larger studies are being conducted to examine whether specific endocrine disruptors such as phthalates and BPA may perturb the developing fetal endocrine system and increase the risk for behavioral disorders. Such an effect may be related to changes in the gestational sex steroid milieu, as noted in animal studies. Outcomes to be addressed include, but are not limited to, visual and spatial abilities and a determination of whether males or females are more vulnerable to specific chemicals.

The general toxicology assessments conducted by the NTP usually involve exposures of rats and mice of both sexes to test chemicals for periods of 14 days or 13 weeks. The assessments that almost always are performed include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The NTP long-term toxicology and carcinogenesis studies (bioassays) in rodents generally employ both sexes of rats (Harlan Sprague Dawley) and mice (B6C3F1 hybrid), with three exposure concentrations, plus untreated controls in groups of 50 animals for 2 years. Both sexes are evaluated to determine whether there are differences in outcome caused by sex differences.

Several NIEHS grantees studying the effects of endocrine disruptors are finding sexually dimorphic effects. One researcher has shown that neonatal exposure to BPA in rats altered the expression of estrogen receptor alpha, estrogen receptor beta, and kisspeptin in the anterior and mediobasal hypothalamus. Within the anterior hypothalamus, expression of estrogen receptor alpha was increased by BPA in females early but then fell to male levels. Kisspeptin expression was diminished by BPA in the anterior hypothalamus, especially in females. Overall, these results indicate that neonatal hypothalamic estrogen receptor and kisspeptin expression are sensitive to BPA. These effects show that estrogen receptor expression is specific to brain region, and changes may alter sexually dimorphic hypothalamic organization, underlie adult reproductive deficiencies, and contribute to sex differences in sociosexual behavior across the lifespan.

The effects of BPA on cardiovascular health and heart development are being elucidated by NIEHS grantees, who are examining the effects of BPA on heart development and function both in vivo and in vitro. Grantees have studied rapid (less than 7 minutes) effects of BPA and estradiol in the heart and ventral myocytes from rodents. In isolated ventricular myocytes from young females but not males, BPA or estradiol rapidly induced arrhythmogenic-triggered activities. Under conditions of catecholamine stimulation, estradiol and BPA promoted ventricular arrhythmias in female but not male hearts. The cellular mechanism of the female-specific proarrhythmias in females but not males was examined. Exposure to estradiol or BPA rapidly altered myocyte calcium handling, increasing sarcoplasmic reticulum calcium leak and calcium load. The scientists also found that sensitivity to estradiol and BPA was not present in male myocytes and was abolished in myocytes from ovariectomized females. Analysis using selective estrogen receptor agonists showed that estrogen receptor alpha and beta have opposing effects in myocytes and that the balance between them is the prime regulator of the sex specificity toward estrogen. The response of female myocytes to estrogen and BPA is dominated by stimulatory estrogen receptor beta signaling, and in the absence of estrogen or BPA responsiveness in the males is due to counterbalancing suppressive actions on estrogen receptor alpha. This is the first evidence that exposure to estrogenic endocrine-disrupting chemicals has a unique sensitivity to female hearts and may play a role in arrhythmogenesis in female hearts.

NIEHS intramural scientists are studying how estrogen hormone action within target tissues involves the interaction of the hormonal substance with two different receptor proteins. Estrogen receptors are thought to play a crucial role in development, reproduction, and normal physiology. Studies in mice by the Institute's intramural scientists have yielded results that show differences in estrogen receptor genes and other results such as reduced bone density and some alterations in cardiovascular function. Further characterization of the mice and comparison of the individual and double estrogen receptor gene phenotypes will be required to more fully understand the physiological consequences of estrogen receptor–mediated actions and the specific roles of responsiveness to estrogen hormones. Differences in gene responses to hormonal xenobiotics were also seen in some in vitro gene regulation studies. Using a transactivation assay system, trichlorobiphenyl was shown to be more active than estradiol on the lactoferrin gene. Researchers used this estrogen-responsive yeast system to test the xenobiotic estrogen synergy concept and, using a variety of genes, showed

that synergy was not apparent and had no universal application to hormone-responsive systems. In addition, investigators found that lavender and tea tree oils were acting as endocrine disruptors (estrogenic and antiandrogenic), causing abnormal enlargement of breast tissue in young males.

Initiatives/Workshops and Conferences

Initiatives

Advancing Novel Science in Women's Health Research (ANSWHR) (R21). The purpose of this Funding Opportunity Announcement (FOA), issued by the ORWH and cosponsoring NIH Institutes and Centers, is to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. ORWH is particularly interested in encouraging extramural investigators to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health, but applications in all areas of women's health and sex/gender research are invited.

Centers for Nanotechnology Health Implications Research (NCNHIR) Consortium (U19 and U01). The NIEHS extramural research program formed the NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) consortium in November 2010 to gain fundamental knowledge regarding the health effects of engineered nanomaterials (ENMs). One part of these efforts involves understanding the influence of ENMs on women's health. These studies are exploring how ENMs may affect various physiologic conditions, such as pregnancy, lactation, and the health of the fetus. These investigations also include developing mathematical models for the disposition and effects of nanoparticles, in order to provide a firm basis for predicting exposure conditions in women under which such materials could elicit adverse effects in the mother, fetus, or neonate.

Research Consortium for 2-Year Bisphenol A Toxicity Study (U01). The objective of this research program is to take advantage of scientific expertise in the extramural community to develop a consortium of investigators who will propose hypothesis-driven mechanistic studies focusing on disease/dysfunction end points which can be added to the chronic study design. The independent scientific ideas and approaches will either use animals generated from the core study or, if needed, add more animals to the core study in order to assess the effects of BPA on specific diseases/dysfunctions over a lifetime.

Workshops and Conferences

Maternal Smoking and Nicotine. In January 2011, the NIEHS Division of the NTP organized a workshop to evaluate the current state of the science on the effects of maternal smoking/exposure to nicotine on the development of infants and children, a topic of increasing public health concern. The main objective of the workshop was to develop recommendations for a research agenda after completing a critical analysis of the literature on humans and experimental animals exposed to certain environmental chemicals. The strongest conclusion from the workshop was that nicotine likely acts as a developmental obesogen in humans. This conclusion was based on the very consistent pattern of overweight/obesity observed in epidemiological studies of the children of mothers who smoked during pregnancy and was supported by findings from laboratory animals exposed to nicotine during prenatal development. It is possible that other components in cigarette smoke may also be contributing to the association between maternal smoking and childhood overweight/obesity, but the studies of nicotine in experimental animals provided compelling evidence that nicotine alone was the causal agent.

NIEHS Expert Panel Workshop Evaluates the State of the Science Regarding the Environment and Autoimmunity. A recent NIEHS Expert Panel Workshop brought together researchers to evaluate the state of the science regarding the role of the

environment in the development of autoimmunity and related diseases. Environmental exposures that may initiate or promote autoimmune diseases are a special area of importance to women's health because women are often disproportionately affected by these diseases. Among the consensus findings from the expert panel was that exposure to crystalline silica, certain solvents, and smoking can contribute to the development of various types of autoimmune diseases. In addition, the panel found an inverse association between exposure to ultraviolet radiation and the development of multiple sclerosis. Much remains to be discovered to increase our understanding of autoimmune diseases, but further investigation will improve diagnosis and treatment, and possibly allow for future preventive strategies.

Inclusion of Mammary Gland Developmental Assessment in Chemical Testing. As a result of Expert Panel Workshops, public comment, and research in methods development within the Division of the NTP at NIEHS, the NTP has modified several of its chemical-testing specifications to include early-life chemical exposures in 2-year carcinogenicity testing, with dose recommendations guided by results of shorter test guidelines. Included in these test specifications are the preparation of mammary gland whole mounts at weaning as well as improved brain evaluations. Plans for improved mammary and uterine evaluations at routine histopathology are under way. In addition, NTP scientists have developed methods for quantitative evaluation and unbiased scoring of mammary gland development in both female and male rodents. These methods will be the first in the world to be integrated into chemical testing as required end points and will have an international impact, as the guidelines are also being adopted by the Organisation for Economic Co-operation and Development (OECD). These integrated methodologies will improve the ability of the NTP to define windows of susceptibility and enhance the ability to detect the compounds that are risk factors for breast/uterine disease or that disrupt normal hormonal responses affecting these important tissues.

Researching Women's Environmental Health 2010. The second Researching Women's Environmental Health (RWEH) Workshop was held in late 2010 in Rochester, New York, at the University of Rochester School of Medicine and Dentistry. This workshop had four goals: (1) to present cutting-edge scientific findings that show how environmental exposures can alter food safety and nutritional content and affect obesity; (2) to present a "case study" that illustrates the successful translation from science to policy in the area of food, nutrition, and the environment; (3) to learn what information policymakers, the media, and community leaders need in order to take appropriate action on scientific findings in the area of food, nutrition, and the environment; and (4) to identify barriers that prevent the translation of environmental health research in these areas to actionable policy, and to understand how to overcome these obstacles.

Health Disparities

Health Disparities Stemming from the 2010 Deepwater Horizon Gulf Spill

The NIEHS-led Deepwater Horizon Research Consortia program supports community-university partnerships aimed at addressing the health effects stemming from the 2010 Deepwater Horizon Gulf spill to help improve community preparedness and responses to disasters and minimize disaster-related health impacts such as stress, exposure to contaminants, and changes in diet. The two studies within the consortia that focus on women and children are being conducted at Louisiana State University and Tulane University and involve minority or ethnic populations:

- Women and Their Children's Health Study (WaTCH). Goal: Determine the mid- and long-term physical, behavioral, social, and economic effects on women and children's well-being.
  - Two substudies on resilience (association between resilience, social capital, and emotional health, and association between subjects' exposure and their emotional and physical health) are being conducted, and a child impact study

is also being conducted. These studies include women from low-income communities, from Vietnamese subsistence communities, and among Houma Nation (Native American) communities.

- Transdisciplinary Research Consortium for Gulf Resilience on Women's Health (GROWH). Goals: Assess mental and reproductive health outcomes and interactions of environmental and social disparities among women who are pregnant or of reproductive age, and characterize women's exposures to select contaminants.
  - Two substudies are being conducted: Lifetime Adversity and Reproductive-Aged Women, and Real and Perceived Exposures in Reproductive-Aged Women. These studies also involve low-income communities and ethnic minorities.

Study of Environment, Lifestyle & Fibroids (SELF): African-Americans and Fibroids

NIEHS intramural scientists are studying a variety of diseases that affect women. An epidemiological study called the Study of Environment, Lifestyle & Fibroids (SELF) is being conducted among African-American women 23 to 34 years of age in the Detroit, Michigan, area. Fibroids are more common in African-American women than in white women, and they are the leading indication for hysterectomy. The reason for the disparity by race is not known. This NIEHS study is a prospective cohort study, with women enrolled before they are diagnosed with fibroids and follow-up for at least 5 years to document the development of new fibroids with ultrasound examinations at approximately 20-month intervals. Researchers will examine a wide range of potential risk factors for the condition to evaluate their associations with the appearance of new fibroids and growth of existing fibroids.

Racial Differences in Circulating Insulin-Like Growth Factor-I and IGF-Binding Protein-3 Levels

Circulating insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels are associated with common diseases. Although family-based studies suggest that genetic variation contributes to circulating IGF-I and IGFBP-3 levels, analyses of associations with multiple IGF-I and IGFBP-3 single nucleotide polymorphisms (SNPs) have been limited, especially among African-Americans. Researchers evaluated 30 IGF-I and 15 IGFBP-3 SNPs and estimated diplotypes in association with plasma IGF-I and IGFBP-3 among premenopausal African-American and Caucasian women. Evidence of a causal association was strongest for the nonsynonymous IGFBP-3 SNP rs2854746 and plasma IGFBP-3 levels. In both races, the rs2854746 CC genotype was associated with higher mean IGFBP-3 levels than were estimated for the GG genotype, while mean levels for the CG genotype were intermediate. In addition, IGFBP-3 diplotypes with the rs2854746 GG genotype had consistently lower mean IGFBP-3 levels than those estimated for referent diplotypes with the CG genotype in both races, while IGFBP-3 diplotypes with the CC genotype had higher mean IGFBP-3 levels. Because African-Americans have more genetic heterogeneity than Caucasians, the frequency of etiologically relevant SNPs may differ, and this may at least partly explain racial disparities in the burden of cancer and CVD. Therefore, assessing IGF-I and IGFBP-3 SNPs that predict circulating IGF-I and IGFBP-3 levels will improve the understanding of the biological role of IGF-I and IGFBP-3 in the etiology of common diseases.

African-American Genetic Obesity Susceptibility

Obesity is about 50 percent more prevalent among African-Americans than European Americans. To determine whether genetic background may contribute to this observed disparity, researchers scanned the genomes of African-Americans, searching for genomic regions where obese individuals had a difference from the average in proportion of African ancestry. By examining genetic data from more than 15,000 African-Americans, they were able to show that the proportion of European ancestry is inversely correlated with body mass index (BMI). In obese individuals, two loci were detected with increased African ancestry on chromosome

X (Xq13.1 and Xq25), and one locus with increased European ancestry was found on chromosome 5 (5q13.3). The 5q13.3 and Xq25 regions both contain genes that are known to be involved in appetite regulation. Because the admixture peaks identified were located on chromosome X, which has a different copy number in men and women, the researchers performed analyses for each gender separately to explore whether the strength of association differed significantly between males and females. They found that the evidence of association at Xq25 was stronger in females than in males and that the association signal at Xq13.1 in males grew stronger, with the local LOD (logarithm of odds) score rising to 4.40. In the more comprehensive linear regression analysis of local ancestry, there was a significant gender difference at Xq13.1. For the two peaks on chromosome X, the researchers further examined whether the effects of local ancestry on BMI were modified by gender. The local ancestry at Xq13.1 tended to be more strongly associated with BMI in males than in females. After researchers adjusted for genome-wide European ancestry, the gender difference at Xq13.1 was significant, a finding that was in line with results of dichotomous admixture scans. At Xq25, the effects of local ancestry did not show significant heterogeneity between the two gender groups either before or after adjusting for genome-wide European ancestry. A potential mechanism for the difference in the strength of association in men and women at the Xq13.1 locus is that women carry two copies of chromosome X, whereas men carry only one, and hence this may simply reflect a difference in the genetics of the two genders on chromosome X. The results suggest that genetic factors may contribute to the difference in obesity prevalence between African-Americans and European Americans. Further studies of the regions may identify the causative variants affecting susceptibility to obesity.

Social Isolation and Breast Cancer

Clinical studies have revealed that social support improves the outcome of cancer patients, and epidemiological studies suggest that social isolation increases the risk of death associated with several chronic diseases. However, the precise molecular consequences of an unfavorable social environment have not been defined. In an NIEHS-supported study, female C3(1)/SV40 T-antigen mice deprived of social interaction after weaning exhibited increased expression of genes encoding key metabolic pathway enzymes in the premalignant mammary gland. Chronic social isolation was associated with upregulated lipid synthesis and glycolytic pathway gene expression. Both pathways are known to contribute to increased breast cancer growth. Consistent with the expression of metabolic genes in premalignant mammary tissue, isolated mice subsequently developed a significantly larger burden of mammary gland tumors than did group-housed mice. Findings showed that isolated mice developed a heightened corticosterone stress response compared with group-housed mice and that a chronically isolated social environment correlated with specifically altered mammary gland gene expression. Furthermore, the complement of differentially expressed mammary gland genes associated with social isolation suggests activation of key cancer-linked metabolic pathways. Understanding the specific molecular networks connecting an individual's environment with his/her physiologic stress response and, ultimately, with tissue gene expression favoring tumor growth is expected to uncover novel mechanisms promoting tumor growth in the context of specific environmental stressors. It is possible that the metabolic gene expression pathways identified in this study may also contribute to the mechanisms underlying the observation that patients with self-reported social isolation are at higher risk for diabetes and hypertension as well as cancer.

Disparities in Biological "Wear and Tear" Measured by Allostatic Load in a Nationally Representative Sample of U.S. Adults

Despite decades of research on socioeconomic status (SES) gradients in health, the underlying causes remain only partially understood. No studies have examined the independent contribution of neighborhood SES (NSES) to allostatic load (AL)

in a nationally representative sample. This study assessed whether NSES is associated with cumulative biological wear and tear, or dysregulation (measured by AL), in a nationally representative sample of U.S. adults after adjusting for individual-level demographic and SES characteristics. Being male, being older, having lower income, having less education, being Mexican-American, and being both black and female were all independently associated with a worse allostatic load. After adjusting for these characteristics, living in a lower NSES area was associated with a worse AL. The relationship between NSES and AL did not vary significantly by gender or race/ethnicity. The authors concluded that living in a lower NSES area in the United States is associated with significantly greater biological wear and tear, as measured by the AL, and that this relationship is independent of individual SES characteristics. The findings show that where a person lives is independently associated with allostatic load, thereby suggesting that policies that improve NSES may yield health returns.

Career Development Initiatives

Building Interdisciplinary Research Careers in Women's Health (BIRCWH)

NIEHS administers one Building Interdisciplinary Research Careers in Women's Health (BIRCWH) K12 Career Development Program at the University of Rochester, with Dr. Deborah A. Cory-Slechta as the program director. The purpose of this award is to foster the career development of junior faculty whose research interests are focused on the role of environmental chemical exposures on women's health across the lifespan. Two scholars are currently being supported. One, in the Department of Biomedical Engineering, is studying the inhibition of bone formation by lead, in the context of attempting a rescue with a targeted polymer therapeutic. Thus, in addition to further understanding the mechanisms of lead-induced osteoporosis in women, this scholar is attempting to develop a targeted therapeutic for its treatment. The other scholar, in the Department of Obstetrics and Gynecology, is focusing on how environmental exposures, particularly to phthalates, affect female fecundity over the lifespan. The particular emphasis has been on how prenatal endocrine disruption influences the developing female reproductive system and the influence of androgen in such events. These studies include secondary analyses on menarche, ovarian function, and menstrual cycling. A third scholar was expected to join the program in March 2013. The research of this scholar will be devoted to the influence of perfluorinated compounds in breast milk on antibody responses in the child.

Women's Health and the Environment over the Entire Lifespan (WHEEL)

Concerns about the potential impacts of environmental chemicals on human and environmental health have increased greatly in the past 10 years. Through their effects on hormonal pathways, environmental chemicals can differentially affect females, particularly at critical and sensitive periods in the lifespan. These periods include stages of particular vulnerability (such as fetal development and late life), major hormonal transitions, and stages of rapid cell proliferation and growth (such as during fetal development, puberty, and lactation). Public and scientific concerns about the potential impacts of environmental chemicals on human and environmental health have increased greatly in the past 10 years. The Women's Health and Environment across the Entire Lifespan (WHEEL) program at the University of Rochester Medical Center will train junior faculty to conduct outstanding interdisciplinary research that will help identify environmental agents that can adversely affect women's health at all stages of life, thus addressing these concerns. Results of this research will provide a strong foundation for risk assessment and regulation, when appropriate, thus decreasing risks to public health.

Female Tenure Track Investigators Program

The NIH Women Scientist Advisors Committee and the Intramural Committee of the NIH Working Group on Women in Biomedical Careers have jointly developed

a new program for basic and clinical tenure-track investigators and assistant clinical investigators. NIH program coordinators have agreed to help coordinate and develop a tenure-track investigators program at NIEHS. The plan is to have five high-profile NIEHS female scientists serve as mentors for this new intramural program.

Office of Fellows' Career Development

The first MOMDADDOCS meeting was recently held at NIEHS. The goal of MOMDADDOCS is to provide an informal mentoring, support, and networking program for NIEHS fellows who are balancing a career and family. The program is open to all, but it is particularly helpful for women looking to share advice and support as they strive for a work/life balance. Another intramural program, the NIEHS Brown Bag Lunch program, has assisted with women's career development in the sciences. That program highlights a different set of Ph.D. careers each month to provide fellows the opportunity to meet scientists with firsthand experience. The lunch provides an informal and intimate atmosphere for fellows to ask questions and hear about potential career options. In all, 14 lunches, with a total of 26 guests, have been hosted. To date, every lunch has featured at least one woman scientist, and 85 percent of all the guests featured have been women. These lunches have provided our female trainees with a unique career development opportunity to learn about the role of women in a broad range of scientific fields.

NIH Strategic Plan for Women's Health Research

NIEHS funds a large number of studies that explore variations due to sex as an integral part of the search for knowledge across the entire research spectrum, beginning at the most basic laboratory level. NIEHS research regarding sex differences encompasses diverse fields, including genetics, immunology, endocrinology, developmental biology, cell biology, epidemiology, microbiology, biochemistry, and toxicology as well the behavioral and social sciences. Described below are examples of NIEHS research activities that further knowledge in this area. The activities support the implementation of the NIH Strategic Plan for Women's Health Research Goal 1: Increase Sex Differences Research in Basic Science Studies.

NIEHS is funding numerous human studies to examine the health effects of prenatal exposures to environmental chemicals on the developing fetus. To date, many studies have reported small but significant changes as they relate to reported sexually dimorphic behaviors. In some studies, pregnant women exposed to a specific class of endocrine disruptors have shown changes in their girls—but not in their boys—as related to depression, but changes in play behavior have been reported in boys but not in girls. Larger studies are being conducted to examine whether specific endocrine disruptors, such as phthalates and BPA, may perturb the developing fetal endocrine system and increase the risk for behavioral disorders. Such an effect may be related to changes in the gestational sex steroid milieu, as noted in animal studies. Outcomes to be addressed include, but are not limited to, visual and spatial abilities and a determination of whether males or females are more vulnerable to specific chemicals. This supports Strategic Plan Objectives 1.2, 1.7, and 1.8.

The general toxicology assessments conducted by the NTP usually involve exposures of rats and mice of both sexes to test chemicals for periods of 14 days or 13 weeks. The assessments that are almost always performed include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The NTP long-term toxicology and carcinogenesis studies (bioassays) in rodents generally employ both sexes of rats (Harlan Sprague Dawley) and mice (B6C3F1 hybrid), with three exposure concentrations, plus untreated controls in groups of 50 animals for 2 years. Both sexes are evaluated to determine whether there are differences in outcome caused by sex differences. This supports Strategic Plan Objectives 1.2, 1.4, and 1.7.

Several NIEHS grantees studying the effects of endocrine disruptors are showing sexually dimorphic effects. One researcher has shown that neonatal exposure to BPA in rats altered the expression of estrogen receptor alpha,

estrogen receptor beta, and kisspeptin in the anterior and mediobasal hypothalamus. Within the anterior hypothalamus, expression of estrogen receptor alpha was increased by BPA in females early and then fell to male levels. Kisspeptin expression was diminished by BPA in the anterior hypothalamus, especially in females. Overall, these results indicate that neonatal hypothalamic estrogen receptor and kisspeptin expression are sensitive to BPA. These effects show that estrogen receptor expression is specific to brain region, and changes may alter sexually dimorphic hypothalamic organization, underlie adult reproductive deficiencies, and contribute to sex differences in sociosexual behavior across the lifespan. This supports Strategic Plan Objectives 1.1, 1.2, 1.7, and 1.8.

The effects of BPA on cardiovascular health and heart development are being elucidated by NIEHS grantees. They are examining the effects of BPA on heart development and function both in vivo and in vitro. Grantees have studied rapid (less than 7 minutes) effects of BPA and estradiol in the heart and ventral myocytes from rodents. In isolated ventricular myocytes from young females but not males, BPA or estradiol rapidly induced arrhythmogenic-triggered activities. Under conditions of catecholamine stimulation, estradiol and BPA promoted ventricular arrhythmias in female but not male hearts. The cellular mechanism of the female-specific proarrhythmias in females but not males was examined. Exposure to estradiol or BPA rapidly altered myocyte calcium handling, increasing sarcoplasmic reticulum calcium leak and calcium load. The scientists also found that sensitivity to estradiol and BPA was not present in male myocytes and was abolished in myocytes from ovariectomized females. Analysis using selective estrogen receptor agonists showed that estrogen receptor alpha and beta have opposing effects in myocytes and that the balance between them is the prime regulator of the sex specificity toward estrogen. The response of female myocytes to estrogen and BPA is dominated by stimulatory estrogen receptor beta signaling, and in the absence of estrogen or BPA, responsiveness in the males is due to counterbalancing suppressive actions on estrogen receptor alpha. This is the first evidence that exposure to estrogenic endocrine-disrupting chemicals has a unique sensitivity to female hearts and may play a role in arrhythmogenesis in female hearts. This supports Strategic Plan Objectives 1.1, 1.2, 1.7, and 1.8.

NIEHS intramural scientists are studying how estrogen hormone action within target tissues involves the interaction of the hormonal substance with two different receptor proteins. Estrogen receptors are thought to play a crucial role in development, reproduction, and normal physiology. Studies in mice by the Institute's intramural scientists have yielded results that show differences in estrogen receptor genes, and results such as reduced bone density and some alterations in cardiovascular function. Further characterization of the mice and comparison of the individual and double estrogen receptor gene phenotypes will be required to more fully understand the physiological consequences of estrogen receptor-mediated actions and the specific roles of responsiveness to estrogen hormones. Differences in gene responses to hormonal xenobiotics were also seen in some in vitro gene regulation studies. Using a transactivation assay system, trichlorobiphenyl was shown to be more active than estradiol on the lactoferrin gene. Use of this estrogen-responsive yeast system also tested the xenobiotic estrogen synergy concept, and, with a variety of genes, showed that synergy was not apparent and had no universal application to hormone-responsive systems. In addition, investigators found that lavender and tea tree oils were acting as endocrine disruptors (estrogenic and antiandrogenic), which caused development of abnormal enlargement of breast tissue in young males. This supports Strategic Plan Objectives 1.1, 1.2, 1.7, and 1.8.

National Institute of General Medical Sciences

Executive Summary

The National Institute of General Medical Sciences (NIGMS) supports research and research training for the basic biomedical sciences. Studies supported by NIGMS do not necessarily target any particular disease or condition, but rather encompass basic research in cellular and molecular biology, chemistry, biochemistry, molecular biophysics, genetics, developmental biology, drug discovery, pharmacology, physiology, bioinformatics, computational biology, and selected areas of behavioral sciences as well as specific crosscutting clinical areas that affect multiple organ systems. NIGMS-supported research often is applicable to a wide variety of diseases or organ systems, including those specific to, or which disproportionately affect, women.

NIGMS supports interdisciplinary research training of predoctoral and postdoctoral scientists in basic medical sciences relevant to its mission. There are 12 predoctoral student training program areas, which span the research interests of the Institute. For example, the NIGMS training program aimed at the chemistry/biology interface has the goal of preparing more chemists with a knowledge and understanding of biological systems. This is an area of study critical to the design of new drugs and diagnostic and preventive approaches. This program complements the NIGMS training program in the pharmacological sciences that prepares young scientists to investigate the biochemical systems that are amenable to pharmacological intervention and to investigate the pharmacology of drug action and drug toxicity. The NIGMS training programs aimed at the behavior/biomedical science interface integrate training in basic behavioral research with similar rigorous training in the biological and biomedical sciences. These programs train students in basic behavioral science that is not targeted to a specific developmental stage or disease but which is fundamental to a range of diseases and health conditions. The institutional postdoctoral research training grants support the training of outstanding clinician-scientists in the four clinically relevant research areas within the mission of NIGMS:

(1) Anesthesiology;

(2) Clinical pharmacology;

(3) Medical genetics and trauma; and

(4) Burn and perioperative injury.

NIGMS supports the training of dual-degree candidates through the Medical Scientist Training Program (MSTP). The postdoctoral research training programs and the MSTP program both graduate doctors who can address basic research problems and relate their findings to clinical areas.

NIGMS is the home NIH Institute for the Institutional Development Award (IDeA) program, which is designed to broaden the geographic distribution of NIH funding for biomedical and behavioral research. The program fosters health-related research and enhances the competitiveness of investigators at institutions located in states in which the aggregate success rate for applications to NIH has historically been low. IDeA Networks of Biomedical Research Excellence (INBRE) promotes the development, coordination, and sharing of research resources and expertise that will expand the research opportunities and increase the number of competitive investigators in IDeA-eligible states. Research at INBRE facilities can include studies relevant to women's health or sex/gender differences. Examples include studies of animal models for human health issues such as low birth weight, basic studies of estrogen receptors, and an examination of the association between arsenic exposure and disturbed glucose metabolism during pregnancy. The Centers of Biomedical Research Excellence (COBRE) support thematic, multidisciplinary centers that augment and strengthen institutional biomedical research capacity. The focus of COBRE centers varies widely, from biomolecular structure to aging and regenerative medicine. A number of studies related to the interests of ORWH have come from these centers.

Research Programs

NIGMS is actively involved in the NIH Working Group on Women in Biomedical Careers and other working group committees.

In July 2008, on behalf of the NIH Working Group on Women in Biomedical Careers, NIGMS published a request for applications (RFA) to support research on causal factors and interventions that affect the careers of women in biomedical and behavioral science and engineering. In October 2009, NIH funded 14 grants estimated to total $16.8 million over 4 years with support from 11 ICs as well as 4 Offices within the NIH Office of the Director.

The aims of the program are to support research on 1) causal factors explaining the current patterns observed in the careers of women in biomedical and behavioral science and engineering, and 2) the efficacy of programs designed to eliminate sex/gender disparities and promote the careers of women in these fields.

A November 2012 workshop served as a forum for data presentations from all the grantees of this trans-NIH initiative, as well as an opportunity for discussion of the results, their implications, and potential next steps regarding implementation. Three groups of presentations, representing 1) observational studies, 2) longitudinal studies, and 3) intervention studies, were each followed by a moderated panel discussion. Four key themes emerged from the presentations and discussion:

- Building Evidence: Framing Gender Equity as a Scientific Problem
- Transferring Knowledge to Practice
- Achieving Cultural Change
- Work-Life Balance: Establishing a Healthy Climate

NIGMS is also taking part in the funding opportunity "Advancing Novel Science in Women's Health Research (ANSWHR)," (*http://grants.nih.gov/grants/guide/pa-files/PAS-10-226.html*), which seeks to promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences.

Accomplishments

Sexual Fate Is Not Final

Sex in mammals is determined in the fetal gonad by the presence or absence of a Y chromosome gene, which controls whether precursor cells differentiate into testicular cells or ovarian cells. This key decision in a single gonadal cell type ultimately controls sexual differentiation throughout the body. Sex determination can be viewed as a battle for primacy in the fetal gonad between a male regulatory gene network and a female regulatory gene network. It is known that in females the primary sex-determining decision is not final. Dr. David Zarkower of the University of Minnesota and his collaborators now have found that sexual fate also is labile in males: loss of the DMRT1 transcription factor in mouse testicular cells, even in adults, activates a regulatory gene network that reprograms testicular cells into ovarian cells. This reprogramming due to loss of DMRT1 also may help explain the cellular basis of human syndromes linked to DMRT1, including disorders of sexual differentiation.

Molecular Mechanism of "Pumping up" the X Chromosome

Females have two X chromosomes in their genomes, while males have an X and a Y. As a result, cells must work to emphasize, or "upregulate," the lone X chromosome in males and deemphasize, or "downregulate," the extra X chromosome in females. To try to determine how the X chromosome is upregulated, Dr. Erica Larschan and colleagues of Brown University measured the amount of active RNA polymerase II in the X chromosome in the model organism *Drosophila*, the fruit fly. RNA polymerase II, an enzyme, converts DNA instructions into RNA code to express genes. The researchers found that RNA polymerase II moved farther along the X chromosome than along other chromosomes. Because MSL (male-specific lethal) complex was known to increase transcription on the single X chromosome of *Drosophila* males, they then interfered with the MSL complex, reducing the amount of MSL complex in cells,

and determined that no greater amount of RNA polymerase persisted along the X chromosome genes than along any other genes in the genome. Thus, surprisingly, MSL complex is not regulating at the beginning of the gene but instead is regulating the entry of polymerase into the rest of the gene.

Toward Design of Inhibitors of Breast or Prostate Cancers

Cytochrome P450 17A1 is an enzyme involved in the synthesis of many human steroid hormones. This protein is an important target for the treatment of certain breast and prostate cancers. In order to understand how inhibitors of cytochrome P450 work and to design better inhibitors, the atomic structures of cytochrome P450 17A1 when bound to two clinically relevant inhibitors have been solved. The binding modes of the inhibitors differ significantly from those that were predicted by homology models and from structures that have been seen in other steroid-metabolizing cytochrome P450 enzymes. Although the inhibitors occupy the majority of the enclosed active site, the active site extends beyond the inhibitors in several directions. Based on the structure, new inhibitors could be devised that fill the active site more completely and thus might be more effective. Structure-based design may aid in the development of inhibitors that bind only cytochrome P450 17A1 and solely inhibit its activity specific to its roles in breast or prostate cancers. This work was done by Drs. Natasha DeVore and Emily Scott at the University of Kansas.

Implementation of the ORWH Strategic Plan Goals

The November 2012 workshop, which followed up on the RFA to support research on causal factors and interventions that affect the careers of women in biomedical and behavioral science and engineering, addressed Goal 6.3:

- Address the organizational, institutional, and systemic factors that impede recruitment, retention, and advancement of women in science, and modify practices that impede the careers of biomedical scientists.

The research accomplishments outlined above fit within Goal 1:

- Increase sex differences research in basic science studies.

The work specifically fits the following portions of Goal 1:

- **1.1.** Encourage genetic and epigenetic studies to identify sex differences in gene expression.
- **1.2.** Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.
- **1.7.** Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs. Apply this knowledge to sex differences in disease prevalence, symptoms, management, and outcomes in conditions such as lupus and cardiovascular diseases and to predominantly sex-specific diseases such as breast cancer and uterine fibroids.

National Institute of Mental Health

Executive Summary

The epidemiology and disability burden of mental disorders provide clear evidence of the value of a focus on both sex differences and women's mental health. There are differences in both the prevalence and clinical course of mental disorders between men and women. Starting in childhood, girls have higher rates of anxiety disorders and eating disorders than boys, while boys are more likely to suffer from autism spectrum disorders and attention deficit hyperactivity disorder. After puberty, women have higher rates than men of depression, eating disorders, and anxiety disorders, including posttraumatic stress disorder. There are also differences in the course and severity of mental disorders between men and women. Additionally, some women are at increased risk of depression during certain times of

reproductive change, such as in the perinatal period and perimenopause.

Through its research programs and related programmatic activities, the National Institute of Mental Health (NIMH) has increased scientific understanding of the effects of sex and gender differences in mental health and mental illness. NIMH has also advanced knowledge in the area of specific mental disorders that either affect women exclusively (e.g., perinatal depression), or predominantly (e.g., eating disorders). Through crosscutting efforts such as the Women's Mental Health Team, NIMH has fostered interdisciplinary collaboration and research to improve diagnosis, treatment, services, and the prevention of mental disorders in women. Through new initiatives in global mental health, revitalized efforts in promoting research on mental health disparities, and increased training in both of these areas, NIMH is laying the groundwork for accelerated research in global health and disparities research that often includes projects on women's health research. This FY 2011–FY 2012 NIMH report highlights NIMH offices and groups designated to focus on women's mental health. The report also highlights published findings on sex differences and women's mental health research, specific workshops and initiatives to promote research in the areas described above, and efforts on behalf of special populations of women. Research highlights, initiatives, and workshops are grouped by relationship to the goals of the NIH Strategic Plan for Women's Health Research, with the relevance to specific NIH objectives described in each goal section. Separate sections are demarcated on sex steroids, women and trauma, women and aging, sexual minorities, and pregnancy. Findings regarding adolescents, low-income women, rural women, and mental health disparities are featured throughout the research highlights.

Offices and Groups Designated to Focus on Women's Mental Health

The Women's Mental Health Program is located organizationally in the Office for Research on Disparities and Global Mental Health (ORDGMH) within the Office of the NIMH Director. The Women's Mental Health Program was established to ensure coordination of NIMH-funded research on women's mental health and on sex and gender differences. Other functions include serving as an organizational focal point for women's mental health science communication and liaising with ORWH and other governmental and nongovernmental organizations interested in women's issues. The chief of the Women's Mental Health Program serves on a number of NIMH, NIH, and other Federal working groups and committees, which are detailed under Goal 4, in order to contribute to NIH and Federal collaboration in women's mental health research. ORDGMH coordinates NIMH activities that serve to fulfill the congressional mandate for tracking the inclusion of women and minorities in clinical research.

The Women's Mental Health Team serves as the focal point for coordination of NIMH scientific activities related to women's health and sex/gender differences research. Members of the team include representatives from all five extramural research divisions and the Division of Extramural Activities as well as the Office of Science Policy, Planning, and Communications (OSPPC), the Office of Constituency Relations and Public Liaison (OCRPL), and the Executive Office. Team members work together across disciplinary boundaries to plan workshops, prepare and review science reports, and create funding opportunities related to women's mental health.

Accomplishments, Initiatives, and Research Highlights

In this section, NIMH accomplishments, initiatives, and research highlights are organized as they relate to the NIH Strategic Goals for Women's Health Research.

Goal 1. Increase sex differences research in basic science studies.

Research on Sex Differences in Brain and Behavior

Many mental disorders have striking gender disparities in prevalence, as shown in population-based epidemiology studies of U.S. adults. For example, adult women

experience major depression at almost twice the rate of adult men. Sex differences can be due to a variety of factors, including the effects of sex-linked genes, sex hormones, and differences in environmental stressors that impact brain structure and function. Understanding the mechanisms underlying these sex differences may provide clues as to why men and women are differentially vulnerable to certain mental illnesses. The continued commitment of NIMH to fostering research in this area is illustrated by the meeting and the funding opportunity announcements (FOAs) summarized below. Recent findings from NIMH supported research studies are provided below and illustrate the Institute's efforts in relation to many of the objectives of Goal 1. The basic and translational research findings on the effects of trauma upon women are summarized separately below.

Meeting

On February 28–March 1, 2011, NIMH convened a workshop on Sex Differences in Brain, Behavior, Mental Health and Mental Disorders and invited experts in the field to discuss recent findings and gaps within the study of sex differences in the brain. Research in the domains of cognition, affect, and social behavior were highlighted, and the presentations and discussion were used to inform the writing of the set of FOAs noted below.

FOAs

In December 2011, NIMH announced the following set of FOAs, with set-aside funding for FY 2013 and beyond:

Neural Processes Underlying Sex Differences Related to Risk and Resilience for Mental Illness. The FOAs notified researchers of funding for new R21 applications as well as supplements to existing R01s and P50s:

- *http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-13-020.html*
- *http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-13-021.html*
- *http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-13-022.html*

Nine R21 grants have been accepted for funding in FY 2013–2014, with cofunding from ORWH. These FOAs, as well as the bulk of NIMH-funded research on sex differences, focus on:

- Objective 1.5: Promote neuroscience research to study sex/gender differences in vulnerability to and clinical course of neurological, psychiatric, and substance abuse disorders.

Recent Findings

NIMH-funded studies include the published examples summarized below, which follow several other objectives of Goal 1:

- Objective 1.2: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems;
- Objective 1.3: Study sex differences using a systems-biology–based approach; and
- Objective 1.4: Include sex parameters in the design of experiments using animal models.

A Structural Basis for Sex Differences in Emotional Arousal. Dysregulation of the noradrenergic system is a hallmark of chronic stress and stress disorders such as major depression and posttraumatic stress disorder (PTSD). NIMH grantee Rita Valentino has been investigating the mechanisms by which such dysregulation might arise by studying the locus coeruleus (LC) in rats. Because stress-related disorders are more common in women than in men, Dr. Valentino and her associates have focused on sex differences in LC structure and function. Recently, the group has shown that the dendrites of female LC neurons are different from those of males. Specifically, the group's work indicates that female LC dendrites are longer, cover a greater area, have more branch points, and make more synaptic contacts than those of their male counterparts. These results suggest that LC neurons in females may receive more inputs, giving rise to heightened emotional arousal and a susceptibility to stress disorders (Bangasser, D. A., Zhang, X., Garachh, V., Hanhauser, E., &Valentino, R. J. (2011). Sexual dimorphism in locus coeruleus dendritic morphology: A structural basis for sex differences in emotional arousal. *Physiology & Behavior, 103*, 342–351).

XX vs. XY: Sex Chromosome Genes Lead to Sexual Dimorphisms in Frontal Cortex and Cerebellum. Many sex differences depend on hormone exposure. Investigators have recently examined the direct effects of differences in the sex chromosomes themselves. One method involves the four-core genotype (FCG) mouse model, in which chromosomal complement and gonadal type can be separated. Using this model, NIMH grantee Emilie Rissman and her associates have shown that the calcium-binding protein calbindin is expressed at higher levels in the frontal cortex and cerebellum of XX versus XY juvenile mice. This finding provides a demonstration of a nonhypothalamic, chromosomally based sexual dimorphism. Given the multiple critical functions that calcium and calcium binding play in neuronal function and communication, this finding could have important implications for sex differences in a wide range of mental-health-relevant behaviors. The research group is investigating one such set of behaviors, social interactions, in juvenile FCG mice (Abel, J. M., Witt, D. M., & Rissman, E. F. (2011). Sex differences in the cerebellum and frontal cortex: Roles of estrogen receptor alpha and sex chromosome genes. *Neuroendocrinology, 93*, 230–240; Cox, K. H., & Rissman, E. F. (2011). Sex differences in juvenile mouse social behavior are influenced by sex chromosomes and social context. *Genes, Brain and Behavior, 10*, 465–472).

Signaling Molecule Disruption Shows Importance of Sex-Specific Cerebellum Development and Function to Cognitive and Social Behavior. A recent study examined a novel role for secreted molecules, called prostaglandins, in the development of the cerebellum, a structure best known for controlling movement but which has recently been implicated in regulating social cognition. The cerebellum has especially high levels of receptors for these molecules; when scientists disrupted prostaglandin synthesis, they found an initial period of cell overgrowth in both sexes, followed by cell decline that was more pronounced in males than females. Interestingly, while motor control was unaffected, there were deficits in social interactions and sensory processing that were also more pronounced in males than females. The anatomical and behavioral deficits are similar to those seen in autism, which is characterized by initial overgrowth of cells, followed by social and sensory deficits. These results identify a new role for prostaglandins in cerebellar development and strengthen the link between cerebellar dysfunction and autism (Dean, S. L., Knutson, J. F., Krebs-Kraft, D. L., & McCarthy, M. M. (2012). Prostaglandin E2 is an endogenous modulator of cerebellar development and complex behavior during a sensitive postnatal period. *European Journal of Neuroscience, 35*, 1218–1229).

Astrocytes in the Rat Medial Amygdala Are Responsive to Adult Androgens. Research has demonstrated that a number of brain regions in mammals are sexually dimorphic because of differences in neuron number and complexity between males and females and that these differences are dependent on exposure to gonadal hormones during development and throughout life. A recent study supported in part by NIMH extends this research to demonstrate that differences in the number and complexity of astrocytes between males and females in the medial amygdala are also dependent on exposure to gonadal hormones in the adult. The researchers found that in females, androgens appear to support increased astrocyte numbers in the right medial amygdala compared with the left, but they do not influence astrocyte morphology. However, in males, androgens increase the complexity of astrocyte morphology in this region but not the overall number of astrocytes. The amygdala is of particular interest because it is associated with fear/anxiety and social/mating behaviors and a variety of psychiatric disorders that exhibit sex biases in prevalence rates (Johnson, R. T., Schneider, A., DonCarlos, L. L., Breedlove, S. M., & Jordan, C. L. (2012). Astrocytes in the rat medial amygdala are responsive to adult androgens. *Journal of Comprehensive Neurology, 520*, 2531–2544).

Estrogen Effects on Mood Relevant Signaling in Brain, Insight into Modulatory Effects of Social Stress. Ovarian hormones have inconsistently been shown to modulate mood and anxiety symptoms. A new study suggests how social factors may contribute

to the variable effects of the ovarian hormone estradiol (E2) in females. In a study of ovariectomized adult female rhesus monkeys, chronic administration of E2 decreased levels of serotonin metabolites in the cerebrospinal fluid of only those dominant females who also expressed a specific variant of the serotonin transporter. Chronic administration of E2 decreased levels of the dopamine metabolite in a manner independent of social status, genotype, or their interactions. Overall levels of dopamine and serotonin metabolites were increased in subordinate females, although this effect of social stress was not influenced by genotype variation. Together, these data underscore how E2 can modulate central neurotransmitter systems and indicate that social subordination in female monkeys is a valid model for examining how chronic psychosocial stress alters sensitivity to E2 (Asher, J., Michopoulos, V., Reding, K. M., Wilson, M. E., & Toufexis, D. (2013). Social stress and the polymorphic region of the serotonin reuptake transporter gene modify oestradiol-induced changes on central monoamine concentrations in female rhesus monkeys. *Journal of Neuroendocrinology, 25*, 321–328).

The Effect of Sex Steroids

NIMH, in both its extramural and intramural programs, supports research on naturally occurring sex steroids and their effects upon development and vulnerability to mental illness. In addition, exposure to environmental hormones is under investigation.

- Objective 1.7: Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs; and
- Objective 3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

Sexually Dimorphic Effects of Gestational Exposure to Bisphenol A (BPA). BPA is a component of plastics thought to affect brain development during gestation. BPA binds to a range of steroid receptors, including estrogen receptors, and its effects may be sexually dimorphic. NIMH awardee Emilie Rissman and her associates have been investigating the effects of adding BPA to maternal diets on the brain development and behaviors of juvenile mice. Recently, the group reported that exposure to relatively high doses of BPA during gestation increased anxiety primarily in juvenile males. On the other hand, when BPA levels were calibrated to those seen in humans, the behavioral impact was seen in females. In this case, gestational BPA increased peer social interactions in females. Embryonic gene expression levels were also assessed (Cox, K. H., Gatewood, J. O., Howeth, C., & Rissman, E. F. (2010). Gestational exposure to bisphenol A and cross-fostering affect behaviors in juvenile mice. *Hormones and Behavior. 58*, 754–761; Wolstenholme, J. T., Taylor, J. A., Shetty, S. R., Edwards, M., Connelly, J. J., & Rissman, E. F. (2011). Gestational exposure to low dose bisphenol A alters social behavior in juvenile mice. *Public Library of Science One, 6*, e25448).

Basic, Genetic, Translational, and Clinical Findings on the Effects of Trauma upon Women

These findings relate to the objectives listed under Goal 1, as well as Goals 2 and 3.

- Objective 2.6: Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery; and
- Objective 3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

Post-Traumatic Stress Disorder (PTSD) Is Associated with PACAP and the PAC1 Receptor in Women. Pituitary adenylate cyclase-activating polypeptide (PACAP) is known to broadly regulate the cellular stress response. NIMH awardees Kerry Ressler and his associates reported in highly traumatized subjects a sex-specific association of PACAP blood levels with fear physiology. Forty-four single nucleotide polymorphisms (SNPs) spanning the PACAP (encoded by ADCYAP1) and PAC1 (encoded by ADCYAP1R1) genes were examined, and a sex-specific association with PTSD was found. A single SNP in a putative estrogen response element within ADCYAP1R1, rs2267735, was found to predict PTSD diagnosis and symptoms in

females only. Findings suggest that perturbations in the PACAP-PAC1 pathway are involved in abnormal stress responses underlying PTSD and that the sex-specific effects may occur via estrogen regulation (Ressler, K. J., Mercer, K. B., Bradley, B., Jovanovic, T., Mahan, A., Kerley, K., … May, V. (2011). Posttraumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature, 470*, 492–497).

Genetic Vulnerability Plus Trauma Exposure Can Lead to Post-Traumatic Stress Disorder (PTSD) in Women. NIMH-funded researchers studied PTSD in women already enrolled in an ongoing study of sexual revictimization who were on a college campus in 2008 when a mass shooting occurred. A cohort of female undergraduate students, who had been interviewed prior to the shooting and on whom prior measures of PTSD and trauma had been obtained, completed follow-up trauma-related measures, including PTSD symptom severity. The follow-up survey was launched 17 days after the shooting. Salivary samples were collected from 276 women, and these were genotyped for variants of the serotonin transporter promoter region. Findings indicate that differential function of the serotonin transporter may mediate differential response to a severe trauma. When examined in a relatively homogenous sample with shared trauma and known prior levels of child and adult trauma, the 5-HTTLPR multimarker genotype may serve as a useful predictor of risk for PTSD-related symptoms in the weeks and months following a trauma (Mercer, K. B., Orcutt, H. K., Quinn, J. F., Fitzgerald, C. A., Conneely, K. N., Barfield, R. T., … Gillespie, C. F. (2012). Acute and posttraumatic stress symptoms in a prospective gene x environment study of a university campus shooting. *Archives of General Psychiatry, 69*, 89–97).

Startle Responses and Sex-Specific Correlates of Posttraumatic Stress Disorder. To further understand mechanisms of PTSD, NIMH-supported researchers examined the dark-enhanced startle response, a psychophysiological correlate of anxiety, and heart rate variability in traumatized individuals with and without PTSD. PTSD was associated with a greater degree of dark-enhanced startle in women but not in men. The associations of these measures with PTSD may be sex-specific because of their associations with the bed nucleus of the stria terminalis, a sexually dimorphic brain structure in the limbic system (Kamkwalala, A., Norrholm, S. D., Poole, J. M., Brown, A., Donley, S., Duncan, E., … Jovanovic, T. (2012). Dark-enhanced startle responses and heart rate variability in a traumatized civilian sample: Putative sex-specific correlates of posttraumatic stress disorder. *Psychosomatic Medicine, 74*, 153–159).

The Role of Sex Hormones in Female Fear Extinction. Given that increased levels of estradiol are associated with enhanced fear extinction, NIMH-funded researchers hypothesized that hormonal contraceptives (HCs) may impair fear extinction memory in women and female rats and that increasing estradiol levels following cessation of HCs may return HC-associated fear extinction to normal. The results show that HC dose-dependently impaired fear extinction in healthy women and in female rats, while the termination of HC treatment following fear conditioning prevented impairments in extinction recall in female rats. The data also show that HC-associated impairments in fear extinction in female rats can be rescued by systemic administration of estrogen agonists and that women treated with estradiol exhibited significantly reduced recovery of fear. Because a single dose of estrogen administered 30 minutes before extinction training rescued fear extinction in rats and women, these data suggest that changes in estrogen levels may have rapid physiological consequences on the regulation of memory processes underlying fear extinction. The results highlight the importance of estrogen in fear extinction processes and the necessity of conducting future studies that consider the use of HCs and hormonal status in women in clinical settings (Graham, B. M., & Milad, M. R. (2013). Blockade of estrogen by hormonal contraceptives impairs fear extinction in female rats and women. *Biological Psychiatry, 73*, 371–378).

Effects of Sex Hormones on Emotional and Traumatic Memories. Levels of estrogen and progesterone change significantly during different phases of the menstrual cycle

and can be altered by exogenous hormonal contraception. In a series of recent studies, NIMH-supported researcher Larry Cahill and his colleagues have demonstrated that alterations in sex hormone levels can significantly affect emotional memory. In two studies of naturally cycling women, these researchers found enhanced encoding and spontaneous intrusive recollections of negatively valenced emotional images by women in the luteal versus the follicular phase. These differences were attributable primarily to higher progesterone levels during the luteal phase (Ertman, N., Andreano, J. M., & Cahill, L. (2011). Progesterone at encoding predicts subsequent emotional memory. *Learning & Memory, 18*, 759–763; Ferree, N. K., Kamat, R., & Cahill, L. (2011). Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. *Consciousness and Cognition, 20*, 1154–1162).

Dr. Cahill has extended his work by investigating the effects of sex hormone differences for recovery from traumatic events. In a study of women seen in a Sexual Assault Response Team center, he found that emergency contraceptive administration reduced the frequency of PTSD symptoms reported 5–7 months postassault. The emergency hormonal contraceptives appeared to reduce primarily the intrusive recollections. Furthermore, when two types of contraceptives were compared, it was found that Ogestrel® (two doses of 0.1 mg ethinyl estradiol/0.5 mg levonorgestrel) had a greater impact than Plan B (single dose of 1.5 mg levonorgestrel). These results provide support for targeting sex hormone status in the development of preventive measures for PTSD (Ertman, N., Andreano, J. M., & Cahill, L. (2011). Progesterone at encoding predicts subsequent emotional memory. *Learning & Memory, 18*, 759-763; Ferree, N. K., Kamat, R., & Cahill, L. (2011). Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. *Consciousness and Cognition, 20*, 1154–1162; Ferree, N. K., Wheeler, M., & Cahill, L. (2012). The influence of emergency contraception on post-traumatic stress symptoms following sexual assault. *Journal of Forensic Nursing, 8*, 122–130).

PTSD, Genotype, and Childhood Maltreatment Interaction in Women. Building on evidence that genetic variation, in combination with adverse early-life experiences, shapes risk for later mental illness, NIMH-funded researchers enrolled 495 women from the Detroit Neighborhood Health Study in a study of how a particular gene variant was associated with PTSD in women. PTSD, posttraumatic stress (PTS), depression, and childhood maltreatment (CM) exposure were assessed via structured interviews. Researchers found no main effect of the candidate genotype on either PTSD or PTS severity. They did find that carriers of a particular version of the gene who had CM exposure exhibited enhanced risk for PTSD and PTS in the past month. No significant main or interaction effects were observed for past-month depression/depression severity. Thus, this study provides further evidence for the interaction of CM and trauma in the etiology of PTSD in women (Uddin, M., Chang, S. C., Zhang, C., Ressler, K., Mercer, K. B., Galea, S., … Koenen, K. C. (2013). Adcyap1r1 genotype, posttraumatic stress disorder, and depression among women exposed to childhood maltreatment. *Depression and Anxiety, 30*, 251–258).

Borderline Personality Disorder and Dialectical Behavioral Therapy. Suicidal behavior and self-injury are frequent and often chronic hallmarks of the borderline personality disorder (BPD). Patients with BPD have been shown to respond positively to dialectical behavior therapy (DBT). This study developed and pilot-tested a prolonged exposure (PE) therapy to be added to DBT to target PTSD in recently suicidal and self-injuring individuals diagnosed with BPD. The treatment was associated with significant reductions in PTSD, with the majority of patients no longer meeting criteria for PTSD at posttreatment. Concerns about a "contagion effect" and possible exacerbation of self-injury are frequently raised in clinical settings in which treatment focuses on self-injury and when patients with BPD are treated in a group. Although a minority of patients engaged in intentional self-injury during the study, there was no evidence that the DBT PE protocol led to exacerbations of intentional self-injury urges or behaviors,

PTSD, treatment dropout, or use of a crisis service. Improvements were also found for suicidal ideation, dissociation, trauma-related guilt cognitions, shame, anxiety, depression, and social adjustment, indicating that this integrated BPD and PTSD treatment may be a feasible adjunct after other treatment and an effective approach in this complex and high-risk patient population (Harned, M. S., Korslund, K. E., Foa, E. B., & Linehan, M. M. (2012). Treating PTSD in suicidal and self-injuring women with borderline personality disorder: Development and preliminary evaluation of a Dialectical Behavior Therapy Prolonged Exposure Protocol. *Behaviour Research and Therapy, 50,* 381–386).

Women Who Are Forced into Sex Work Are at Higher Risk for HIV and Violence. Sex trafficking is a significant global concern. An estimated 150,000 women and girls are forced into sex work across South Asia every year. Research was undertaken in Andhra Pradesh, India, to gain a greater understanding of the number of women who are forced into sex work and the associations between sex trafficking and recent violence experiences and HIV vulnerability. In a sample of over 800 female sex workers, 1 in 5 met the United Nations definition of sex trafficking. A history of sex trafficking was associated with a greater vulnerability to recent violence and HIV risk behaviors. Additionally, women who had been forced into sex work were less likely to access female sex worker services. Thus, women who are the victims of sex trafficking may require additional HIV prevention services to address their needs (Gupta, J., Reed, E., Kershaw, T., & Blankenship, K. M. (2011). History of sex trafficking, recent experiences of violence, and HIV vulnerability among female sex workers in coastal Andhra Pradesh, India. *International Journal of Gynecology and Obstetrics, 114,* 101–105).

Gender-Based Violence Serves as a Risk to HIV Infection and a Barrier to HIV Testing. Violence, abuse, and rape are highly prevalent worldwide. One in three women worldwide will be victims of rape or attempted rape, and equal numbers will experience abuse of any kind. Studies have documented the link between gender-based violence and HIV infection. HIV testing is a crucial step in helping women to access the care needed if they do become HIV positive; however, women who experience gender-based violence may experience barriers to HIV testing. This study interviewed 97 South African women who had experienced relationship violence of a physical, emotional, sexual, or financial nature. Almost half of the women had sought HIV testing. Women who had gone to the police for help were more likely to have been tested for HIV. Given the low rates of HIV testing, HIV testing services should be integrated into services for women who are the victims of gender-based violence (Adams, J. L., Hansen, N. B., Fox, A. M., Taylor, B. B., van Rensburg, M. J., Mohlahlane, R., & Sikkema, K. J. (2011). Correlates of HIV testing among abused women in South Africa. *Violence Against Women, 17,* 1014–1023).

Goal 2. Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs.

Research on Sex Differences and Disorders in Women Using Neuroimaging

Recent Findings

Many NIMH-funded published findings make use of advanced neuroimaging techniques that also lead to further development of these approaches; the three sets of findings described below follow Objective 2.6 of NIH Goal 2 or Objective 3.5 of NIH Goal 3.

- Objective 2.6: Exploit high-resolution bioimaging technologies to provide structural and functional imaging of sex differences in a variety of areas such as pain, brain activity, metabolism, infectious diseases, inflammation, and drug delivery; and
- Objective 3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

Puberty and Circulating Hormones Influence Brain Development in Boys and Girls. The brains of boys and girls change during adolescence and differ from one another, but are these differences because they go through puberty at different ages? In

a study that controlled for both sexual maturity and age, researchers found that pubertal hormones were correlated with cortical thickness, with regions of high and low sensitivity to hormones (as measured by hormone receptor density) differing in developmental patterns in boys and girls. These findings help explain normal brain development and potentially have implications for understanding why boys and girls are at risk for different mental illnesses that have their onset during adolescence (Bramen, J. E., Hranilovich, J. A., Dahl, R. E., Forbes, E. E., Chen, J., Toga, A. W., … Sowell, E. R. (2011). Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. *Cerebral Cortex, 21*, 636–646).

Boys and Girls with ADHD Have Different Patterns of Anomalous Brain Development. Elementary school-aged boys are diagnosed with attention deficit hyperactivity disorder (ADHD) at higher rates than girls, and they may experience different sets of behavioral symptoms. Using structural magnetic resonance imaging, a team of researchers has examined brain structure in boys and girls aged 8–13 years with and without ADHD. Compared with typically developing children, both boys and girls with ADHD showed reduced gray and white matter volume in the left supplementary motor complex. However, there were also significant differences between boys and girls. Girls with ADHD showed reduced gray matter volume in the left premotor cortex, and this reduction was correlated with trial-by-trial variability on a task that measured impulsivity. Boys with ADHD showed reduced white matter volume in the left medial prefrontal cortex (Mahone, E. M., Ranta, M. E., Crocetti, D., O'Brien, J., Kaufmann, W. E., Denckla, M. B., & Mostofsky, S. H. (2011). Comprehensive examination of frontal regions in boys and girls with attention-deficit/hyperactivity disorder. *Journal of the International Neuropsychological Society, 17*, 1047–1057).

Delayed Effects of Early Life Stress in Females. Early life stress (ELS) and function of the hypothalamic-pituitary-adrenal axis predict later psychopathology. This study prospectively investigated the roles of ELS and childhood levels of basal cortisol in the development of adolescent resting-state functional connectivity (assessed by functional connectivity magnetic resonance imaging) in the amygdala-prefrontal cortex (PFC) circuit. In females only, greater ELS predicted increased childhood cortisol levels, which predicted lesser connectivity between the amygdala and the ventromedial prefrontal cortex (vmPFC) 14 years later. For females, adolescent amygdala-vmPFC functional connectivity was inversely correlated with concurrent anxiety symptoms but positively correlated with depressive symptoms, suggesting differing pathways from childhood cortisol levels function through adolescent amygdala-vmPFC functional connectivity to anxiety and depression. These data highlight that, for females, the effects of ELS and early HPA-axis function may be detected much later in the intrinsic processing of emotion-related brain circuits (Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E, K., Armstrong, J. M., Oler, J. A., … Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nature Neuroscience, 15*, 1736–1741).

Goal 3: Actualize personalized prevention, diagnostics, and therapeutics for girls and women.

Translational and Clinical Research on Disorders in Women: Risk Factors, Etiology, Course of Illness, and Therapeutics

Recent Findings

NIMH intramural and extramural-funded research focuses on risk factors for mental disorders, the etiology and course of these disorders, and intervention research, following Objectives 3.1 and 3.9 of Goal 3.

- Objective 3.1: Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan; and
- Objective 3.9: Examine health disparities among women stemming from differences

in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

Initiatives and findings on pregnant women/perinatal disorders, women and aging, and sexual minority issues are highlighted separately at the end of this section, with their respective Goal 3 objectives.

Older Age of Menarche and Risk for Depression. Previous research suggests that earlier menarche predicts more depression in adolescence. This prospective longitudinal study of a diverse cohort of girls, however, controlled for the potentially confounding effects of childhood depressive symptoms. The investigators found that higher levels of childhood depressive symptoms and earlier menarche have independent effects on adolescent depressive symptoms. Childhood depressive symptomatology predicted later age of menarche, although the magnitude of this effect was small. Taken together, the results suggest that early childhood depressive symptoms and early menarche represent independent pathways to later depressive symptoms (Black, S. R., & Klein, D. N. (2012). Early menarcheal age and risk for later depressive symptomatology: The role of childhood depressive symptoms. *Journal of Youth and Adolescence, 41*, 1142–1150).

Mood Measures Predict Physiological Response in Asymptomatic Girls at Risk for Depression. In two studies, never-depressed adolescent daughters of either recurrently depressed mothers (RISK) or mothers who had not experienced depression (CTL) underwent social stressors while their physiological responses were measured (cortisol level and heart rate). In both studies, mood or affective responses to the stressors predicted physiological responses in RISK girls, but not in CTL girls. For RISK girls, decreased positive affect in response to stress predicted increased cortisol reactivity; in addition, decreased positive affect and increased negative affect were associated with poorer heart rate recovery and habituation, respectively. Future research is needed to examine explicitly whether this coherence between affect and physiology is a mechanism underlying the increased risk for psychopathology in children of depressed parents (Waugh, C. E, Muhtadie, L., Thompson, R. J., Joormann, J., & Gotlib, I. H. (2012). Affective and physiological responses to stress in girls at elevated risk for depression. *Development and Psychopathology, 24*, 661–675).

Statistical Measures Show High Accuracy in Predicting Symptom Response in PMDD. A majority of women with premenstrual dysphoric disorder (PMDD) show symptomatic improvement in response to leuprolide, a drug that suppresses ovarian function, but it has been very difficult to either predict or understand why some women respond while others do not. When several complementary statistical methods were applied to mood-rating data to determine possible predictors of response for women with PMDD, greatly enhanced prediction was achieved. The statistical measures may have broad and direct applicability to behavioral studies for many psychiatric disorders, facilitating both accurate diagnosis and the prediction of response to treatment (Pincus, S. M., Alam, S., Rubinow, D. R., Bhuvaneswar, C. G., & Schmidt, P. J. (2011). Predicting response to leuprolide of women with premenstrual dysphoric disorder by daily mood rating dynamics. *Journal of Psychiatric Research, 45*, 386–394).

Premenstrual Dysphoric Disorder (PMDD) Quickly Responds to Antidepressant Treatment. Women diagnosed with PMDD were treated with fluoxetine (20 mg daily) during the luteal phase of the menstrual cycle. Ratings showed significant improvement in irritability as well as sadness, anxiety, and mood swings, compared with women with PMDD who were rated but not treated with fluoxetine (Steinberg, E. M., Cardoso, G. M., Martinez, P. E., Rubinow, D. R., & Schmidt, P. J. (2012). Rapid response to fluoxetine in women with premenstrual dysphoric disorder. *Depression and Anxiety, 29*, 531–540).

Understanding the Association Between Depression and Primary Ovarian Insufficiency (POI). POI is associated with an increased lifetime risk for major depression. In a study of women with POI, NIMH intramural researchers found that the onset of depression frequently preceded the

diagnosis of POI but occurred after the onset of menstrual irregularity. Analyses standardizing the periods of risk for depression showed that similar numbers of depressions occurred before and after these events. The association between POI and depression suggests an overlapping pathophysiology rather than a causal relationship. Attention to the presence of depression should be an important part of the care for women with POI (Schmidt, P. J., Luff, J. A., Haq, N. A., Vanderhoof, V. H., Koziol, D. E., Calis, K. A., … Nelson, L. M. (2011). Depression in women with spontaneous 46, XX primary ovarian insufficiency. *The Journal of Clinical Endocrinolology and Metabolism, 96,* E278–E287).

Women and Aging

These findings relate to Objectives 3.7 and 3.8:

- Objective 3.7: Explore differences in response to therapeutic interventions among samples of elderly women, including those with comorbid conditions; and
- Objective 3.8: Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

Menopausal Transition. NIMH-funded researchers studied mental-health-related patterns in women associated with their experience of the menopausal transition. Hadine Joffe and her colleagues found that health-related quality of life (QOL) during menopause is strongly influenced by a history of affective illness (major depressive disorder or anxiety disorder) in a manner that is largely independent of such other menopausal features as vasomotor symptoms and sleep disturbance, although sleep disturbance also influences QOL and interacts with psychiatric history to some extent. The analysis by Jill Cyranowski and her colleagues indicates that women with a history of both depression and anxiety disorder as comorbid conditions tend to continue to experience more psychiatric disorder, distress, stressful events, and poor social support during menopause, as compared with women whose psychiatric histories involve one or the other diagnosis but not both as comorbid conditions (Joffe, H., Chang, Y., Dhaliwal, S., Hess, R., Thurston, R., Gold, E., … Bromberger, J. T. (2012). Lifetime history of depression and anxiety disorders as a predictor of quality of life in midlife women in the absence of current illness episodes. *Archives of General Psychiatry, 69,* 484–492; Cyranowski, J. M., Schott, L. L., Kravitz, H. M., Brown, C., Thurston, R. C., Joffe, H., … Bromberger, J. T. (2012). Psychosocial features associated with lifetime comorbidity of major depression and anxiety disorders among a community sample of mid-life women: The SWAN mental health study. *Depression and Anxiety, 29,* 1050–1057).

Depression and Other Medical Comorbidity in an Older Female Cohort. NIMH-funded researchers studied women in old age, analyzing mental health data from the large Study of Osteoporotic Fractures. They found that older women's risk of experiencing either persistent or increasing severity of depressive symptoms was associated with such factors as greater medical comorbidity, physical disability, small social networks, and negative lifestyle features such as smoking, obesity, and low physical activity. Another group of NIMH-funded researchers documented the ways in which depression is associated with greater sleep disturbance in these women, while a third group determined that even in advanced old age, depression continues to operate as a risk factor that increases women's risk for developing subsequent cognitive dysfunction 5 years later (Byers, A. L., Vittinghoff, E., Lui, L. Y., Hoang, T., Blazer, D. G., Covinsky, K. E., … Yaffe, K. (2012). Twenty-year depressive trajectories among older women. *Archives of General Psychiatry, 69,* 1073–1079; Maglione, J. E., Ancoli-Israel, S., Peters, K. W., Paudel, M. L., Yaffe, K., Ensrud, K. E., & Stone, K. L. (2012). Depressive symptoms and subjective and objective sleep in community-dwelling older women. *Journal of the American Geriatric Society, 60,* 635–643; Spira, A. P., Rebok, G. W., Stone, K. L., Kramer, J. H., & Yaffe, K. (2012). Depressive symptoms in oldest-old women: Risk of mild cognitive impairment and dementia. *The American Journal of Geriatric Psychiatry, 20,* 1006–1115).

Sexual Minority Issues

NIMH participated in the NIH Lesbian, Gay, Bisexual, Transgender and Intersex (LGBTI) Research Coordinating Committee, which was formed in 2011, and participated in writing the "Consideration of the Institute of Medicine (IOM) Report on the Health of Lesbian, Gay, Bisexual, and Transgender Individuals," which was completed in 2012. NIMH also participated in the National Action Alliance for Suicide Prevention's (NAASP's) LGBT Task Force, and the Institute supports a number of research grants in this area. In order to encourage more research in this area, NIMH participated in the NIH set of program announcements titled "Research on the Health of LGBTI Populations," which was released in 2012:

- *http://grants.nih.gov/grants/guide/pa-files/PA-12-111.html*
- *http://grants.nih.gov/grants/guide/pa-files/PA-12-112.html*
- *http://grants.nih.gov/grants/guide/pa-files/PA-12-113.html*

Research on Pregnancy and the Perinatal Period

- Objective 3.3: Encourage research on safe and effective interventions for conditions affecting pregnant women;
- Objective 3.4: Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring; and
- Objective 3.5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

The Patient Protection and Affordable Care Act of 2010 called for continued Federal research on postpartum depression. The two program announcements listed below, which were on "Women's Mental Health during Pregnancy and the Postpartum Period" and were issued in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute on Drug Abuse, outline research areas of interest that span basic and clinical research, clinical course, epidemiological and risk factors research, and intervention and services research.

- *http://grants.nih.gov/grants/guide/pa-files/PA-12-215.html*
- *http://grants.nih.gov/grants/guide/pa-files/PA-12-216.html*

Risk Factors Associated with Perinatal Depression. NIMH-funded researchers studied 116 pregnant urban adolescents and found that a history of physical or sexual abuse was a significant factor related to the severity of depressive symptoms in pregnant adolescents, independent of a history of alcohol, drug use, or depression. Their findings also suggest that an assessment of history of alcohol use, as well as abuse history, may increase the likelihood of identifying adolescents at risk for antenatal depression. Another set of NIMH-funded researchers examined trauma history in relation to the outcomes of an interpersonal therapy trial for perinatal depression. Women with more childhood trauma had greater depression severity and poorer outcomes at 3 months after baseline. At 6 months postpartum, they had outcomes indicating remission in depression and functioning, but they also had more residual depressive symptoms than those with less trauma exposure (Tzilos, G. K., Zlotnick, C., Raker, C., Kuo, C., & Phipps, M. G. (2012). Psychosocial factors associated with depression severity in pregnant adolescents. *Archives of Women's Mental Health, 15*, 397–401; Grote, N. K., Spieker, S. J., Lohr, M. J., Geibel, S. L., Swartz, H. A., … Katon, W. (2012). Impact of childhood trauma on the outcomes of a perinatal depression trial. *Depression and Anxiety, 29*, 563–573).

In other studies of etiology and risk involving over 9,000 new mothers, NIMH-funded researchers examined whether there are seasonal influences on postpartum depression and found (although with high variability) that the risk for depression was highest in December. They detected no seasonal variation in suicidal ideation. In an examination of factors other than pregnancy and giving birth as related to postpartum symptoms, another research team studied depression and anxiety among postpartum and adoptive mothers and found comparable levels

of depressive symptoms, although adoptive mothers reported greater well-being and less anxiety (Sit, D., Seltman, H., & Wisner, K. L. (2011). Seasonal effects on depression risk and suicidal symptoms in postpartum women. Depression and Anxiety, 28, 400–405; Mott, S. L., Schiller, C. E., Richards, J. G., O'Hara, M. W., & Stuart, S. (2011). Depression and anxiety among postpartum and adoptive mothers. *Archives of Women's Mental Health, 14*, 335–343).

Effects of Depression During Pregnancy on the Child. In a meta-analysis of 29 prospective studies of antenatal depression that included at least 1 measure of an adverse birth outcome, NIMH-supported researchers found that the risk of low birth weight associated with depression during pregnancy was significantly larger in developing countries than in the United States or Europe. In the United States, risk of having a preterm infant was greater among depressed women of lower socioeconomic status. Overall, women with depression during pregnancy are at increased risk for preterm birth and low birth weight, but in this study the magnitude of the effect varied as a function of depression measurement, country location, and U.S. socioeconomic status (Grote, N. K., Bridge, J. A., Gavin, A. R., Melville, J. L., Iyengar, S., & Katon, W. J. (2010). A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Archives of General Psychiatry, 67*, 1012–1024).

Treatment and Outcome Studies. Several groups of NIMH-funded researchers have published findings on nonmedication interventions during pregnancy and the postpartum period, including one group that piloted an interpersonally based intervention for low-income women with intimate partner violence, which was found to be effective in reducing depressive and PTSD symptoms. A second group studied social support, which is known to be an important factor in determining risk and outcome but has been little studied. The results of this study suggest that identifying support needs and expectations of new mothers is important for mothers' recovery after childbirth. A third group conducted a postpartum behavioral-educational intervention study for Black and Latina mothers, which demonstrated positive effects 6 months after completion. A fourth group conducted a feasibility study of a telemedicine intervention for Latina women, with promising early results indicating that the intervention seems feasible and acceptable (Zlotnick, C., Capezza, N. M., & Parker, D. (2011). An interpersonally based intervention for low-income pregnant women with intimate partner violence: A pilot study. *Archives of Women's Mental Health, 14*, 55–65; Negron, R., Martin, A., Almog, M., Balbierz, A., & Howell, E. A. (2013). Social support during the postpartum period: Mothers' views on needs, expectations, and mobilization of support. *Maternal and Child Health Journal, 17*, 616–623; Howell, E. A., Balbierz, A., Wang, J., Parides, M., Zlotnick, C., & Leventhal, H. (2012). Reducing postpartum depressive symptoms among Black and Latina mothers: A randomized controlled trial. *Obstetrics and Gynecology, 119*, 942–949; Baker-Ericzén, M. J., Connelly, C. D., Hazen, A. L., Dueñas, C., Landsverk, J. A., & Horwitz, S. M. (2012). A collaborative care telemedicine intervention to overcome treatment barriers for Latina women with depression during the perinatal period. *Family, Systems & Health, 30*, 224–240).

Goal 4. Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research.

Creation and Maintenance of Alliances and Partnerships

The Office for Research on Disparities and Global Mental Health (ORDGMH) has encouraged the chief of the Women's Mental Health Program to create and maintain NIH, HHS, and other alliances. Simultaneously, new global efforts and initiatives were undertaken in FYs 2011 and 2012 by ORDGMH and NIMH, allowing staff to work to integrate knowledge and opportunities for women's health issues and research with those for global mental health, HIV/AIDS research, and mental health disparities, because much of the research in these areas is related to pregnancy and maternal and child health. Outreach and collaborations by other

NIMH offices as well as the NIMH Division of Intramural Research Programs and funded researchers are also described in this section. Finally, groups of investigators have been brought together by ORDGMH to revitalize and coordinate research efforts in mental health disparities research. These efforts dovetail with Goal 4.

Initiatives and Collaborations

NIMH efforts are described below and have followed a number of Goal 4's strategic objectives:

- Objective 4.2: Establish new ventures and initiatives with a wide cross-section of partners, including NIH Institutes, Centers, and Offices; academia; other Federal agencies; international organizations; private foundations; and industry;
- Objective 4.3: Promote an environment that uses multiple avenues and technologies to facilitate continuing input from partners committed to improving women's health and promoting research;
- Objective 4.4: Create solid partnerships by engaging in scientific briefings and ad hoc meetings with policymakers, elected officials, and advocacy groups;
- Objective 4.5: Partner with professional societies to include women's health research issues in national scientific meetings and conferences, including issues involving career training and development; and
- Objective 4.6: Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries.

Global Grand Challenges. In FY 2011, NIMH published the Grand Challenges in Global Mental Health, a synthesis of the views of more than 400 researchers, advocates, and clinicians working in 60 countries on mental health issues, which led to identification of 25 priorities for mental health research. Research specifically focused on solving these challenges could significantly transform the field and the lives of people with mental disorders. This collaborative initiative coincides with and has led to the prioritization of a number of activities relevant to women's health research. In April 2012, NIMH hosted a meeting titled Grand Challenges in Global Mental Health: Integration and Implementation in Research, Policy, and Practice. The workshop participants discussed how addressing mental illness can improve outcomes in maternal-child health and other priority global health areas. A subsequent policy workshop led to the development of manuscripts focused on integrating mental health into maternal and child health programs and into other global health programs (Collins, P. Y., Patel, V., Joestl, S. S., March, D., Insel, T. R., Daar, A. S., … Scientific Advisory Board, & Executive Committee, Grand Challenges on Global Mental Health. (2011). Grand challenges in global mental health. *Nature, 475*, 27–30).

Global Research Hubs. Concurrently, in FY 2011 and FY 2012, NIMH launched the Collaborative Hubs for International Research on Mental Health, a set of four funded regional hubs in South Asia, Sub-Saharan Africa, and Latin America whose aim is to reduce the mental health treatment gap in low- and middle-income countries. The hubs conduct research on task sharing for the delivery of mental health services in low- and middle-income countries, support mental health research capacity building in countries in their regions, and will use the network they form to answer mental health services questions across different health system environments. The South Asian Hub for Advocacy, Research and Education (SHARE), funded in FY 2011, will develop an innovative, effective, and sustainable approach for the delivery of an established psychological treatment that should reduce the burden of depression in mothers in South Asia.

Collaboration and Committees. The Women's Mental Health Program chief began working with three new groups in FYs 2011 and 2012: the National Action Alliance for Suicide Prevention's Research Task Force, the NIH Lesbian, Gay, Bisexual, Transgender and Intersex Research Coordinating Committee, and the White House Working Group on the Intersection of HIV/AIDS, Violence against Women and Girls, and Gender-Related

Health Disparities. The program chief continued service on the following committees and workgroups: the NIH Coordinating Committee on Research on Women's Health, the Women and Trauma Federal Partners' Committee, the NIH Clinical Center Ethics Committee, the NIMH Steering Committee, and the NIMH Diversity and Re-entry Supplements Committee, all of which contribute to NIH, HHS, and Federal coordination of women's mental health research issues and related policy.

Outreach to Advocacy Groups. The Office of Constituency Relations and Public Liaison in the Office of the Director, NIMH, maintains a robust outreach effort to mental health advocacy groups, including a number of women's health-related groups, which participate in the twice-a-year NIMH Alliance for Research Progress meetings. Women's health groups that are members of the NIMH Alliance and participated in FYs 2011 and 2012 include: Postpartum Support International, the Society for Women's Health Research, the Eating Disorders Coalition for Research, Policy & Action, and the National Eating Disorders Association.

Researchers and Workgroup Recommend That Premenstrual Dysphoric Disorder Be Listed as a Disorder. The Diagnostic and Statistical Manual-V (DSM-V) Mood Disorders Work Group, composed of a number of NIMH-funded researchers, along with other researchers who have studied premenstrual dysphoric disorder, proposed that the information on the diagnosis, treatment, and validation of the disorder has matured sufficiently for it to qualify as a full category in the DSM-V. Expert reviews of the literature conclude that this disorder affects 2–5 percent of premenopausal women and that recognition of it as a category, rather than a criterion set in need of further study, will provide greater legitimacy for the disorder and encourage the growth of evidence-based research, ultimately leading to new treatments (Epperson, C. N., Steiner, M., Hartlage, S. A., Eriksson, E., Schmidt, P. J., Jones, I., & Yonkers, K. A. (2012). Premenstrual dysphoric disorder: Evidence for a new category for DSM-5. *American Journal of Psychiatry, 169*, 465–475; O'Brien, P. M., Bäckström, T., Brown, C., Dennerstein, L., Endicott, J., Epperson, C. N., … Yonkers, K. (2011). Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: The ISPMD Montreal consensus. *Archives of Women's Mental Health, 14*, 13–21).

Utilizing New Communication and Social Network Technologies. NIMH utilizes new media technologies (e.g., Twitter, Facebook, YouTube, and RSS feeds) to disseminate research findings and cultivate relationships with advocacy groups, as described above, as well as to identify and provide training resources to potential new neuroscience researchers. Many global researchers, as described under Goal 4 above and Goal 6 below, are interested in maternal and child health and women's mental health issues. Several relevant initiatives are described below.

Meetings

- Building Research Capacity and Collaboration in Global Mental Health, March 24–25, 2011
- Grand Challenges in Global Mental Health Integration and Implementation in Research, Policy, and Practice, April 2–3, 2012
- Addressing Mental Disorders: The Missing Link to Effective HIV Prevention, Care, Treatment, and Support—Satellite meeting of the 19th International AIDS Conference, July 24, 2012
- Closing the Gaps: Reducing Disparities in Mental Health Treatment through Engagement, September 12–13, 2011

Goal 5. Develop and implement new communication and social networking technologies to increase understanding and appreciation of women's health and wellness research.

Communication and Social Networking

NIMH has responded to numerous requests for expert information from NIH, HHS, and Congress, as well as over 100 annual requests from investigators on women's health research opportunities. Several efforts

and initiatives newly undertaken in FYs 2011 and 2012 are described below, along with an example of research findings in this area.

Initiatives, Meetings, and Research Findings

Objectives 5.1, 5.2., and 5.3 were followed in items listed under Goal 4 above as well as in the items below:

- Objective 5.1: Serve as a key informational resource for Federal and State agencies, elected representatives; the media, health and advocacy organizations; and the public on women's health research issues;
- Objective 5.2: Expand collaboration with other NIH Institutes and Centers and Federal agencies in outreach activities on issues related to women's health; and
- Objective 5.3: Expand strategic alliances and partnerships with key national and international organizations to maximize the communication and impact of women's health research.

New Listserv and Newsletter on Global Research. As part of the ORDGMH effort to disseminate information to a growing cadre of investigators in global mental health about funding opportunities, meetings, and training, a listserv and newsletter, GlobalTracks, was developed and expanded in FYs 2011 and 2012. This platform was recently joined to an Institute-wide virtual platform for disseminating health news and scientific developments. Membership on the listserv is currently 500 individuals.

Guidance on Treatment During Pregnancy Disseminated to Clinical Social Workers. NIMH originated and implemented a novel outreach effort to over 800 members of the Greater Washington Society for Clinical Social Work, via the organization's listserv, on the use of antidepressants during pregnancy, using existing NIMH and NIH resources. Material is being shared with ORWH, the National Library of Medicine, and the NIMH Outreach Partnership Program.

Collaboration with Two Key Lesbian, Gay, Bisexual, and Transgender (LGBT) Groups. Participation by the Women's Mental Health Program chief on the NIH Lesbian, Gay, Bisexual, Transgender and Intersex Research Coordinating Committee, which was formed in 2011, as well as participation by the chief on the National Action Alliance for Suicide Prevention's (NAASP's) LGBT Task Force, allowed useful exchange of information between the two groups as well as consultation to one of the NAASP's member advocacy organization on possible future research efforts and collaborations.

Goal 6. Employ innovative strategies to build a well-trained, diverse, and vigorous health research workforce.

Training Efforts

NIMH continued funding diversity and reentry supplements, revamped and expanded efforts to provide additional training to early-stage investigators who have received diversity supplements, and conducted outreach to potential and early-stage researchers in global mental health. A number of these grantees and students are pursuing research interests on topics in women's health, such as perinatal depression and maternal and child health. Objectives followed include 6.1 and 6.2:

- Objective 6.1: Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH; and
- Objective 6.2: Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs; encourage evaluation of mentoring practices.

Meetings and Initiatives

Staff Training. NIMH continues to fund underrepresented minority early-stage researchers, as well as researchers who have had to take a break from their careers, through the Diversity and Re-entry Supplements programs. In order to increase the expertise of program staff in the use of these supplements, NIMH held a staff training session on February 22, 2012, as part of the NIMH Policy and Operating Procedures Forum.

Training of Diversity Supplement Grantees. On July 5–6, 2011, ORDGMH sponsored a workshop, Navigating Your Way through a Successful Research Career: An NIMH Workshop for Early Stage Investigators. The workshop was designed to provide early-stage investigators currently supported by diversity and reentry supplements with the tools necessary to continue along the path of competitive research support and the transition to independence. This workshop aimed to instill the importance of producing innovative research within the overall mission of NIMH in these promising early-career researchers. Content of the workshop emphasized issues relating to grantsmanship and strategies for successfully navigating obstacles and developing potential solutions on the journey to a successful research career. A number of these grantees and students are pursuing research interests in topics of interest in women's health.

Training of Global Researchers. ORDGMH established the Global Mental Health Careers listserv to build an ever-growing community of budding investigators, engaging with them through bimonthly publication of the GlobalTracks newsletter. The listserv and newsletter are vehicles for the dissemination of training news, upcoming global meetings, and funding oppurtunity annoucements. A number of these grantees and students are pursuing research interests in topics in women's health. On March 24–25, 2011, NIMH held what is believed to be the first meeting for early-career investigators seeking to engage in/build a sustainable research career in global mental health. Building Research Capacity and Collaboration in Global Mental Health brought together U.S. early-career investigators, funders, and other stakeholders to discuss research career options, career pathways, and funders' priorities in global mental health research. Again, a significant portion of global mental health research is focused on women's health.

National Institute on Minority Health and Health Disparities

Executive Summary

The National Institute on Minority Health and Health Disparities (NIMHD) promotes and supports research to improve minority health and eliminate health disparities. It also plans, leads, coordinates, and assesses the efforts of NIH as a whole to reduce and eliminate health disparities. To achieve its mission, NIMHD employs a multifaceted strategy to conduct and support research in basic, clinical, social, and behavioral sciences; disseminate information; promote research infrastructure and training; foster emerging programs; and extend its reach to health disparity communities. Congress mandated the development of three principal programs within NIMHD aimed at addressing health disparities—the Centers of Excellence Program (COE), the Loan Repayment Program (LRP), and the Research Endowment Program. Additionally, NIMHD supports the Community-Based Participatory Research (CBPR) initiative, the Building Research Infrastructure and Capacity (BRIC) program, the Minority Health and Health Disparities International Research Training (MHIRT) program, the Transdisciplinary Collaborative Centers for Health Disparities Research (TCC) program, the NIMHD Science Education Initiative, the NIMHD Resource-Related Minority Health and Health Disparities Research Program, and the Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) programs. In FY 2012, NIMHD assumed administration of the Research Centers in Minority Institutions (RCMI) Program, which includes the G12 Research Centers, the RCMI Infrastructure for Clinical and Translational Research (RCTR), the RCMI Translational Research Network (RTRN), and the Clinical Research Education and Career Development (CRECD) in Minority Institutions. Additionally, the NIMHD has a long history of collaborating with other NIH ICs and Federal agencies.

Recent accomplishments in women's health resulting from NIMHD programs and collaborations during FY 2011–FY 2012 are summarized below. Because NIMHD supports research that is focused on the health of racial/ethnic minorities and other health disparity populations, the range of diseases and conditions under investigation by NIMHD researchers is broad. It includes, for example, cardiovascular disease, obesity, diabetes, cancer, HIV/AIDS, depression, and substance abuse. Some of these projects involve research on women only, while others examine differences between men and women or boys and girls. Within these diseases and conditions, researchers conduct research on both biological and nonbiological factors using various study types and interventions, such as prevention studies, comparative effectiveness studies, and community-based participatory research studies as well as behavioral, educational, and health services interventions. NIMHD investigators also provide training to new investigators and engage communities in innovative efforts to improve minority health and to reduce and eliminate health disparities. Two central concepts found in many of the NIMHD-supported studies are cultural competency and culturally tailored interventions.

NIMHD Research on Women's Health Report

NIMHD Organizational Components

While there is no office or branch in NIMHD specifically designated to address research on women's health issues, women's health is an integral part of the Institute's health disparities scientific research portfolio, which is administered through its extramural grants, cofunding with other ICs, and collaborations with other Federal agencies.

Accomplishments of NIMHD

Consistent with its mission to improve minority health and to eliminate health disparities, NIMHD supports research on the broad range of diseases and conditions experienced by health disparity populations. Health disparity populations include African-Americans, Hispanics, American Indians/Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders, low-income populations, and rural populations. Thus, NIMHD-supported research is not limited to combating a specific disease or condition or to a specific organ or body system, as it embraces the entire range of biological and nonbiological areas and factors contributing to the existence and persistence of health disparities. The NIMHD also works in partnerships with other NIH ICs and other Federal agencies in these efforts. Examples of NIMHD-supported research are highlighted below, categorized according to specific objectives from the NIH Strategic Plan for Women's Health Research.

Strategic Plan Goal 1, Objective 6: Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases including HIV/AIDS, urinary tract, and sexually transmitted infections.

- **Multilevel Modeling of Social Disparities in Sleep and Health.** Sleep problems affect a substantial proportion of the U.S. population and cost the U.S. health care system hundreds of billions of dollars annually. Social disparities (including those related to age, sex, socioeconomic status [SES], and race/ethnicity) in health have been repeatedly documented. The current literature on social disparities in sleep, however, is in conflict regarding the existence of social disparities, their origins, and how social disparities in sleep may manifest themselves in social disparities in health. The multilevel modeling project, conducted by investigators from the New England Research Institutes, uses data from the Boston Area Community Health (BACH) Survey, which includes 5,606 White, Black, and Hispanic participants, to examine age-, sex-, SES-, and racial/ethnic group-specific longitudinal associations between sleep and the subsequent development of hypertension, obesity, diabetes, and cardiovascular disease as well as all-cause mortality. Results thus far indicate that among both men and women, racial/ethnic minorities had fewer hours of sleep and more restless sleep than did Whites. Poor sleep quality was associated with increased

risk of obesity in men and cardiovascular disease in women. In addition, poor sleep quality was associated with increased risk of diabetes across sexes, but it did not explain racial/ethnic disparities in diabetes incidence, indicating the need to further explore the additional social determinants of health that affect both sleep quality and diabetes outcomes.

Strategic Plan Goal 1, Objective 8: Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.

- **Effects of a Housing Policy Experiment on Youth Behavioral Problems.** Adverse neighborhood contexts predict poor mental health and externalizing behavior among adolescents. The vast racial inequalities in neighborhood environments may play an important role in creating and maintaining racial disparities in health. A project conducted by investigators from Northeastern University in Boston used data from the Moving to Opportunity for Fair Housing (MTO) study, in which low-income families in the Section 8 housing program were randomly assigned to remain in their communities or to relocate to a low-poverty neighborhood. Original MTO study results indicated that relocation resulted in improved mental health for girls but increased behavior problems for boys. This project explored these patterns in greater depth by examining additional contextual and neighborhood factors. The primary finding was that the impact of relocation on boys and girls was moderated by crime victimization in the family. Girls from families with no crime victimization had improved mental health outcomes after relocation to low-poverty neighborhoods; relocation had no impact on mental health outcomes for girls from families victimized by crime. Boys from families victimized by crime had worse mental health and behavioral outcomes after relocation; relocation had no impact on outcomes for boys from families with no crime victimization. The findings suggest that children from vulnerable families may not be able to take advantage of the potential opportunities afforded by moves to improved neighborhood environments and may have faced special barriers after these moves. Additional support services, such as case management, and linkage to health care access, benefits, or educational services may be needed in order for adolescents, particularly boys, to benefit from such residential transitions.

Strategic Plan Goal 3, Objective 1: Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the lifespan.

- **Intergenerational Obesity: Do Early Adversity and Pregnancy Explain Disparities?** This study by researchers at the University of California, Berkeley, uses data from the National Longitudinal Survey of Youth to investigate racial/ethnic differences in factors that may increase maternal body mass index (BMI) at midlife as well as obesity in offspring. These factors include early maternal social environment (e.g., SES and family structure), pregnancy-related weight (e.g., excessive gestational weight gain and postpartum weight retention), and adverse maternal childhood experiences (e.g., physical abuse, substance abuse, or mental illness in the home). The ultimate goal is a new understanding of obesity and the development of new interventions for the prevention of obesity health disparities. Preliminary findings indicate that being raised by a mother with low education was significantly associated with both high prepregnancy BMI and excessive gestational weight gain (GWG) in mothers. Mothers who experienced a breakdown of their family structure (through the death of a parent, foster care, being removed from home by child protective services) before age 18 were more likely to experience excessive GWG in pregnancy than were those with intact home conditions. Women with excessive GWG had a higher BMI at age 50 than did those with recommended GWG, indicating the long-term impact of excessive weight gain during pregnancy.

Strategic Plan Goal 3, Objective 3: Encourage research on safe and effective interventions for conditions affecting pregnant women.

- **Teach-With-Stories: Lay Educator Prenatal Outreach Program for Hispanics.** Hispanic women are twice as likely to receive late or no prenatal care as are non-Hispanic White women. The goal of this small business grant from Auger Communications (Durham, NC) is to improve access to linguistically and culturally appropriate prenatal education and care for Hispanic women. The project is adapting De Madre a Madre/From Mother to Mother prenatal care photonovels, a series of easy-to-read, bilingual, culturally appropriate photo stories designed for prenatal education and literacy instruction for distribution via the Teach-With-Stories™ Free Publication Network. An 8-week, group health education program featuring the photonovels has been pilot tested with pregnant Latinas at two sites. Participants indicated that they learned important prenatal information, shared the photonovels with others, and gained valuable social support from other women in the program. The photonovel series will now be tested in a larger field trial.

Strategic Plan Goal 3, Objective 4: Expand research on pregnancy-related conditions such as pre-eclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.

- **Trans-generational Impact of Maternal Obesity and Diabetes on Health.** As obesity and diabetes increasingly affect women of childbearing age, understanding the public health impact of these two disorders on the health of offspring is paramount. Black and Hispanic women are not only more likely to be obese and have diabetes during pregnancy than non-Hispanic white women, but they also have a different distribution of body fat, their diabetes is more severe, and they have higher cardiovascular risk than do non-Hispanic White women. This project involving investigators from Clemson University and the Medical University of South Carolina is investigating the epidemiology of diabetes and obesity during pregnancy in South Carolina and using a simulation model to predict the potential impact of these maternal conditions across multiple generations. Findings thus far indicate that in South Carolina between 1996 and 2008 the prevalence of reported diabetes during pregnancy increased more than 75 percent in non-Hispanic Whites and non-Hispanic Blacks and more than 125% in Hispanics. The negative effects of diabetes during pregnancy were greater in non-Hispanic Blacks than in non-Hispanic Whites and increased with greater maternal BMI. Additionally, for both non-Hispanic White and non-Hispanic Black women there was a strong association between greater gestational weight gain and higher infant birth weight, a finding with implications for subsequent obesity of the offspring, a factor to be examined in the simulation models.
- **NIMHD Center of Excellence on Adverse Pregnancy Outcomes Among African-American Women.** This Center of Excellence at Virginia Commonwealth University conducts research, trains junior scientists, and conducts community dissemination activities related to adverse pregnancy outcomes among African-American women. The first cycle of the Center (years 2007–2012) included research projects on the genetics of preterm birth in African-Americans, immunological responses to periodontal infection that may lead to premature birth, and evaluation of a safer-sex skills intervention among pregnant women at high risk for HIV infection. The second cycle of the Center (years 2012–2017) includes research projects on the genetic basis for the vulnerability of African-American women to preterm premature rupture of membranes, the leading identifiable cause of preterm birth; racial/ethnic variation in the virulence of vaginal bacteria in causing intrauterine infections that result in preterm birth; and gene-environment interactions that result in elevated risk of preterm birth for African-American women.

Strategic Plan Goal 3, Objective 5: Identify and validate sex-specific biomarkers for disease risk and prognosis across the lifespan.

- **NIMHD Center of Excellence on Women's Health Disparities.** This Center of Excellence at the University of North Texas Health Science Center conducts research, training and mentoring, and community dissemination activities related to the health of women from racial/ethnic minority populations. Funded in 2012, the Center includes subprojects to identify novel biomarkers that are implicated in racial/ethnic and sex disparities in HIV disease progression in non-Hispanic Whites, African-Americans, and Hispanics; and to identify specific biomarkers for triple-negative breast cancer that could be targeted by novel therapies to decrease the disproportionate rates of breast cancer-related mortality in African-American women.

Strategic Plan Goal 3, Objective 6: Study sex/gender differences in the aging process.

- **Epidemiology of Suicidal Behavior in Racially/Ethnically Diverse Older Americans.** In older Americans, suicide rates are 30 percent higher than in the general population, and among non-Hispanic White men aged 85 years or older, they are 5 times as high. However, little is known about suicide-related behaviors (i.e., ideation, plans, and attempts) in older adults, particularly those from racial/ethnic minority groups. A project involving investigators at the University of California, San Francisco, is using three nationally representative epidemiologic datasets to investigate the prevalence and predictors of suicidal ideation and related behaviors over the lifetime of more than 3,600 racially and ethnically diverse adults aged 55 or older. Differences between men and women are being examined within and across racial/ethnic groups. Preliminary results indicate that while there were numerous racial/ethnic differences in the prevalence of suicidal ideation and behavior, men and women were largely similar, with the exception that women were more likely to have a lifetime suicide attempt than were men. Only 70 percent of older adults experiencing suicide-related symptoms sought help, highlighting the need for better detection and treatment in this population.

- **Causes of Asian American Mortality Understood by Socio-economic Status.** Asian Americans are the fastest-growing racial/ethnic group in the U.S., with a current population of over 14 million that is projected to reach nearly 34 million by the year 2050. However, much of the work on Asian American health examines this population as an aggregated group. Very little is known about the morbidity and mortality of Asian American racial/ethnic subgroups, which have a wide range of disease risks, immigration histories, and sociodemographic characteristics. Using data from the U.S. Census, the American Community Survey, and local, state, and national death/mortality datasets, this project, which is conducted by investigators from the Research Institute of the Palo Alto Medical Foundation, is examining racial/ethnic, nativity, and geographic differences in mortality for Asian American subgroups compared with other racial/ethnic groups (e.g., non-Hispanic Whites, African-Americans, and Hispanics). All analyses examining racial/ethnic group or subgroup differences are stratified by gender. Initial findings have focused on mortality due to coronary heart disease (CHD). Results show that for different Asian subgroups there is greater variation in the proportion of CHD mortality among men than among women. Some groups of Asian men (Asian Indian, Filipino, and Japanese) have a higher proportion of mortality due to CHD than do White men, while other groups (Chinese, Vietnamese, and Korean) have a comparatively lower proportion of CHD mortality. In contrast, White women have a higher proportion of mortality due to CHD than do women from all Asian subgroups except Asian Indians.

Strategic Plan Goal 3, Objective 8: Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent living, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

- **The Risk of Long-Term Care in Older Mexican-American Families.** Older people of Mexican origin make up one of the

fastest-growing segments of the U.S. population, and their numbers are projected to increase sevenfold by year 2050. This demographic explosion will place serious demands on the long-term care system, from family caregivers to federally sponsored sources of care. Mexican Americans suffer disproportionately from disabling conditions like diabetes that increase their risk of having to receive care in a nursing home or assisted-living facility. In this project, investigators from the University of Texas at Austin are using data on 3,952 older adults from the Hispanic Established Populations for Epidemiologic Study of the Elderly (H-EPESE) to examine how immigration factors and family resources moderate how changes in functional status induce changes in care and living arrangements among older Mexican Americans. The project has produced a number of important findings, including some specific to older Mexican American women. For example, the investigators found that high fertility rates and multiple pregnancies are implicated in the elevated prevalence of lower-body dysfunction among Mexican American women relative to Mexican American men and to women from other ethnic groups. In an examination of the risk of long-term care in Mexican American women, investigators found that family caretaking demands, in the absence of adult children to share the caregiving load, predicted entry into a nursing home or assisted-living facility. Medicaid/Medicare coverage was not predictive, indicating that familial factors were more significant than cost factors in predicting utilization of the long-term care system for older Mexican American women.

Strategic Plan Goal 3, Objective 9: Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.

NIMHD funds a wide range of research projects that focus on women or girls from health disparity populations. Examples of projects in key research domains are highlighted below.

- Basic Biomedical Research on Minority Health and Health Disparities
  - **Role of p53 Polymorphisms in Disparities in Breast Carcinogenesis and Outcome.** This project, which involves investigators from the University of Texas MD Anderson Cancer Center, examines the biological and genetic mechanisms underlying the increased incidence of early-onset, aggressive breast cancer in African-American women. Early results indicate that ethnic/racial differences in pregnancy as a protective factor against breast cancer are related to gene polymorphisms found disproportionately in African-American women. Future activities will examine the impact of hormone therapy on these polymorphisms to better understand response to cancer treatment in African-American women.
  - **Weight Gain, Type 2 Diabetes, and Factors that Affect Neuroendocrine Function.** African-American women are disproportionately affected by obesity and type 2 diabetes, with a heavy burden of associated health problems. This project, which involves investigators from the Boston University Medical Campus, is investigating whether early postnatal factors, such as low birth weight or having been breastfed, and adult psychosocial stressors and other factors that unfavorably alter the neuroendocrine system (which is involved in the regulation of body weight), contribute to increased weight gain and diabetes incidence in African-American women.
- Epidemiological/Health Services Research on Health Disparities
  - **Does Violence Against Women Result in Disparities in Cancer Care for Women with Breast, Colorectal, or Cervical Cancer?** Appalachian women experience elevated rates of intimate partner violence relative to other groups of women. This project, which is being conducted by investigators at the University of Kentucky, examines whether women who experience interpersonal violence have more negative

outcomes for cancer care than women who do not. If violence is found to influence cancer care, interventions can be developed to provide appropriate support to ensure receipt of recommended care among women experiencing violence. Preliminary results indicate that women who experience intimate partner violence report greater distress and depression at the time of cancer diagnosis and experience poorer cancer-related well-being than women who do not experience intimate partner violence. Future analyses will examine the extent to which behavior of the partner facilitates or impedes receipt of appropriate cancer care.

- **Social Determinants Predicting Trajectories of HIV with Recent Latina Immigrants.** As part of the NIMHD Center of Excellence at Florida International University, this project is examining how culturally relevant social factors associated with HIV/AIDS risk such as familial relationships, SES, religiosity, gender roles, and stigma interact with family and peer relationship factors to affect HIV/AIDS risk behaviors, substance use, and access to health care resources in recent Latina immigrants aged 13–18.

- Preventive Interventions with Health Disparity Populations
  - **The Native Proverbs 31 Health Project.** This project, which involves researchers at Wake Forest University Health Sciences in Winston-Salem, NC, is developing and implementing a culturally appropriate cardiovascular disease prevention program among Lumbee Indian women in Robeson County, NC, that focuses on the biblical messages in Proverbs 31. Expected primary outcomes for this study are changes in health behaviors (e.g., diet, physical activity) and motivation to reduce or stop tobacco use.
  - **An Integrated Risk Reduction Intervention for Abused African Caribbean Women.** The prevalence of intimate partner violence among women in the U.S. Virgin Islands is higher than that of sociodemographically similar women in the mainland US. As part of the NIMHD Center of Excellence at the University of the Virgin Islands, this project is evaluating a culturally tailored intervention to reduce the risk of intimate partner violence and associated risks of sexually transmitted infections (STIs) in African Caribbean women in the U.S. Virgin Islands.

- Treatment/Service Interventions with Health Disparity Populations
  - **Treatment of Urinary Incontinence for American Indian Women in the Northern Plain.** This project, a component of the NIMHD Center of Excellence at the University of South Dakota, is evaluating the feasibility and effectiveness of an outpatient, minimally invasive surgery for American Indian women from a rural reservation community in the Northern Plains who are suffering from stress urinary incontinence. While many other interventions for stress incontinence are focused on inpatient surgical interventions, an outpatient, office-based procedure from urogynecological specialists is essential for a rural and minority population of women who may have limited access to inpatient hospital facilities.
  - **Extending Cancer Navigation to Underserved Suburban Women.** This community based-participatory research grant, led by researchers at Northwestern University, is evaluating a patient navigation intervention to help low-income, predominantly Latina and African-American suburban women with abnormal cervical or breast cancer screening tests receive appropriate follow-up services. Over 500 women were enrolled in the patient navigation intervention. Results indicate that those receiving navigation were much less likely to be lost to follow-up and received follow-up screening more quickly than women not receiving navigation services.

Strategic Plan Goal 5, Objective 5: Support research to explore and evaluate the ability of women and men of different ages to access, process, and act on health-related information.

- **Health Literacy Disparities and Transition in Teens with Special Healthcare Needs.** Nearly 20 percent of U.S. adolescents have special health care needs that require health or health-related services beyond those required by children generally. This population of adolescents includes those with chronic health conditions, developmental or physical disabilities, and mental health or emotional problems. During adolescence, these youth begin the transition from parental management to self-management of their health and health care and from pediatric to adult care providers. Health literacy is an important tool in this transition, but little is known about patterns of health literacy in adolescents with special health care needs and their importance in self-care. This project, conducted by investigators from Nationwide Children's Hospital in Columbus, OH, explores racial/ethnic disparities in health literacy and associated health outcomes in adolescents with special health care needs. Investigators are examining a range of factors that may be associated with youth health literacy, including gender, primary language spoken at home, rural/urban residence, and parental health literacy.
- **m-Health and Health IT Applications to Improve Minority Health and Reduce Health Disparities.** NIMHD supported a number of projects in FYs 2011 and 2012 using m-Health (mobile health) and health information technolgy applications to improve health and prevent illness, including the following projects:
  - **Innovative Communication Technology for Health of Young African American Women.** This is a project based at Boston Medical Center to improve preconception health for African-American women aged 18–25 through an innovative Internet-based health communication system that provides personalized health information through interaction with an animated character.
  - **Using Technology to Prevent Obesity Among African American Girls.** This is a project at Baylor College of Medicine to improve physical activity levels and fruit and vegetable consumption in African-American girls aged 8–10 using a Web-based intervention featuring animated characters who model healthy behaviors.
  - **Computer-Based HIV Prevention Package for Drug Using African American Women.** A small business grant was made by ISA Associates (Alexandria, VA) to develop a computer-based application for the evidence-based HIV behavioral intervention Female and Culturally Specific Negotiation Intervention (FCSNI), which was developed specifically for drug-using African-American women who have sex with men.
  - **Developing Computer-Based STI/HIV Prevention Interventions for Hispanic Women.** This project is supported by a small business grant from Sociometrics Corporation (Los Altos, CA) to develop and evaluate culturally tailored, English- and Spanish-language computer-delivered versions of Project Sexual Awareness for Everyone (SAFE), an existing efficacious HIV prevention program for minority women.
  - **HPV Vaccine Education Intervention for Medically Underserved High-Risk Populations.** This project was made possible by a small business grant from Valdez and Associates to develop and evaluate a multicultural, multilingual health literacy intervention to promote knowledge about the HPV (human papillomavirus) vaccine and foster informed HPV immunization decisions among parents of preadolescent girls and among adolescent girls at high risk for HPV infection. The populations of interest in this study are Koreans, Vietnamese, Filipinos, African-Americans, and Latinos.

Sex/Gender Analysis and/or Gender Specific Studies

These are described in the above section, "Accomplishments of NIMHD."

FY 2011–2012 Initiatives

Table 1. NIMHD Initiatives

FOA Number	FOA Title	Objective
Community-Based Participatory Research Program		
RFA-MD-12-006	NIMHD Community-Based Participatory Research (CBPR) Initiative in Reducing and Eliminating Health Disparities: Planning phase (R24)	To provide support to develop and strengthen partnerships between researchers and communities to plan and pilot interventions to reduce health disparities. This initiative has two additional competitive cycles, an intervention phase and a dissemination phase.
RFA-MD-13-001	Limited Competition: NIMHD Community-Based Participatory Research (CBPR) Initiative in Reducing and Eliminating Health Disparities: Dissemination phase (R24)	To provide continuing support for NIMHD CBPR intervention Research phase grantees to implement and disseminate evidenced-based interventions designed to reduce health disparities using a community-based participatory research approach.
Health Disparities R01 Program		
RFA-MD-12-004	NIMHD Basic and Applied Biomedical Research on Minority Health and Health Disparities (R01)	To solicit innovative grant applications on biological and genetic research to explore disease mechanisms or pathways that influence health outcomes in minority and health disparity populations.
RFA-MD-12-003	NIMHD Social, Behavioral, Health Services, and Policy Research on Minority Health and Health Disparities (R01)	To solicit innovative social, behavioral, health services, and policy research that can directly and demonstrably contribute to the elimination of health disparities.
RFA-MD-12-001	NIMHD Health Disparities Research (R01)	To solicit innovative biological, epidemiological, or social/behavioral research that can directly contribute to the elimination of health disparities.
Research Centers in Minority Institutions (RCMI) Programs		
RFA-MD-12-005	Limited Competition: Research Centers in Minority Institutions (RCMI) Translational Research Network (RTRN) (U54)	To support a center to enhance collaboration across RCMI institutions in order to increase the efficiency of the implementation and dissemination of research advances to improve health outcomes.
PAR-11-132	Research Centers in Minority Institutions Program (G12)	To expand the national capability for research in the health sciences by providing grant support to minority institutions that offer doctoral degrees in the health professions or health-related sciences.
PAR-11-325	Clinical Research Education and Career Development (CRECD) in Minority Institutions (R25)	To expand the national capability to improve diversity for biomedical research by developing the research workforce in clinical and translational sciences though grant support to minority institutions that offer doctorate degrees in the health professions or health-related science.
Centers of Excellence		
RFA-MD-11-002	NIMHD Exploratory Centers of Excellence (P20)	To support infrastructure and capacity building, building and sustaining novel partnerships, research training, and health disparities research in non-research-intensive institutions.
RFA-MD-11-003	NIMHD Comprehensive Centers of Excellence (P60)	To support infrastructure and capacity building, building and sustaining novel partnerships, research training, and health disparities research in research-intensive institutions.
RFA-MD-11-007 RFA-MD-11-008	Limited Competition: NIMHD Revision Applications To Support Environmental Health Disparities Research (P20, P60)	To support environmental health disparities research, training, and dissemination activities in existing NIMHD Centers of Excellence.

Table 1 continued

Loan Repayment		
NOT-OD-11-087	Extramural Loan Repayment Program for Health Disparities Research (LRP-HDR)	To facilitate the recruitment and retention of highly qualified individuals as independent health disparities researchers by offering repayment of student loans.
NOT-OD-11-089	Extramural Clinical Research Loan Repayment Program for Individuals from Disadvantaged Backgrounds (LRP-IDB)	To facilitate the recruitment and retention of highly qualified individuals from disadvantaged backgrounds as independent clinical researchers by offering repayment of student loans.
Other Programs		
RFA-MD-12-007	NIMHD Transdisciplinary Collaborative Centers for Health Disparities Research (TCC) (U54)	To establish centers that support transdisciplinary coalitions of academic institutions, community organizations, service providers and systems, government agencies, and other stakeholders to conduct health disparities research at the regional level.
RFA-MD-11-004	NIMHD Science Education Initiative (R25)	To support educational, mentoring, and/or career development programs for individuals from underrepresented or health disparity populations to enhance the pool of health disparity researchers.
RFA-MD-11-005	NIMHD Resource-Related Minority Health and Health Disparities Research (U24)	To provide support for conducting minority health and health disparities resource-related research activities in the priority areas of bioethics research, global health, data infrastructure and dissemination, and health care for rural populations.

Table 2. NIMHD Participation in Trans-NIH Initiatives

FOA Number	FOA Title	Objective
Small Business Grants		
PA-11-096	PHS 2011-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR) [R43/R44]	To support small business concerns to develop medical technologies and other products that contribute to the R&D (research and development) mission of NIH.
PA-11-097 PA-12-089	Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR) [R41/R42]	To support small business concerns to promote the commercialization of medical technologies and other products that contribute to the R&D mission of NIH
RFA-EB-11-001 RFA-EB-12-001	Development and Translation of Medical Technologies To Reduce Health Disparities (R43/R44)	To support small business concerns to develop and translate medical technologies aimed at reducing disparities in health care access and health outcomes.
RFA-OD-12-003 RFA-OD-12-004	Small Business Alzheimer's Disease Research (SBIR)[R41/R42, R43/R44	To solicit Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) applications from eligible small business concerns in the area of Alzheimer's disease
Administrative Supplements		
PA-12-100	Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp)	To provide support to existing grants to meet increased costs that are within the scope of the approved award but which were unforeseen when the competing application or grant progress report was submitted.
PA-12-149	Research Supplements To Promote Diversity in Health-Related Research (Admin Supp)	To improve the diversity of the research workforce by supporting and recruiting students, postdoctoral scholars, and eligible investigators from groups shown to be underrepresented in health-related research.
PA-12-150	Research Supplements To Promote Re-entry into Biomedical and Behavioral Research Careers (Admin Supp)	To support individuals with high potential to reenter an active research career after an interruption for family responsibilities or other qualifying circumstances.

Table 2 continued

Other Programs		
PA-12-212	NIH Support for Conferences and Scientific Meetings (Parent R13/U13)	To support high-quality conferences relevant to the public health and to the scientific mission of the participating NIH ICs.
PAS-12-165	Limited Competition: Revision Applications To Advance Evidence-Based Research Related to Protections for Human Subjects (U24)	To support revision applications to cooperative agreements to conduct research on the effectiveness of current human subjects protections and/or the development of tools and methods to examine evolving, evidence-based approaches to improve human subjects' protections.
PA-12-111 PA-12-112 PA-12-113	Research on the Health of LGBTI Populations (R01, R03, R21)	To support research that will increase scientific understanding of the health status of LGBTI (lesbian, gay, bisexual, transgender, and intersex) population groups and improve the effectiveness of health interventions and services for individuals within those groups.
RFA-ES-11-006	Deepwater Horizon Disaster Research Consortia: Health Impacts and Community Resiliency (U19)	To create consortia of university-community partnerships to address health issues of concern to the residents of the Gulf States affected by the Deepwater Horizon disaster, enhance capacity to respond to potential future disasters, and prevent or minimize adverse health effects arising from them.
PAR–10-133	Understanding and Promoting Health Literacy (R01)	To encourage empirical research on health literacy concepts, theory, and interventions as these relate to the U.S. Department of Health and Human Services' public health priorities that are outlined in its Healthy People initiative.
PAS-10-226	Advancing Novel Science in Women's Health Research (ANSWHR) (R21)	To promote innovative, interdisciplinary research that will advance new concepts in women's health research and the study of sex/gender differences.

Health Disparities and Special Populations

All NIMHD-supported research is categorized as minority health or health disparities research. The target populations and communities include racial/ethnic minority populations, low-income populations, and rural populations.

Career Development Activities

- **Spelman College Center for Health Disparities Research and Education.** As part of an NIMHD Research Infrastructure in Minority Institutions (RIMI) award, Spelman College in Atlanta, GA, provided an intensive 4-year research-training program for 21 undergraduate students with an interest in health disparities. The goal of this program was to increase the number of female undergraduate students entering graduate programs in the health sciences. During their senior year, all participating students had been accepted to a graduate or professional program, a post baccalaureate bridge program, or fellowship (including a Fulbright Fellowship).
- **Broadening Access to Science Education.** This science education grant to Fairfield University in Fairfield, CT, offers an annual, 2-week, residential, summer, science-enrichment program for high school juniors and seniors from the nearby community of Bridgeport, CT. The program specifically targets young women as a way of addressing their underrepresentation in the scientific workforce.
- **Gaining Options: Girls Investigate Real Life Through Health Related STEM Disciplines.** This science education grant to Wayne State University in Detroit, MI, provides a range of activities to increase the number of girls from the Detroit metropolitan area entering college and pursuing health-related disciplines. Programs include summer academies, workshops throughout the school year, and mentorship support through social networking sites for high school girls and their parents.

- **Other NIMHD Training Programs.** Although not targeted exclusively toward women, a range of other NIMHD programs provide training opportunities in health disparities research for women, including the NIMHD Centers of Excellence, Research Centers in Minority Institutions (RCMI), NIMHD Loan Repayment Programs (LRP), NIMHD Minority Health and Health Disparities International Research Training (MHIRT) Program, and NIMHD Disparities Research and Education Advancing Mission (DREAM) Career Transition Award. The majority of participants in the MHIRT and LRP programs are women, and to date 100 percent of DREAM fellows have been women.

NIMHD Programs that Support the Implementation of the NIH Strategic Plan for Women's Health Research

Under "Accomplishments of NIMHD," research projects were categorized by NIH Strategic Plan for Women's Health Research objectives. The top objective for NIMHD is Goal 3, Objective 9: Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions. Additional activities in support of the strategic plan are highlighted below.

Strategic Plan Goal 1, Objective 9: Incorporate sex/gender considerations into discussions in scientific conferences and meetings.

- **NIMHD Health Disparities Course.** In July 2011, NIMHD offered the 2nd Translational Health Disparities Course: Integrating Principles of Science, Practice and Policy in Health Disparities Research. The 2-week intensive course, offered on a competitive basis to 75 individuals from the extramural community as well as Federal agencies, focused on the integration of disciplines (including biological, social, behavioral, physical, and environmental sciences, and law and economics) to understand science, practice, and policy issues in health disparities research. Course seminars included examination of sex/gender factors among the multitude of biological, social, cultural, political, and environmental factors that interact with one another to affect health and health disparities. Many of the guest speakers and panelists were experts in women's health within diverse health-disparity populations.
- **NIMHD Support of Scientific Conferences.** NIMHD supports conference grants to share information, identify priorities, and foster collaborations to address various topics in health disparities. Related to women's health, NIMHD supported a 2011 conference at Howard University in Washington, DC, on uterine fibroids in African-American women (this conference received cofunding from ORWH), a 2012 conference at the University of North Texas Health Science Center on breast cancer health disparities in Texas, and a 2012 conference at the Fox Chase Cancer Center in Philadelphia on female reproductive cancers among women of African/Caribbean descent.

Strategic Plan Goal 4, Objective 5: Partner with professional societies to include women's health research issues in national scientific meetings and conferences, including issues involving career training and development.

- **Student National Medical Association (SNMA) Annual Medical Education Conference: Physician Researcher Initiative.** NIMHD provided support for the 2012 SNMA Annual Medical Education Conference (AMEC). The AMEC program incorporates several component tracks, each addressing a different level of educational and professional development. The Physician-Researcher Initiative (PRI) track addresses the lack of minority physician researchers needed to combat health disparities. PRI complements and aligns with the strategic objectives of NIH to develop the next generation of biomedical and behavioral scientists capable of addressing health disparities. One component of the PRI education track is to provide the Dr. Wilbert C. Jordan Student Research Forum Poster Forum Awards in target research areas such as cancer, mental health,

diabetes, allergies and infectious diseases, alternative medicine, and woman's health. These awards provide an opportunity to showcase the accomplishments of SNMA members and add incentive for student attendance and active participation.

Strategic Plan Goal 4, Objective 6: Expand global strategic alliances and partnerships aimed at improving the health of women and girls throughout the world, particularly in developing countries.

- **Building Health Research Capacity in the Caribbean.** As part of the NIMHD Resource-Related Minority Health and Health Disparities Research program, NIMHD is supporting two global health projects that are poised to generate data and findings to promote the health of women and girls in the Caribbean region. The U.S.A.-Caribbean Alliance for Health Disparities Research (USACAHDR), led by the Sullivan Alliance to Transform the Health Professions, reflects a partnership between researchers from U.S. academic institutions and the University of West Indies to study the prevalence of and risk factors for chronic disease, including cardiovascular disease, stroke, cancer, diabetes, asthma, and depression in Caribbean and Caribbean-origin populations. This project focuses on the identification and compilation of existing datasets to allow for more comprehensive analysis across multiple Caribbean counties and the United States. To complement these secondary data analysis activities, the second global health project, the Eastern Caribbean Health Outcomes Research Network (ECHORN), is conducting a longitudinal cohort study to examine lifestyle, sociocultural, and environmental risk and protective factors in the development of chronic disease in the Caribbean. Led by researchers at Yale University, ECHORN represents a coalition of investigators from Yale and other U.S. mainland institutions, Puerto Rico, the U.S. Virgin Islands, Barbados, and Trinidad & Tobago. Both projects provide research technical assistance to emerging researchers in the Caribbean. These projects will develop the knowledge base and infrastructure to facilitate health research in the Caribbean for many years to come.

National Institute of Neurological Disorders and Stroke

Executive Summary

The mission of the National Institute of Neurological Disorders and Stroke (NINDS) is to reduce the burden of neurological disease, a burden borne by every age group, by every segment of society, by people all over the world. Most disorders of the nervous system affect men and women equally, but certain disorders, such as chronic pain, epilepsy, Rett syndrome, stroke, traumatic brain injury (TBI), multiple sclerosis (MS), and migraines disproportionately affect women or have specific health implications for them. NINDS supports basic, translational, and clinical research on these disorders, as well as targeted research to understand sex-based differences in normal development and function of the nervous system, behavior, cognition, and perception.

Chronic pain is caused by the improper function of neuronal pain circuits and results in abnormal pain that persists for weeks, months, or even years. Certain chronic pain conditions like migraine headaches, temporomandibular joint disorders, endometriosis, and fibromyalgia are diagnosed more often or exclusively in women, and women often have more than one of these conditions.

Epilepsy affects 1 in 26 people during their lifetime, and currently, there are an estimated 2.5 to 3 million individuals with epilepsy in the United States. Because there are so many different types of epilepsy and many different causes for this disorder, including TBI, genetic changes, and brain tumors, among others, the research community now refers to epilepsy collectively as "the epilepsies." Even with all of the treatments currently available for the epilepsies, only about 30 percent of individuals will benefit from these treatments. Women with epilepsy face special problems during phases of the menstrual cycle, and those who take certain antiepileptic drugs during pregnancy face higher than

normal rates of birth defects in their children. Of importance for the development of future treatments is the need to understand the varying roles of steroid hormones in the epilepsies in both males and females.

Rett syndrome is a childhood neurological disease characterized by features that are observed in many other disorders, ranging from autism to Parkinson's disease and dystonia. The disorder affects about 1 in 10,000 females and is most often caused by mutations in the gene that encodes methyl-CpG-binding protein 2 (MeCP2), a transcriptional regulatory protein. Many of the features of Rett syndrome are reversible in mouse models of the disease; this indicates that these features are probably due to dysfunction of neurons and supporting cells rather than to neural degeneration. These findings provide hope that some symptoms, and perhaps most symptoms, can be reversed in affected individuals if we discover effective therapies that can overcome the consequences of loss of function or dysfunction of MeCP2.

Stroke is caused by a rapid disruption in the blood supply to part of the brain as a result of either blood vessel blockage (ischemic stroke) or blood vessel rupture (hemorrhagic stroke). A stroke can result in sudden numbness or weakness; confusion; trouble with vision, speech, or coordination; or a sudden, severe headache. Although women in general have a lower risk of stroke than men, because of their longer life expectancy, they account for 60 percent of stroke fatalities in the United States.

TBI is one of the more prevalent and debilitating of neurological disorders, affecting approximately 2 million people annually in the United States. In addition, TBI is the leading cause of death and disability for young people in this country. Annually, more than 200,000 children in the United States suffer a TBI. Currently, there are no effective pharmacologic treatments for pediatric TBI.

MS, a chronic and often disabling disease of the central nervous system, is two to three times more common in women than in men. The progress, severity, and specific symptoms of MS are unpredictable and vary from one person to the next. Affecting more than 2 million people worldwide, the cause of MS is still not known. Ongoing research indicates that a combination of several factors may be involved, including immunology and genetics.

Migraines are painful headaches often accompanied by nausea, vomiting, and sensitivity to light. Migraine can begin at any age, although most people experience their first migraine during adolescence. Women are three times more likely to have migraines than men. Headaches tend to affect boys more than girls during childhood, but by the time of puberty, more girls are affected. Up to 90 percent of people with migraines have a family history of migraine attacks. Research to understand the genes involved in familial forms of migraine is shedding new light on the possible causes of these often debilitating headaches.

Coordination of Women's Health Research at NINDS

Research on women's health at NINDS is coordinated across a number of extramural research "clusters," or teams or program directors organized around scientific and disease areas. The Office of Clinical Research, in collaboration with the Office of Minority Health Research, oversees and tracks the recruitment of women and minorities in clinical trials. NINDS actively participates in NIH women's health research initiatives by designating a program director as the Institute's primary representative on the NIH Coordinating Committee for Research on Women's Health.

Highlights

Epilepsy

NINDS is highlighting research on the epilepsies in both clinical and basic science.

Addresses Objective 3.3 of the NIH Strategic Plan for Women's Health Research: Expand research on safe and effective interventions for conditions affecting pregnant women.

Cognitive Outcomes in Children Exposed In Utero to Antiepileptic Drugs. Women with epilepsy who are considering pregnancy, and the physicians caring for them, face a great deal of uncertainty about the risks and benefits of continued antiepileptic drug (AED) use during pregnancy. Effective seizure control for the potential mother is extremely important but often difficult to maintain as a result of unpredictable pharmacokinetic changes during pregnancy. In addition, the need for total seizure control is balanced against the possibility of serious adverse outcomes for the child exposed to AEDs during gestation and/or breastfeeding. Pregnancy registries have found an association between the use of two AEDs, valproate and topiramate, and increased risks to the fetus, including risks of congenital malformations and low birth weight. In addition, the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study, documented a significant risk of lower IQ in 3-year-old children exposed to valproate. A series of practice parameters on management of pregnant women with epilepsy, issued in 2009 by the American Academy of Neurology (AAN) and the American Epilepsy Society (AES), identified multiple areas related to clinical management for which evidence was inconclusive or lacking. These areas included rates of obstetrical complications and changes in the frequency of seizures, adverse perinatal outcomes, and rates of teratogenesis (structural and behavioral) for most AEDs; in addition, the guidelines noted insufficient data on changes in AED blood levels during pregnancy and on risks of breastfeeding when taking AEDs.

Meador, K. J., Baker, G. A., Browning, N., Clayton-Smith, J., Combs-Cantrell, D. T., Cohen, M., … Loring, D. W.; NEAD Study Group. (2009). Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *New England Journal of Medicine, 360*(16), 1597–1605.

Meador, K. J., Baker, G. A., Browning, N., Cohen, M. J., Bromley, R. L., Clayton-Smith, J., … Loring, D. W.; NEAD Study Group. (2013). Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): A prospective observational study. *Lancet Neurology 12*(3), 244–252.

Addresses Objective 1.2 of the Strategic Plan: Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems; and Goal 1.7: Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs.

Sex-Specific Modulation of the Brain by Steroid Hormones. Research to understand the role of hormones in the brain has shown that the steroid 17β-estradiol (E2) influences hippocampal functions such as memory, affective behaviors, and epilepsy. There is growing awareness that in addition to responding to ovarian E2, the hippocampus of both males and females synthesizes E2 as a neurosteroid that can acutely modulate synaptic function. Recently, it was shown that E2 rapidly suppresses inhibitory synaptic transmission in the hippocampus. Remarkably, this effect of E2 is sex specific, occurring in females but not in males. Acute E2 modulation of endocannabinoid tone and consequent suppression of inhibition provide a mechanism by which neurosteroid E2 could modulate hippocampus-dependent behaviors in a sex-specific manner.

Huang, G. Z., & Wooley, C. S. (2012). Estradiol acutely suppresses inhibition in the hippocampus through a sex-specific endocannabinoid and mGluR-dependent mechanism. *Neuron, 74*(5), 801–808.

Accomplishments

Chronic Pain

Headache Common Data Elements. The Headache Common Data Elements (CDE) Working Group convened its first in-person meeting in Washington, D.C., on June 4, 2011, to discuss identifying and defining data elements across headache domains. CDEs are content standards that enable clinical investigators to systematically collect, analyze, and share data across the research community. Thematically defined subgroups met regularly after the initial meeting to define the CDEs for their domains and to recommend standardized, validated instruments for headache research. The project is now

complete and posted on the NINDS Web site. NIH-funded researchers are required to use these CDEs in their clinical studies, and other researchers are encouraged to use them.

Centers of Excellence for Pain Education. In May 2012, The NIH Pain Consortium selected 11 health professional schools as designated Centers of Excellence in Pain Education (CoEPEs). The CoEPEs will act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, and pharmacy schools to enhance and improve the ways in which health care professionals are taught about pain and its treatment. Twenty Institutes, Centers, and Offices at NIH are involved in the Consortium. The new CoEPEs were funded through a contract solicitation process and review. The awardees are the University of Washington, Seattle; the University of Pennsylvania Perelman School of Medicine, Philadelphia; Southern Illinois University, Edwardsville; the University of Rochester, N.Y.; the University of New Mexico, Albuquerque; the Harvard School of Dental Medicine, Boston; the University of Alabama at Birmingham; the Thomas Jefferson University School of Medicine, Philadelphia; the University of California, San Francisco; the University of Maryland, Baltimore; and the University of Pittsburgh. Many of the new CoEPEs will build curricula across several of their health professional schools.

Workshop on Chronic Overlapping Pain Conditions (August 13-14, 2012). NIDCR, NINDS, NICHD and ORWH, together with the NIH Pain Consortium, sponsored this workshop. Chronic overlapping pain conditions represent a complex set of painful disorders that occur frequently in the population. However, there is a lack of firm mechanistic understanding of the conditions and the need for hypothesis-driven research is great. This workshop brought together researchers with expertise in various pain conditions and other relevant expertise to discuss the conditions and to develop a forward-thinking research agenda. Following an overview and a review of the epidemiology of chronic overlapping pain conditions, discussions focused on risk factors, mechanisms of disease, treatment, patient outcomes, leveraging of current data sets, and new scientific approaches that incorporate systems biology. Breakout groups met to discuss knowledge needed, research opportunities, and training needs in four topic areas, including patient classification, common and specific mechanisms of disease, risk factors for disease trajectory, and diagnostics and outcomes measures that will advance understanding of these conditions. A set of recommendations for the research community resulted from this workshop.

The NIH Pain Consortium 6th Annual Symposium on Advances in Pain Research (April 14, 2011). This symposium focused on mechanisms and management of overlapping chronic pain and associated conditions. The presentations covered three major areas:

- Neurological mechanisms that may contribute to comorbid pain conditions;
- Psychosocial factors that may contribute to pain conditions; and
- Treatment strategies and obstacles to managing overlapping pain conditions.

The NIH Pain Consortium 7th Annual Symposium on Advances in Pain Research (May 29-30, 2012). This symposium focused on novel approaches and therapy development for pain management. The presentations covered three major areas:

- Novel approaches in opioid analgesic development and use;
- Novel approaches in nonopioid analgesic development and use; and
- Development and use of nonpharmacological strategies as important adjuncts to pain management.

Rett Syndrome

Adult Neuronal Function Requires MeCP2. Multiple features of Rett syndrome can be recapitulated following deletion of MeCP2 in an adult mouse model of the disease. Disease symptoms, behavioral deficits, gene expression changes, and premature death are all recapitulated in the animal model, indicating that expression of MeCP2 during early life provides little, if any, protection against the

disease. These findings also indicate that the temporal association of disease with the postnatal period of neurodevelopment may be unrelated to any "developmental" or stage-restricted function of MeCP2, at least in mouse models. This research shows that the mature brain is dependent on MeCP2 function and that therapies developed for Rett syndrome will need to be continuously maintained throughout the lifespan.

McGraw, C. M., Samaco, R. C., & Zoghbi, H. Y. (2011). Adult neural function requires MeCP2. *Science 333*(6039), 186.

Setting Priorities for Rett Syndrome Research. NINDS held a workshop titled, "Setting Priorities for Therapy Development in Rett Syndrome" on September 25-27, 2011. Discussions focused on how to optimize the predictive value of animal models in Rett syndrome preclinical research and avoid the pitfalls that often lead to failure on clinical translation. The outcomes of this workshop included summaries of the phenotypes of currently available mouse models of Rett syndrome and discussion of their utility for translational studies, identification of current knowledge gaps, and recommendations of best-practice guidelines for preclinical study design, which ideally will optimize the ability of the Rett syndrome research community to translate basic findings into new therapeutic approaches.

Katz, D. M. (2012). Preclinical research in Rett syndrome: Setting the foundation for translational success. *Disease Models & Mechanisms (5)*, 733–745.

Stroke

Stroke Severity in Older Women. In postmenopausal women, hormone therapy increases the risk and severity of ischemic stroke. Previous work by the investigators using an animal model of menopause (reproductive senescence) indicated that estrogen treatment was neuroprotective in younger females, but that estrogen paradoxically increased infarct volume in older females. Subsequent work by the investigators found that Insulin-like growth factor-1 (IGF-1) levels were significantly reduced in reproductive senescent females and further reduced by estrogen at all ages. The neuroprotective effect of estrogen on induced cortical infarct volume in mature adult female animals was reversed by intracerebroventricular injections of IGF-1 receptor antagonist JB-1. Similarly, estrogen's neurotoxic effects on cortical infarct volume in senescent females were attenuated by concurrent IGF-1 treatment, and reversed when IGF-1 was infused 4 hours after the onset of ischemia (delayed IGF-1 treatment). Delayed IGF-1/estrogen treatment also suppressed ischemia-induced ERK1 phosphorylation, reduces protein oxidation, and stimulated an early increase in prostaglandin E(2) at the infarct site. In this study, IGF-1 treatment was only protective in senescent females that received estrogen, indicating that the neuroprotective actions of this peptide required interaction with the steroid hormone receptor. The data support the hypothesis that stroke severity in older females is associated with decreased IGF-1 and further indicates that short-term postischemic IGF-1 therapy may be beneficial for stroke.

Selvamani, A., & Sohrabji, F. (2010). The neurotoxic effects of estrogen on ischemic stroke in older female rats is associated with age-dependent loss of insulin-like growth factor-1. *Journal of Neuroscience 30*(20), 6852–6861.

Role of the Immune Response in Stroke. An evaluation of infarct volumes and infiltrating immune cell populations in mice after middle cerebral artery occlusion (MCAO) strongly implicated a mixture of both pathogenic and regulatory immune cell subsets in stroke pathogenesis and recovery. Larger infarct volumes, higher mortality, more severe functional deficits, and increased numbers of activated T cells, macrophages, microglial cells, and neutrophils were observed in the affected brain hemisphere of MCAO-treated animals versus control animals. These findings are the first to implicate IL-10-secreting B cells as a major regulatory cell type in stroke and suggest that enhancement of regulatory B cells might have application as a novel therapy for this devastating neurological condition.

Ren, X., Akiyoshi, K., Dziennis, S., Vandenbark, A. A., Herson, P. S., Hurn, P. D., & Offner, H. (2011). Regulatory B cells limit

CNS inflammation and neurologic deficits in murine experimental stroke. *Journal of Neuroscience 31*(23), 8556–8563.

Carotid Revascularization Endartectomy Versus Stenting Trial (CREST). In 2011, a study examining sex differences in outcomes of stenting versus endarterectomy was published by the CREST investigators in Lancet. Periprocedural risk of events seemed to be higher in women who had carotid artery stenting than in those who had carotid endarterectomy, whereas there was little difference in men. Additional data are needed to confirm whether this differential risk should be taken into account in decisions for treatment of carotid disease in women.

CREST long-term follow-up will also assess whether there are effect modifiers of the long-term durability of the two procedures. Potential "high priority" effect modifiers will include age, sex, preoperative degree of stenosis, and symptomatic status.

Howard, V. J., Lutsep, H. L., Mackey, A., Demaerschalk, B. M., Sam, A.D. 2nd, Gonzales, N. R., … Brott, T. G.; CREST investigators.(2011). Influence of sex on outcomes of stenting versus endarterectomy: A subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurology, 10*(6). 530-537.

Traumatic Brain Injury

Importance of Environmental Enrichment in Traumatic Brain Injury. Environmental enrichment consistently induces marked benefits in male rats after TBI, but whether similar efficacy extends to female rats has not been well established. Recent studies found that providing environmental enrichment to female animals conferred robust benefits in female animals after a controlled cortical impact. These findings lend further credence to environmental enrichment as a model of neurorehabilitation in animal models of TBI and its potential beneficial use in humans following TBI.

Monaco, C. M., Mattiola, V. V., Folweiler, K. A., Tay, J. K., Yelleswarapu, N. K., Curatolo, L. M., … Kline, A. E. (2013). Environmental enrichment promotes robust functional and histological benefits in female rats after controlled cortical impact injury. *Experimental Neurology.* Advance online publication. Retrieved from *http://www.sciencedirect.com/science/article/pii/S0014488613000204*

Biomarkers for Pediatric Traumatic Brain Injury. A peripheral indicator (biomarker) of the presence and magnitude of brain injury would be an extremely helpful tool for health care providers. Neuron-specific enolase, but not S100B or myelin basic protein, was found to increase after injury in all age groups in an animal model of TBI. However, neuron-specific enolase had only a fair to poor predictive value for the extent of injury. In a clinical setting, where the types of injuries are varied, more investigation is required to yield a panel of serum markers that can reliably predict the extent of injury, sex-specific changes, and the extent of injury and response to treatment.

Costine, B. A., Quebeda-Clerkin, P. B., Dodge, C. P., Harris, B. T., Hillier, S. C., & Dubaime, A. C. (2012). Neuron-specific enolase, but not S100B or myelin basic protein, increases in peripheral blood corresponding to lesion volume after cortical impact in piglets. *Journal of Neurotrauma, 29*(17), 2689–2695.

Future Plans

Epilepsy

The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study was funded by NINDS to develop Class I evidence for the management of women with epilepsy during pregnancy. This study will provide information about how to direct epilepsy care for pregnant women so that seizure control is maximized while obstetrical, neonatal, and neurodevelopmental complications are minimized. The study results will be directly relevant to the needs identified in the 2009 AAN Practice Guidelines.

Stroke

Several funded studies that aim to study sex differences in stroke are under way. Short descriptions of these studies (a-d) are provided below.

(a) In women, the disruption of the endocrine environment during menopause amplifies the risk for stroke and neuroinflammatory disease. Moreover, women are at a greater risk for stroke than men after menopause, and estrogen therapy in this group unfortunately increases the risk and severity of this disease. New research will explore the observation that estrogen is neuroprotective following ischemic stroke in young reproductively mature female rats but increases tissue damage in reproductively senescent females, leading to the hypothesis that this difference is due to the cooperative interaction of estrogen with insulin-like growth factor (IGF)-1, which undergoes an age-related decline. This research has the potential to significantly advance understanding of how estrogen exerts its signaling and neuroprotective effects in the brain, and it may provide a mechanistic understanding of why estrogen failed to exert beneficial cardiovascular and neural effects in the Women's Health Initiative study, where replacement was initiated long after the onset of menopause.

(b) Cardiovascular disease, including stroke, is the single largest cause of death among women worldwide. The mechanisms of stroke differ between men and women, and currently there is no therapy that specifically targets stroke in women. Research in this area is examining a novel mechanism of cerebrovascular injury specifically induced in female mice after reproductive senescence. The research is potentially highly significant clinically, as it may advance understanding of mechanisms underlying cerebrovascular endothelial dysfunction, and it may lead to the translational development of therapeutic agents specifically targeting epoxyeicosatrienoic acids and the signaling of their metabolizing enzyme, soluble epoxide hydrolase, as a mean of improving vascular function and stroke outcome in postmenopausal women.

(c) Research is investigating the impact of changes in obesity, physical inactivity, and use of hormone replacement therapy on stroke incidence and mortality among women who participated in the California Teachers Study. By examining how exposures to these common, modifiable risk factors over a woman's lifespan influence stroke incidence and mortality, this study will provide critical new knowledge that can serve as the basis for behavioral public health interventions that will benefit women on a population-wide scale.

(d) Neonatal stroke occurs more frequently in males than females across diverse ethnic backgrounds and nationalities. Research funded by NINDS will study the role of testosterone in the sexual dimorphism observed in neonatal stroke. This dimorphism is in part shaped by events early in development, specifically testosterone exposure during sexual differentiation of the brain. The work is significant because it will characterize a potential key factor in determining what aspects of cellular ischemic sensitivity in the neonatal brain are modifiable versus developmentally programmed, as well as predict whether existing or new therapies are likely to be equally efficacious in male and female neonates.

Health Disparities Research

The NINDS-funded Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is an observational study with over 24,000 participants, 59 percent of them women, that is exploring the role of geographic differences in determining the prevalence of risk factors for stroke, stroke incidence, and stroke mortality. The study is also exploring race, gender, genetics, and lifestyle choices as risk factors for stroke. In the 2011–2012 period, the REGARDS investigators published over 60 reports on the cohort; most of the publications included male/female analysis. Recent analysis in REGARDS of the incidence of coronary heart disease (CHD) by Black and White race and by sex showed that the higher risk of fatal CHD among Blacks was associated with a greater burden of risk factors for cardiovascular disease and that these relationships may differ by sex.

Low adherence to medications and apparent treatment-resistant hypertension were also found to be associated with risk of CHD in the REGARDS study. The study also provided a unique opportunity to examine associations between unhealthy lifestyle factors and treatment-resistant hypertension in individuals taking antihypertensive medications from three or more classes. After adjustment for age, sex, race, and geographic region of residence, none of the unhealthy lifestyle factors was associated with treatment-resistant hypertension. The association between each unhealthy lifestyle factor and treatment-resistant hypertension remained nonsignificant after additional adjustment for education, income, depressive symptoms, total calorie intake, and comorbidities.

NINDS supported the Brain Attack Surveillance in Corpus Christi (BASIC) study to examine the practice patterns for treatment of acute stroke with intravenous thrombolysis. The study found that women were likely to benefit more than men from thrombolysis, but it also found that there was an underutilization of this therapy in women but not in men.

The BASIC study also found that men were at higher risk for stroke until age 79, but after age 79, no sex difference in stroke was observed in non-Hispanic Whites or Mexican Americans.

Reeves, M. J., Wilkins, T., Lisabeth, L. D., & Schwamm, L. H. (2011). Thrombolysis treatment for acute stroke: Issues of efficacy and utilization in women. *Women's Health, 7*(3), 383–390.

Sealy-Jefferson, S., Wing, J. J., Sanchez, B. N., Brown, D. L., Meurer, W. J., Smith, M. A., … Lisabeth, L. D. (2012). Age- and ethnic-specific sex differences in stroke risk. *Gender Medicine, 9*(2), 121–128.

Meador, K. J., Baker, G. A., Browning, N., Cohen, M. J., Bromley, R. W., Kalayjian, L. A., … Loring, D. W.; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): A prospective observational study. *Lancet Neurology, 12*(3), 244–252.

National Institute of Nursing Research

Executive Summary

The National Institute of Nursing Research (NINR) supports clinical and basic research to build the scientific foundation for clinical practice, prevent disease and disability, manage and eliminate symptoms caused by illness, and enhance end-of-life and palliative care. Confronting these issues requires a shift to a patient-provider partnership paradigm that is increasingly person-centered rather than disease-oriented, that focuses on preventing the development of chronic illness rather than treating it, and that features the person as an active participant in his or her own health. The Institute's multidisciplinary and interdisciplinary scientific approach unites the biological and behavioral sciences to better understand the complex interactions between the physiological factors of health and disease and the knowledge, beliefs, and behavior of the individual, family, and community. Across all scientific programs, NINR's research addresses the special needs of at-risk, vulnerable, and underserved populations with particular emphasis on eliminating health disparities and promoting health equity.

NINR's research portfolio is ideally suited to explore some of the most important challenges affecting the health of women, including:

- Growth of an aging female population faced with chronic diseases requiring complex management;
- Growth of diverse populations of women from different racial and ethnic backgrounds and the associated issues of health disparities in these at-risk, underserved populations;
- Symptom management for chronic conditions, such as cardiovascular diseases;
- Health promotion and disease prevention through management of physical activity and obesity; and

- The need to build a cadre of next generation of scientists and practitioners in women's health.

In advancing the science of women's health, NINR funds and cofunds programs of research with specific attention to issues surrounding pregnancy, aging and menopause, chronic conditions, health disparities, and the promotion of women in research. Central to the themes within its strategic plan, NINR seeks to strengthen research specific to women, whether as patients, caregivers, or community members. The Institute actively ensures that diverse populations of women are represented in its studies and that disparities experienced by women in minority, rural, immigrant, and other underserved populations are addressed. NINR-supported investigators have contributed to new knowledge by addressing women's health across the lifespan. Numerous findings during FYs 2011 and 2012 have furthered understanding of issues uniquely relevant to women's health, including:

- Chronic and life-limiting conditions, including heart disease and cancer;
- Symptom management for conditions such as pain, fatigue, and depressed mood;
- Promotion of healthy physical and dietary lifestyles to prevent obesity, diabetes, and heart disease;
- Aging and menopause; and
- Pregnancy, the perinatal period, preterm birth, and postpartum depression.

Today's challenges in the field of women's health present opportunities for NINR to further expand its impact on the health of the Nation. The Institute will continue to support innovative studies in areas highlighted in its strategic plan, and results from these studies will inform future strategies that will advance women's health in the future.

NINR and Women's Health

NINR is committed to supporting science that promotes women's health. The Institute has supported a wide range of women's health research that has led to scientific advances in our understanding and treatment of conditions and diseases that primarily impact women and others that affect women in different ways than men. This research occurs through grants to individual researchers, collaborative groups, multisite projects, and research centers, as well as through training grants, all working to develop not only the evidence base for improvements in women's health, but also the body of researchers examining symptoms and conditions that affect women across the United States and the world.

For example, through its funding of the University of Washington's Center for Women's Health and Gender Research (P30), NINR has expanded interdisciplinary collaborations among investigators in basic and clinical research related to women's health across the lifespan. The program is a focused effort to enhance understanding of the biobehavioral and sociocultural dimensions of women's health, advance knowledge of genetics and gender differences, and expand understanding of health disparities among vulnerable subpopulations of women. Through additional support to the Center's training program under a T32 award, NINR continues to build research capacity to enable the study of diverse populations of women in culturally competent ways and to promote the development of research skills and opportunities for scholarship in women's health.

IC Working Groups and Programs Focused on Women's Health

In FYs 2011 and 2012, NINR supported NIH programs that promote research on women's health. Dr. Patricia Grady, Director of NINR, is a member of the NIH Working Group on Women in Biomedical Careers and participates in a number of internal working group subcommittees.

In FYs 2011 and 2012, NINR participated in several workshops on topics related to women's health, including:

- The Study of Women's Health Across the Nation program's person-to-person meetings;
- HIV prevention and treatment in U.S. women;
- The ORWH Research Enhancement Awards Program (served as reviewer); and

- An international conference on uterine fibroids (served as poster reviewer).

Accomplishments

NINR's research portfolio emphasizes clinical research on promoting health and quality of life for individuals across the lifespan, from the perinatal period to the end of life. This is illustrated by the following recent research accomplishments and efforts.

Chronic and Life-Limiting Conditions

NINR supports research focused on chronic and life-limiting conditions, such as the prevention and management of cardiovascular disease. NINR also supports research focused on improving the management of symptoms and quality of life in individuals with cancer, including those experiencing the effects of cancer treatment. NINR-supported advances in women's health research focused on chronic and life-limiting conditions in FYs 2011 and 2012 included the following:

Monitoring Nighttime Blood Pressure Can Predict Coronary Heart Disease. Coronary heart disease is the number one killer of men and women, but men and women often exhibit different signs and symptoms of the disease. Researchers have found that, at night, aging postmenopausal women with coronary heart disease have higher systolic blood pressure and have smaller dips between systolic and diastolic stages of the heartbeat, which may lead to heart attacks. This discovery may help diagnose coronary heart disease in women at an earlier stage and facilitate the early adoption of lifestyle changes that can help patients and providers better manage this disease.[3]

Tailored Cardiac Rehabilitation Program Improves Health Perceptions More Than Traditional Rehabilitation. Health perceptions have a strong influence on health behaviors. For this reason, understanding and improving the way individuals think about their health may influence adherence to health behavior changes. NINR-supported investigators compared (1) a tailored, woman-centered cardiac rehabilitation program that included motivational interviewing and psychotherapy to (2) a traditional rehabilitation program. The tailored program addressed the fact that women experience higher mortality and morbidity in coronary heart disease compared with men and recognized the unique psychosocial needs of women. The tailored cardiac rehabilitation program improved health perceptions, mental health, vitality, and social functioning, which could lead to an increase in healthy behaviors.[4]

Sleep Disturbances May Predict Heart Attacks in Women. Heart attacks are frequently unrecognized in women because their symptoms are vague and differ from those in men. Analysis of records from over 1,200 female heart attack patients revealed that half of the women experienced sleep disturbances prior to their acute attacks. Sleep disturbances were associated with heart attacks in women who were older and heavier and who reported recent cognitive changes, anxiety, or unusual fatigue. Sleep disturbances before heart attacks were reported in all ethnic and racial groups and may be an important new warning sign for heart attacks in women.[5]

Breast Cancer Patients Experience Specific Symptom Clusters Throughout Their Treatments. Breast cancer patients experience a variety of symptoms during treatment, including depressed mood, cognitive disturbance, fatigue, insomnia, and pain. An NINR study found that there are six symptom clusters that are easily distinguishable from one another. Understanding these symptom clusters and how they vary across the patient population is vital to developing tailored, personalized symptom management interventions for breast cancer patients to improve their quality of life.[6]

[3] McFetridge, J., & Sherwood, A. Heart disease in women: Estrogen effects on hemodynamics (Grant No. R01NR00528)

[4] Beckie, T. A. Women's-only phase II cardiac rehabilitation program (Grant No. R01NR007678)

[5] Pettey, C. Factors affecting hypertension treatment adherence among African Americans (Grant No. F31NR012347); McSweeney, J. Center for Research on Tailored Biobehavioral Interventions (Grant No. P20NR009006); Cole, C. Sleep fragmentation and attention in Alzheimer's disease (Grant No. K23NR009492)

[6] Barsevick, A. Energy conservation and cancer treatment fatigue (Grant No. R01NR004573)

Analysis of Multiple Cell-Signaling Proteins Reveals Distinct Inflammatory Responses to Breast Cancer and Its Treatment. Cytokines, proteins that allow cells to communicate, are involved in inflammation. By taking advantage of advances in technology that allow for analysis of multiple cytokines at once, NINR-supported researchers have identified a distinct inflammatory profile of breast cancer. A biobehavioral approach helps to explain how the inflammatory response might cause specific symptoms and symptom clusters in breast cancer, including fatigue, depression, pain, and sleep disorders.[7]

Nurse-Led Symptom Management Program Reduces Primary Care Visits; Training Women to Properly Use the ER After Ovarian Cancer. In a recent study, teams of advanced practice nurses and psychiatric consultation-liaison nurses provided symptom management, counseling, education, direct nursing care, resource coordination, and referrals to women after surgery for ovarian cancer. These women, when compared with those who received usual care, reported using their primary care providers much less frequently, having learned to recognize symptoms that required urgent care after hours in the emergency room. When women wait to see their primary care providers, they often wait longer than if they had gone to an emergency center; their symptoms also progress further and are harder to treat.[8]

NINR grant activities in chronic and life-limiting conditions in FYs 2011 and 2012 included:

- R01NR010939—Altered Brain Function in Chemotherapy for Breast Cancer;
- R21NR013247—Mother-Daughter Joint Decision Making To Obtain the HPV Vaccine;
- R01NR012667—Epigenetics and Psychoneurologic Symptoms in Women with Breast Cancer;
- R01NR011885—Cost Effectiveness of the Rural Breast Cancer Survivor Intervention Package;
- R21NR012271—Bioelectrical Impedance for Self-Monitoring of Breast Cancer Related Lymphedema;
- F31NR012605—Dietary Quality and Cardiometabolic Risk After Gestational Diabetes; and
- R01NR009270—Genetics, Environment, and Weight Gain Posttransplant.

Obesity, Physical Activity, and Disease Prevention

While obesity is a health problem for both genders, women suffer a disproportionate burden of disease due to overweight and obesity. The prevalence of female obesity in the United States is high, with around 64 percent of adult women overweight or obese. Obesity is more prevalent in minority communities, with 75–78 percent of African-American and Hispanic women either overweight or obese. Furthermore, the link between obesity and diabetes is more pronounced among women than in men. Obesity is also a risk factor for a number of chronic conditions, including heart disease, stroke, high blood pressure, breathing problems, arthritis, depression, and some cancers (such as endometrial, cervical, breast, and ovarian cancers). Such conditions may make physical activity more difficult. Maternal obesity also has a profound impact on infants and children. Nurses have been at the forefront of some of the public health efforts to address the obesity epidemic through community and clinically based research, especially within medically underserved and minority communities. Exploratory findings in this area from NINR-supported scientists in FYs 2011 and 2012 included the following:

Obesity Linked to Ethnicity and Socioeconomic Status in Middle-Aged Women. In a multiethnic study of middle-aged women (40–50 years old), researchers found that ethnicity, annual household income, and level of physical activity were significant predictors of body mass index. This study underscores how ethnicity and socioeconomic status are linked and how

[7] McCain, N. Biobehavioral research in critical health experiences (Grant No. P20NR008988); Pickler, R., & Grap, M. J. Center of Excellence in Biobehavioral Approaches to Symptom Management (Grant No. P30NR011403); Grant No. R01CA127446

[8] McCorkle, R. Nursing's impact on QOL outcomes in ovarian cancer (Grant No. R01NR007778)

they predict obesity (individually and together) in middle-aged women.[9]

Attitudes of Midlife Women Toward Physical Activity Vary by Ethnicity. According to an Internet-based survey of a multiethnic group of midlife women, conducted by NINR-supported scientists, attitudes about physical activity vary. Despite these attitude differences, there were no significant differences in physical activity scores between ethnicities. These diverse attitudes toward physical activity must be taken into account when designing and implementing interventions for diverse populations.[10]

For African-American Women with Diabetes, Television-Watching Should Be Cut and Walking Encouraged. A study found that, for African-American women with Type II diabetes, walking is the preferred form of physical activity; however, not all women have the chance to walk for exercise very often. Further, those women who watched television for more than 2 hours a day and those who were confined to their beds for more than 1 week reported more physiological and psychological problems. Physical activity interventions must address these factors in order to effectively change daily behavior and help African-American females with diabetes to improve their quality of life.[11]

NINR supported research grants in FYs 2011 and 2012 related to obesity, physical activity, diabetes, and women's health including the following:

- R01NR010356—Madres para la Salud (Mothers for Health);
- R01NR011295—Culturally and Linguistically Adapted Physical Activity Intervention for Latinas;
- F31NR013844—Culture and Food Practices of African-American Women with Type 2 Diabetes;
- K01NR013195—Personalized Biobehavioral Weight Loss Intervention for African-American Women;
- K01NR013490—Physical Activity and Health Promotion Among Somali Women;
- R01NR004134—Reducing Health Disparity in AA Women: Physical Activity Adherence; and
- R01NR010589—Web-Based Weight Loss and Weight Maintenance for Older Rural Women.

Aging and Menopause

As part of its research portfolio, which focuses on the entire lifespan, NINR devotes significant efforts to studying the needs of the aging population, including issues specific to women. In 1994, NINR joined with the National Institute on Aging and ORWH to cofund the Study of Women's Health Across the Nation (SWAN), a 20-year, multisite, multiethnic, longitudinal epidemiological study of a cohort of middle-aged women. The study examined and tracked the changes in the women's health as they aged and experienced menopause. NINR directly supported the study at the University of Michigan, home to the hormone laboratory and biorepository for the study. SWAN has undertaken the most comprehensive community based examination of the health and the physiological and psychosocial changes that women undergo from premenopause to postmenopause, providing a broad and deep perspective of the aging process in women. Some of the recent research accomplishments and efforts arising from SWAN include the following highlights:

Genetic Differences and Obesity Linked to Hormone Decline in Menopause. The study found that obesity and genetic differences slow the rate of estradiol decline before and during menopause and lead to an elevated level of the hormone after menopause. While estradiol is a critical hormone in the menstrual cycle and during pregnancy, it also plays a critical role in women's mental health and may activate certain genes that cause cancer. In addition, this difference in the loss

[9] Lee, K. Biobehavioral health in diverse midlife women (Grant No. R01NR04259); Lee, K. Nurse training in symptom management (Grant No. T32NR07088)

[10] Im, E.-O. Ethnic specific midlife women's attitudes toward physical activity (Grant No. R01NR010568)

[11] Melkus, G. Self-care interventions for black women with type 2DM (Grant No. R01NR05341); Grey, M., & Reynolds, N. Research training: Self and family management (Grant No. T32NR008346)

of estradiol may help to explain the slower rate of bone loss in obese women.[12]

Obesity Is an Important Modifiable Risk Factor for Peripheral Nerve Dysfunction. Obesity is a major public health problem, with two-thirds of adults overweight or obese, and it is a major risk factor for diabetes. Peripheral nerve dysfunction is a complication of diabetes, but the relationship between obesity and peripheral nerve dysfunction has been poorly understood. Researchers in the SWAN study found that body size was a significant predictor for peripheral nerve dysfunction over time, independent of levels of glucose intolerance. This is significant because it is the first modifiable risk factor to be identified for peripheral nerve dysfunction.[13]

Besides the SWAN study, NINR also supported other research programs on aging and menopause, as detailed below.

Behavioral Insomnia Treatments with Single Components Are as Successful as Multicomponent Treatment Plans. Older adults often suffer from insomnia, and sleep dysfunction is associated with a number of chronic illnesses, including diabetes, cardiovascular disease, Alzheimer's disease, and depression. Components of behavioral insomnia treatments frequently address circadian, homeostatic, and conditioned factors that lead to the development and maintenance of chronic insomnia. An NINR-supported study examined each component separately and together in a multicomponent program. Generally, all individual treatments resulted in high remission rates, but the multicomponent program had the highest rates of remission over time. Treatment plans with multiple components can be more costly and time-consuming for patients and providers than those with single components, but the study provides evidence that multicomponent treatments for insomnia are more efficient.[14]

Family Support and Perception of Barriers are Central to Facilitating Healthier Diets in Older, Rural Women. Diet change to improve healthy eating and prevent disease is a strong focus of many public health interventions, yet there remains little understanding of the specific factors that cause individuals to change their dietary habits. Scientists conducted a project that provided customized information to older, rural women that directly addressed their personal goals, their perceptions of benefits, and their perceptions of barriers to changing to a healthier diet. The study found that providing this information led to more of the women eating healthier. The study identified those factors most important to encouraging this change: family support during and after the intervention, and an overall perception that barriers to healthier eating had lowered.[15]

During Menopause, Symptoms Cluster in Different Ways. The Seattle Midlife Women's Health Study tracked a group of 300 women for up to 20 years from the late reproductive stage to postmenopause, focusing on the symptoms that they experience through this transition, including sleep problems, cognitive symptoms, emotions, pain, and tension. Three very different groups of symptoms were experienced at different stages of menopause. This finding will help to inform future symptom management interventions.[16]

In FYs 2011 and 2012, NINR funded the following grants:

- R01NR011296—Dissemination of a Theory-Based Bone Health Program in Online Communities
- K23NR014008—Cognitive Behavioral Therapy for Insomnia and Nocturnal Hot Flashes in Menopause

[12] Sowers, M., & Harlow, S. SWAN IV (Grant No. U01NR004061)

[13] Sowers, M., & Harlow, S. SWAN IV (Grant No. U01NR004061)

[14] Epstein, E. R. Behavioral intervention for insomnia in older adults (Grant No. R01NR004951)

[15] Pullen, C. H. Interdisciplinary Healthy Heart Center: Linking rural populations by technology (Grant No. P20NR011404); Walker, S., & Pullen, C. H. Modifying lifestyle in prehypertensive older rural women (Grant No. R01NR004861)

[16] Woods, N. F. Menopause symptom clusters: Refocusing therapeutics (Grant No. R21NR012218); Mitchell, E. Menopausal transition: A biobehavioral model of symptoms (Grant Nos. R01NR004141 & P30NR00400); Woods, N. F. Center for Women's Health Research (Grant No. P50NR002323)

- R01NR012011—Translating Unique Learning for Incontinence Prevention: The Tulip Project

Pregnancy, Childbirth, and Perinatal Health

A significant part of NINR's research portfolio in women's health comprises research on health issues during pregnancy and the perinatal period. NINR investigators continue to make meaningful contributions to improving pregnancy outcomes and improving the health of mothers and their children.

New Tool to Reduce Unnecessary Caesarean and Chemically Induced Births and to Improve Birth Safety and Outcomes. In recent years, rates of chemically induced births and Caesarean sections in the United States have risen dramatically due to a number of causes, including the over-diagnosis of abnormal labor. An NINR-supported scientist developed an improved partograph, a tracking system for measuring the progress of labor. The improved partograph is based more closely on the progress of normal labor, updating the currently used partograph that was developed in the 1950s. This improved partograph could significantly reduce birth complications for mothers and infants, reduce the rates of unnecessary chemical inductions and Caesarean sections, and reduce health care costs for normal, low-risk births.[17]

Predicting Preterm Births in Latinas Through Biomarkers and Psychological Factors. Nurse researchers are beginning to explore the emerging field of psychoneuroimmunology, which examines the interface between psychology and the nervous and immune systems of the body. A recent study found that measuring levels of specific cytokines, small proteins that help cells communicate, can predict the risk of preterm birth in Latinas. The same study also revealed that undiagnosed depression in Latinas contributes to preterm birth by altering hormone ratios. The identification of these biomarkers and psychological factors could allow for better prediction and prevention of preterm birth.[18]

A Community-Based Screening Program Can Help Identify New Mothers at Risk for Postpartum Depression. Postpartum depression is a common childbirth complication, estimated to affect 13 percent of postpartum women. Screening for postpartum depression is important for identifying women experiencing (or at risk for) this condition. NINR-supported researchers recently have demonstrated the feasibility and the effectiveness of a community-based postpartum depression screening program.[19]

Delayed Umbilical Cord Clamping Can Prevent Cerebral Hemorrhage. Premature infants run the risk of cerebral hemorrhage, which can cause lifelong neurological disability. Currently, there are no treatments that can stop this form of cerebral hemorrhage, and it can only be treated with blood transfusions. Scientists found that delaying the clamping of the umbilical cord in stable premature infants provides a simple, yet effective, way to reduce the incidence of cerebral hemorrhage in this vulnerable population.[20]

In addition to these advances, NINR supported the following grants during FYs 2011 and 2012:

- F31NR013120—Identifying Barriers to Breastfeeding Initiation in African-American Families;
- F31NR011379—Genomics of Endoglin Pathway in Preeclampsia;
- R01NR010552—Mechanisms Underlying Preterm Birth in Minority Women;
- R03NR012052—Models of Prenatal Care and Perinatal Health Indicators in Disaster Recovery Areas; and
- R21NR013094—The Association Between Preterm Milk Immunology and Infant Health.

[17] Neal, J. L. Inflammatory markers as predictors of active labor onset among nulliparous women (Grant No. R03 NR011493)

[18] Ruiz, R. J. Psychoneuroimmunology: Preterm birth in Hispanics (Grant No. R01NR007891)

[19] Horowitz, J. A. CARE intervention for depressed mothers and their infants (Grant No. R01NR008033)

[20] Mercer, J. S. Protective effects of delayed cord clamping on VLBW infants (Grant No. R01NR010015)

Sex/Gender Analysis at NINR

NINR has funded and continues to support a number of studies that are specifically designed to analyze gender differences in symptoms, responsiveness to treatment, or impact of chronic conditions on quality of life. These studies underscore the need to include women in clinical research and clinical trials, as women often respond to medications and other therapies differently than men and they have historically been excluded from clinical research studies and pharmaceutical development.

For example, one study is exploring the sex differences in the occurrence, treatment, and outcome of ischemic stroke. It is hypothesized that these differences are due to interactions between estrogen and antiplatelet drugs. Women suffer more strokes and are less likely to recover from stroke. Antiplatelet therapy is a common treatment for stroke to prevent formation of additional blood clots, and is also used with myocardial infarctions. The study found that, in a rabbit model, antiplatelet therapy provided primary stroke protection in females but may not provide primary prevention for heart attacks. The opposite may be true for males.[21]

The American Heart Association recommends all patients who present to the emergency department with complaints of chest pain symptoms receive an initial electrocardiogram (ECG) within 10 minutes. However, a study examining the implementation of this standard of care revealed gender differences between those who received a prompt ECG and those whose ECGs were delayed. Women waited almost twice as long as men (34 minutes vs. 53 minutes) for their initial ECGs.[22]

Breast cancer and prostate cancer are the two most common cancers in women and men, respectively. Attentional fatigue is experienced as a decreased ability to concentrate, engage in purposeful activity, and maintain social relationships when there are competing demands on attention. Breast cancer patients have commonly reported attentional fatigue, but it has previously not been studied in prostate cancer patients. A recent study revealed differences between self-reported attentional fatigue in these two populations prior to radiation treatment, with women reporting higher levels of attentional fatigue. When initiating cancer treatments, it is important for clinicians to understand that there are differences in patients' abilities to direct attention to and understand treatment options.[23]

Coronary heart disease may be the number one killer of men and women, but each sex experiences the disease in different ways, with different signs, symptoms, and responses to treatment. NINR-supported scientists have also identified different symptom clusters in women versus men. Women experience greater anxiety and lower perceptions of control, with fewer socioeconomic resources to address their health care needs.[24]

Initiatives

Chronic Fatigue Syndrome: Pathophysiology and Treatment (PA-08-246, PA-08-247). NINR is a cosponsor of this ORWH-led initiative, which seeks to examine the etiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome in diverse groups across the lifespan. Of particular relevance to the strategic goals of NINR, the initiative calls for research into behavioral factors that influence chronic fatigue syndrome and ways to manage symptoms and improve quality of life. NINR has funded five grants through this initiative.

Maternal Nutrition and Prepregnancy Obesity: Effects on Mothers, Infants and Children (PA-12-061). NINR cosponsors this initiative with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to fund interdisciplinary research on maternal nutrition and prepregnancy obesity in mothers

[21] Meyer, D. M. rLOAD: Loading of aspirin and clopidogrel in rabbit model of ischemic stroke (Grant No. F31NR011120)

[22] Drew, B. Tele-electrocardiography in emergency cardiac care (Grant No. R01NR007881)

[23] Lee, K. Nursing research training in symptom management (Grant No. T32NR007088); Miaskowski, C. Fatigue, pain, and sleep problems during radiation (Grant No. R01NR004835)

[24] Dracup, K. Reducing prehospital delay acute myocardial infarction (Grant No. R01NR007952)

and their children. Obesity in pregnancy has profound impacts on fetal development and children's health and development after birth. Obesity is also a contributing factor in poor maternal outcomes such as gestational diabetes, pregnancy-induced hypertension, preeclampsia and eclampsia, and venous thromboembolism. Obesity can also lead to a higher rate of instrumental delivery, a higher rate of Caesarean section, and longer postpartum hospital stays compared with nonobese women.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Etiology, Diagnosis, Pathophysiology, and Treatment (PAR-12-032, PAR-12-033). With other ICs and ORWH, NINR cosponsors this funding opportunity to supports research on myalgic encephalomyelitis, also called chronic fatigue syndrome. NINR supports research on the relationships between behavioral interventions and biological outcomes in symptom management. NINR-supported efforts in biobehavioral research explore designs and methods to evaluate the effectiveness of integrated biological and behavioral interventions and elucidate the biological bases and predictors of response to behavioral interventions, among other activities. NINR has funded four grants through this initiative.

Advancing Novel Science in Women's Health Research (ANSWHR) (PAS-10-226). NINR cosponsored this ORWH-led initiative to promote (1) innovative interdisciplinary research that advances new concepts in women's health research; (2) the study of sex/gender differences; and (3) team science approaches. NINR has funded 20 grants through this initiative since 2007.

Etiology and Pathophysiology of Sleep Disordered Breathing in Pregnancy (PA-11-122). With NICHD and the National Heart, Lung, and Blood Institute, NINR cosponsors this initiative to understand the impact of maternal sleep disordered breathing (SBD). In particular, research under this initiative examines the etiology of SBD; the impact of maternal SBD on maternal heart, lung, and blood pathophysiology; and mechanisms that link maternal SBD to the uterine environment and fetal development.

Pregnancy in Women with Disabilities (PAR-11-258, PAR-11-259). With NICHD, NINR is cosponsoring a funding opportunity to explore the incidence, course, and outcomes of pregnancy among women with disabilities. Funded research will also include studies that inform preconception and antenatal counseling, address barriers to prenatal care, and inform management of pregnancy to optimize outcomes for women with physical, intellectual, developmental, and/or sensory disabilities.

Administrative Supplements for Research on Sex/Gender Differences (PA-13-018). NINR participates in this supplement program to support the study of sex/gender differences or similarities. Supplements support the inclusion of additional study subjects to examine whether sex/gender differences exist in the experience of a disease or condition or in response to therapies.

Women's Health, Health Disparities, and Special Populations Research at NINR

The investigation and elimination of health disparities are a major area of research emphasis throughout NINR's research portfolio. Special populations studied in NINR-supported research include rural women, adolescents and women of racial and ethnic minorities, and women in poverty. Finally, NINR's training portfolio places a special emphasis on health disparities, supporting the education and development of the next generation of nurse scientists and researchers focused on health disparities. Presented below are examples of NINR-supported women's health research findings and current efforts that focus on health disparities and/or special populations.

Rural Women

Loneliness Should Be Considered an Important Factor in Nursing Care for Rural Women with Chronic Illness. NINR-supported researchers have found that loneliness can be high among rural women with chronic conditions. The pain of loneliness can be a factor in an individual's overall health, and these women's physical and emotional isolation should be considered when

developing plans for managing their chronic illnesses. Online forums offer one way to reach them. Such forums allow these women to share their experiences with each other and to learn from teaching modules about managing their chronic illnesses.[25]

Satisfactory Social Support and HIV Disclosure Reduces Depression in Rural African-American Women. Rural African-American women face many challenges in their daily lives, especially if they are HIV-positive. Researchers have found that the availability of social support and the satisfaction with this support can reduce these women's risk of depression, and satisfactory support is associated with the disclosure of their HIV status, especially to their children. These factors are important in the design of interventions to reduce depression and improve quality of life within this population.[26]

Grants funded in rural women's health include:

- R01NR012450—Palliative Care Symptom Management for Rural Communities; and
- F31NR013101—Regarding Sexual Health and HIV Risk Among Female Farmworkers.

Adolescents and Women of Racial and Ethnic Minorities

Perceptions of Pain Discourage Minority Women from Scheduling Their First Pap Exam. Understanding why women, especially minority women, are reluctant to have regular Pap smears is vital to reducing health disparities in cervical cancer. NINR-supported researchers have found that many minority women (including African-Americans, Latinas, and Arab women) perceive Pap smears to cause considerable pain. After a community-based educational intervention, women in all groups except Latinas had significantly reduced perceptions of pain, and were more likely to schedule their first Pap smear. Understanding psychological barriers to diagnostic and therapeutic procedures is essential to improving health outcomes for underserved populations. This ongoing project is determining the effectiveness of the Kin Keeper Cancer Prevention program. This program uses the regular lines of communication in families to improve health literacy and increase screening rates for cervical and breast cancer amongst medically underserved populations, including African-American, Hispanic, and Arab women.[27]

Adverse Birth Outcomes are Associated with Lifetime Trauma Exposure in Low-Income African-American Women. An NINR-supported study found that African-American women living in poverty reported high levels of exposure to trauma over their lifetimes, leading to high rates of depressive symptoms, anxiety, and stress. These women often had adverse birth outcomes, with higher rates of premature rupture of membranes and longer hospital stays after birth. These women also experienced high rates of antenatal depressive symptoms, associated with exposure to social conflict, trauma, and discrimination, and with limited economic resources. Understanding how a lifetime of exposure to social conflict and traumatic experiences leads to poor maternal mental health and birth outcomes is essential for designing better interventions in this population.[28]

Postmigration Stressors Increase the Risk of PTSD and Major Depressive Disorder in U.S. Arab Immigrant Women. Researchers have found high levels of psychological problems among U.S. Arab immigrant women, but it was unclear whether this is due to premigration exposure to trauma or to postmigration experiences. In an NINR-supported study, postmigration stressors were significantly linked to the development of clinical diagnosis of PTSD and major depressive disorders. Understanding the stresses associated with migration and the postmigration experience is necessary to developing more

[25] Weinert, C. Rural chronically ill women: Online support network (Grant No. R01NR007908); Weinert, C. Nursing intervention: Rural dwellers and chronic illness (Grant No. R55NR004422)

[26] Pugh, L. Nurse intervention for low income breastfeeding women (Grant No. R01NR004958)

[27] Williams, K. Reducing health disparities: Survey validation for black, Latina and Arab women (Grant No. R21NR010366)

[28] Dailey, D. Stress, coping, and birth outcomes among black women (Grant No. F31NR008055); Lee, C. Nursing research training in symptom management (Grant No. T32NR007088)

tailored interventions to reduce psychological problems among U.S. Arab immigrant women.[29]

NINR-supported grants in FYs 2011 and 2012 exploring the health of minority women and adolescents included:

- F31NR011106—Skin Elasticity and Skin Color: Understanding Health Disparity in Sexual Assault;
- F31NR013326—East African Immigrant Females: Adolescent Developmental Protective/Risk Factors; and
- R01NR011589—Injury in Latina Women After Sexual Assault: Moving Toward Health Care Equity.

Women in Poverty

Public Health Nurse Case Management Increases Health Care Use and Overall Family Health. NINR-supported researchers examined the outcomes of case management by public health nurses among women in urban and rural areas with chronic health problems who were receiving Temporary Assistance for Needy Families. This intervention increased health care visits, including mental health visits; improved Medicaid knowledge and skills; and led to better health and functional status. Public health nurse case management also led to improvements in depression.[30]

Low-Income Urban Women Face Environmental Barriers to Accessing Healthy Foods and Develop Adaptive Strategies to Cope. NINR researchers examined the challenges that low-income African-American urban women face in accessing healthy foods, including material, economic, and social barriers. The scientists found that the women responded by developing strategies to cope with this lack of access. However, despite intentions to improve their families' diets, women do not entirely overcome environmental obstacles with these strategies. The study underscores the importance of understanding community contexts when designing interventions to improve diets: The physical and social environments of food stores must be taken into account in addition to food availability and prices.[31]

In FYs 2011 and 2012, NINR-supported research on women's health in the context of poverty and low income included:

- F31NR013809—In Their Own Words: Exploring Family Pathways to Housing Instability;
- R21NR013538—Enhancing Psychological Capital to Foster Health Outcomes in Homeless Young Women; and
- R21NR013628—Rapid HIV Testing and Counseling in High-Risk Women in Shelters.

HIV/AIDS and Women's Health

Globally, women account for 25 percent of all new cases of HIV, while the proportion of AIDS diagnoses reported among women have more than tripled since 1985. In the United States in 2009, 64 percent of women diagnosed with HIV were African-American. All told, African-American and Hispanic women constitute 26 percent of the female population in the United States, but they account for a disproportionate 82 percent of AIDS cases among women. NINR has supported a number of studies examining HIV/AIDS experiences and interventions to improve the quality of life of HIV positive individuals, especially women.

Physical, Psychological, and Social Factors Associated with Quality of Life Among Rural Women Living with HIV. A variety of factors are associated with quality of life for women living with HIV. This disease can be especially difficult for rural women who also face a lack of access to care or positive social support. In a study of this population, scientists found that symptom frequency, problem-focused coping skills, perceived control over situations, stigma, and race were all significant predictors of quality of life, the frequency of symptoms, and the degree to which symptoms were bothersome.

[29] Aroian, K. Mother-child adjustment in Arab immigrants and refugees (Grant No. R01NR008504)

[30] Kneipp, S. M. CBPR to reduce health disparities thru TANF (Grant No. R01NR009406)

[31] Zenk, S. Activity space environments, behaviors, and body weight status in urban adults (Grant No. K01NR010540)

Identifying such factors is vital to designing better, more effective interventions to improve quality of life.[32]

Group Motivational Interviewing Promotes Adherence to Antiretrovirals and Risk Reduction Behaviors. Promoting adherence and reducing risky behaviors in HIV-positive women has proven difficult with traditional group health-promotion programs. NINR-supported researchers have developed and tested a motivational interview program tailored for groups of HIV-positive African-American women, and have found that this program improves adherence to antiretroviral medication schedules and reduces risky sexual behaviors. More frequent attendance at the program also increases its benefits over time.[33]

In FYs 2011 and 2012, NINR-supported research on HIV-positive women and their health included:

- F31NR012108—Urban American Indian Adolescent Female Sexual-Risk Behavior;
- R21NR012415—Feasibility of a Stigma-Reduction Intervention for HIV-Infected Women; and
- F31NR013864—Social Patterns and Pathways of HIV Care Among HIV-Positive Transgender Women.

Training in Health Disparities and Women's Health

NINR supports a number of institutional training grants (T32) that focus on health disparities research. A major research and training focus of these grants is women's health and special populations of women, including minorities, rural women, and women of lower socioeconomic status. Grants include:

- Interdisciplinary Training in Health Disparities (Allen; T32NR007968);
- Reducing Health Disparities Through Informatics (Bakken; T32NR007969);
- Reducing Disparities in Underserved Populations (Dancy; T32NR007964);
- Vulnerable Populations/Health Disparities Research (Nyamathi; T32NR007077);
- Transdisciplinary Training in Health Disparities Science (Reifsnyder; T32NR12718); and
- Health Promotion/Risk Reduction Interventions with Vulnerable Populations (Villaruel; T32NR007073).

Career Development, Women, and Women's Health

NINR has historically placed a special emphasis on training the next generation of nurse scientists, designating 8 percent of its appropriated funding annually to extramural grants that support training and career development. While nurses of both genders pursue advanced degrees, the nursing workforce is 95 percent female and much of this funding supports the research and education of women. NINR uses a variety of mechanisms to support these training and research experiences, including the Ruth L. Kirschstein National Research Service Award program (F31, F32, and T32) and mentored career-development grants. These research training awards support individual and institutional predoctoral and postdoctoral trainees at institutions across the United States. An expanded scientific workforce will significantly contribute to evidence-based improvements and reforms to the health care system in the coming years. Two of the NINR institutional training programs focus directly on women's health, especially women from vulnerable populations (Research on Vulnerable Women, Children, and Families [Sommers; T32007100]; Health Promotion/Risk Reduction Interventions with Vulnerable Populations [Villaruel; T32NR007073]). Collectively, NINR training activities address the national shortage of nurses by contributing to the development of the nursing faculty needed to teach and mentor individuals entering the field.

In addition to these training opportunities, NINR-supported grantees are studying women in the scientific workforce. While parity has been largely achieved between

[32] Moneyham, L. Telephone peer counseling for rural women with HIV (Grant No. R01NR004956)

[33] Holstad, M. Motivating HIV+ women: Risk reduction and ART adherence (Grant No. R01NR008094)

men and women in early stages of training, there are still large differences in the number of women working as professors in the sciences. An NINR grant funded in FYs 2011 and 2012 is examining this phenomenon, focusing not on the barriers that may impede women and minorities from joining the professorate, but on identifying the decision-making processes that lead women and minorities away from science careers. The study is also examining the outcomes of interventions to encourage underrepresented groups to go into science careers.[34] Similarly, another grant is examining the careers of women in science, by following the careers of two prospective cohorts of students in the National Longitudinal Surveys of Youth of 1979 and 1997. The study will identify obstacles these women faced, as well as the career impacts of life choices such as marriage and childbirth, from women's entry to their retention in the scientific workforce.[35] Both studies will illuminate the barriers and obstacles to the full utilization of the scientific workforce, especially of women trained as scientists and engineers.

NIH Strategic Plan for Women's Health Research and NINR

NINR's research and training programs support the implementation of the NIH Strategic Plan for Women's Health Research. In particular, NINR's training program and portfolio on the science of symptom management meet the plan's goals and objectives.

Goal 6. Employ innovative strategies to build a well-trained, diverse women's health workforce.

As stated earlier, NINR is strongly invested in training the next generation of nurse scientists through individual and institutional training grants and mentored career development grants that facilitate career development. These training programs provide the next generation of scientists with the necessary interdisciplinary education and research skills that will enable them to improve clinical practice, enhance quality of life for those with chronic illness, and support preventative health. While not all of these trainees were pursuing women's health research, the grants largely went to women scientists; a recent evaluation of the NINR training program from 1992 to 2012 found that 93 percent of NINR-supported trainees were female.

In addition to supporting predoctoral and postdoctoral research fellowships and career development awards in the extramural community, NINR also leads and participates in a number of training programs through its Intramural Research Program (IRP). For example, NINR sponsors the annual Summer Genetics Institute, a 1-month program designed to increase the genetic research capabilities of graduate students and faculty in nursing and to develop and expand the basis for clinical practice in genetics among clinicians. NINR also participates in the NIH Graduate Partnerships Program, in which doctoral students from schools of nursing with established NINR-supported training programs can complete their dissertation research within IRP. NINR also sponsors the Symptoms Methodologies Boot Camp, a 1-week, intensive research-training course at NIH in symptoms research methodologies. This course includes distinguished guest speakers, classroom discussions, and laboratory training, aimed at increasing the research capabilities of graduate students and faculty.

The objectives met by this activity are:

- Objective 6.1: Connect and empower scientists across career stages by developing a central career advice/development resource that includes contact with knowledge-rich people at the NIH.
- Objective 6.2: Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs; encourage the evaluation of mentoring practices.
- Objective 6.3: Address the organizational, institutional, and systemic factors that impede the recruitment, retention, and advancement of women in science, and modify practices that impede the careers of biomedical scientists.

[34] McGee, R. Pivotal careers decisions guiding potential women science faculty (Grant No. R01NR011987)

[35] Marcus, B. H. Entry and retention of women in the sciences: A cohort comparison (Grant No. R01NR011295)

Goal 3. Actualize personalized prevention, diagnostics, and therapeutics for girls and women.

Developing new and better ways to manage adverse symptoms is vital to improving quality of life for those with chronic illnesses. Millions of Americans suffer from adverse symptoms such as fatigue, pain, and insomnia that can inhibit their ability to lead normal lives. Often, these symptoms are associated with a chronic condition, such as the insomnia experienced by those living with chronic heart failure, or they may be treatment-related, as in the case of cancer patients who experience pain associated with chemotherapy. Throughout its history, NINR has supported research on new and better ways to manage the symptoms of illness. Symptom-management research supported by NINR focuses on understanding the biological and behavioral aspects of symptoms such as pain and fatigue, with the goal of developing new knowledge and strategies for improving patient health and quality of life. The Institute supports research at universities, hospitals, and other institutions across the nation on a broad range of topics related to symptom management. In addition, NINR maintains a robust intramural research program on the NIH campus in Bethesda, MD, dedicated to improving the understanding of symptoms' underlying biological mechanisms, their effects on patients, and the biological and behavioral bases for patient response to interventions.

Although the science of symptom management addresses symptoms of both men and women, much of the research that NINR supports both in its intramural and extramural programs focuses on illnesses and symptoms that mostly affect women. For example, current research in the NINR IRP focuses on the pain and fatigue associated with fibromyalgia, as well as pain in gastrointestinal conditions such as irritable bowel syndrome; fibromyalgia and irritable bowel syndrome overwhelmingly affect women.

In NINR's extramural research portfolio, the science of symptom management in women's health includes research on irritable bowel syndrome and cancer, among other conditions. Grants supporting research on symptoms, symptom clusters, and symptom management in women's health in FYs 2011 and 2012 included the following:

- P30NR011403—Center of Excellence in Biobehavioral Approaches to Symptom Management;
- R01NR010735—Web-Based Ovarian Cancer Symptom Management: Nurse-Guided vs. Self-Directed;
- R21NR012288—Menopause Symptom Clusters: Refocusing Therapeutics;
- R01NR010730—Protocol- vs. Patient-Oriented TCM Practices: A RCT for IBS Symptom Management;
- R01NR012479—Mechanisms of Cancer-Related Symptoms;
- R01NR012667—Epigenetics and Psychoneurologic Symptoms in Breast Cancer;
- R01NR012012—The Influence of Gender on Symptom Characteristics During Acute Coronary Syndrome; and
- R01NR013695—Symptom Management for Irritable Bowel Syndrome Constipation (IBS-C).

The objective met by this research area is:

- Objective 3.8: Conduct research on aging women with emphasis on prevention of frailty, promotion of healthy lifestyles, maintenance of independent women, self-management of symptoms, preservation of cognitive functions, and health-related quality of life.

National Library of Medicine

Executive Summary

The mission of the National Library of Medicine (NLM) is to acquire, organize, disseminate, and preserve the biomedical knowledge of the world for the benefit of the public health. Through advanced information systems, a cutting-edge informatics research portfolio, and extensive partnerships

in information dissemination, NLM plays a pivotal role in enabling biomedical research, supporting health care and public health, and promoting healthy behavior. Its National Center for Biotechnology Information serves as a national resource for molecular biology information, developing new information technologies to aid in the understanding of fundamental molecular and genetic processes that control health and disease. As the largest biomedical library in the world, NLM provides access to online information services that are used by millions of scientists, health professionals, and the public more than 1 billion times each year.

NLM research programs related to women's health include medical informatics and bioinformatics approaches to diagnosis, treatment, prediction, and prevention of women's health conditions. Its information resource programs focus on enhancing access to and promoting the use of online health information systems that offer authoritative information related to women's health.

In FY 2011–2012, NLM supported informatics and molecular biology research projects addressing Goal 2 of the NIH Strategic Plan for Women's Health Research related to the design and application of new technologies. Informatics research projects employed machine learning, clinical decision support, data-mining, and advanced imaging tools to address diagnostic issues in breast and cervical cancers. For example, the goal of one extramural project was to develop clinical decision support tools that improve accuracy in estimating breast cancer risk from breast biopsy results. In another project, intramural researchers developed advanced imaging tools for cervical cancer research that allow experts to mark boundaries on digitized images.

Molecular biology research projects addressed gene regulation, causal pathway analysis, and genome-wide association studies (GWAS). For example, one extramural project sought new causal pathway discovery methods to improve understanding of molecular mechanisms that cause and control the development and progression of breast cancer. Another conducted GWAS studies on breast and lung cancer to gain new knowledge about their genetic bases. A third project developed data-mining methods for analyzing molecular biomarker profile data, thereby generating new experimental data for early detection of breast cancer.

The NLM's information resource projects address Objective 5 of the NIH Strategic Plan for Women's Health Research related to communication and social networking technologies. The Women's Health Resources Web Portal, developed in partnership with ORWH, provides consumers with the latest information on significant topics in women's health research from scientific journals and other peer-reviewed sources. In FY 2011–2012, associated outreach projects to promote awareness and enhance use of this portal employed social media approaches and partnerships with community groups and historically Black colleges and universities. Additional information portals that contain information directly related to women's health issues include the following: MedlinePlus, with more than 100 health topic pages specifically focused on women's health; PHPartners, which supports the Healthy People 2020 goals for maternal, infant, and child health; the Health Services Research Information Center Portal; and the HSRProj database for health services research projects that are in progress but have not yet published any articles.

NLM does not have a particular unit that is designated to focus on women's health and sex differences research. However, the deputy director of the Specialized Information Services Division at NLM, which is the division that implements the Women's Health Resources Web Portal, serves as the NLM representative on the NIH Coordinating Committee on Research on Women's Health.

Accomplishments

Highlighted below are significant NLM research accomplishments in FY 2011–2012 related to women's health.

Breast Cancer

Integrating Machine Learning and Physician Expertise for Breast Cancer Diagnosis (Goal 2, Objective 2.5). This project aims to develop clinical-decision support tools that will integrate computerized data analysis techniques with physician expertise, resulting in a system that will estimate breast cancer risk from results of breast biopsies more accurately than either the physician or the computer alone. The researchers propose testing a completely new methodology called Advice-Based-Learning (ABL*e*). By developing ABL*e*, they aim to establish an innovative, collaborative cycle between computer learning and physician expertise. They propose to test the hypothesis that this cycle will increase accuracy beyond what either the computer or human can accomplish separately. It is anticipated that the project will result in a computerized decision tool that will estimate the probability of malignancy after breast biopsy more precisely than current clinical practice. This will help address the challenges of delays in diagnosis and reduce unnecessary surgeries, and it should improve overall care for thousands of women with breast cancer or who are at risk for this cancer.

Bayesian Rule Learning Methods for Disease Prediction and Biomarker Discovery (Goal 2, Objective 2.5). This project will develop data-mining methods for analyzing the large number of datasets arising from high-throughput technologies for molecular biomarker profiling. It will generate new experimental data for early detection of breast cancer, and it has the potential to help create new diagnostic screening tools for three diseases: two of the most common cancers in the world—lung and breast cancers—and a rare neurodegenerative disease, amyotrophic lateral sclerosis.

Gene Regulation in Metastasis and New Methods to Analyze Microarray Profiles (Goal 2, Objective 2.4). The goal of this project is to carry out an integrative study of tumor metastasis progression by analysis of gene expression, transcription regulation, and DNA copy number variation. Chromatin immunoprecipitation (ChIP) experiments with antibodies for key regulators of the epithelial-mesenchymal transition (EMT) will be performed to identify their target genes during tumor metastasis. New algorithms will be developed for analyzing perturbed gene expression profiles to build a regulatory subnetwork specific to the EMT process and identify other EMT regulators for further ChIP-chip experiments. Specifically, the research aims to:

(1) Identify the DNA-binding sites of two key regulators of tumor metastasis (twist and snail) in both normal murine embryonic cells and four murine isogenic mammary carcinoma cell lines (67NR, 168FARN, 4TO7, and 4Tl);

(2) Develop new algorithms to analyze perturbed expression profiles for reverse engineering the regulatory subnetworks involving metastasis-related genes; and

(3) Develop new algorithms to analyze array-based comparative genomic hybridization data for discovering DNA duplication and deletion events during tumor metastasis progression.

This research has the potential to shed new light on the process by which cancer cells spread throughout the body, and it may contribute to the development of new cancer therapies.

Detecting Genome-Wide Epistasis with Efficient Bayesian Network Learning (Goal 2, Objective 2.4). Identifying gene-gene interactions from GWAS data is an important and challenging task in genetic epidemiology. This project will develop and evaluate a pilot GWAS system for performing this task. Advances obtained in analyzing GWAS datasets could enable researchers to learn the genetic basis of many diseases and thereby substantially improve the quality of personalized patient care. Specifically, the principal investigator proposes to conduct GWAS on breast cancer and lung cancer, with the potential for providing important new knowledge about the genetic basis of these diseases of high relevance to women's health.

Methods for Accurate and Efficient Discovery of Local Pathways (Goal 2, Objective 2.4). This project aims to provide new causal pathway discovery methods

that will help bring the biomedical research community substantially closer to its goals of understanding molecular mechanisms that cause and control the development and progression of diseases. This research will have significant and wide methodological and practical implications spanning many areas of biomedicine and will generate immediate benefits for personalized medicine and the development of new drugs and therapies to effectively fight human diseases. The project will focus on breast cancer as one of the two instantiations of the methodology being developed.

Reproductive and Child Health

A Social History of Cesarean Section in the United States (Goal 3, Objective 3.3). This social history of cesarean section in the United States over the last 200 years will examine the historical, cultural, social, and medical factors that have contributed to the current U.S. cesarean section rate of 32 percent. The World Health Organization (WHO) has long estimated that the optimal cesarean section rate is between 5 percent and 10 percent of births and that a rate above 15 percent is apt to do more harm than good; recent studies seem to corroborate the WHO's assertion that the effects of a high cesarean section rate on a largely low-risk population are costly in both monetary and health terms. A thorough exploration of the historical emergence of cesarean section as a routine surgical intervention can help clarify the reasons for the lack of an evidence-based foundation for its frequency and, in doing so, aid in lowering the current cesarean section rate and thereby reduce its negative effects on women's and children's health.

Cervical Cancer Imaging Tools (Goal 2, Objective 2.5). NLM is conducting several research- and-development activities that support women's health. One is to develop advanced imaging tools for cervical cancer research, including the Boundary Marking Tool (BMT), the Virtual Microscope (VM), and the Teaching Tool (TT). The BMT is a system that allows experts to mark boundaries on digitized images and record diagnostic or interpretive data that applies to these individual boundaries, or to the image as a whole. It has been used in multiple studies by the National Cancer Institute on the correlation between visual observations of the cervix and biopsy-based diagnoses. The VM provides Web access to digitized histology images for expert review and evaluation. Because these images tend to be very large, the VM incorporates technology to access and display only the part of the image that corresponds to the user's current pan and zoom level. The VM is used in studies of histology images of the uterine cervix. The TT is designed for teaching and training physicians in colposcopy and in diagnosing cervical cancer from images of the uterine cervix. The TT allows the display of images alongside text that prompts the user for input related to the images. The typical use for the TT is to administer an exam or for self-training in this image-based medical discipline. The TT is used by the American Society for Colposcopy and Cervical Pathology at more than 100 institutions nationwide (e.g., Mayo Clinic) for administering their professional exams.

Standardization of Newborn Screening (Goal 2, Objective 2.3). Of relevance to the health of women and families is newborn screening (NBS), a complex public health program whose goals are to identify seemingly healthy infants who have serious conditions, to begin treatment before they suffer significant disability or death, and in doing so to decrease the burden of disease on society. Until recently, most U.S. NBS programs and laboratories were not using coding standards or electronic methods to report NBS results to hospitals or other providers, and there was a gap in some of the coding standards when it came to NBS terms. Researchers are working with multiple agencies to create new codes for NBS as well as national guidance for standardization and electronic reporting of newborn screening results using HL7 messages that contain a prescribed set of LOINC and SNOMED CT codes, report quantitative test results, and use standardized units of measure. The standard terms and codes would allow NBS programs to efficiently collect interoperable long-term follow-up data, and regional and national registries to improve screening and treatment protocols, all with the ultimate goal of improving patient outcomes.

Neonatal Necrotizing Enterocolitis Study (Goal 2, Objective 2.4). Another effort of NLM is in data-mining the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) database, which contains clinical data for over 30,000 ICU (intensive care unit) encounters for more than 26,000 patients. This database includes patient demographics, laboratory test results, vital sign recordings, and free-text reports. The research effort of NLM is in applying natural language processing techniques to extract information for cohort studies, some of which have relevance to the health of women and families, such as a neonatal necrotizing enterocolitis (NEC) study. Previous studies have reported that blood transfusions may increase the risk of NEC. Other studies have reported a correlation of NEC with feeding practices, both in terms of timing and the type of feeding. However, the role of both factors in the pathogenesis of NEC remains controversial. Researchers are analyzing the role of transfusions and feeding practices in NEC and plan to come up with recommendations for both (indications for transfusions and feeding) in premature infants at risk for NEC.

Women's Health Information Resources

PHPartners Portal (Goal 5, Objective 5.1). The public health portal site PHPartners (*http://phpartners.org*) supports the Healthy People 2020 goals for maternal, infant, and child health, providing tools to facilitate goal-specific searching for research cited in the PubMed database. The site also regularly collects and makes available information directly related to women's health issues. Examples of materials highlighted on the site are the following:

- "New Women's Health Care Report: 20 Percent of U.S. Women Were Uninsured in 2010, Up from 15 Percent in 2000; U.S. Women Much More Likely to Struggle with Medical Bills and Go Without Needed Care than Women in Countries with Universal Coverage" (*http://www.commonwealthfund.org/News/News-Releases/2012/Jul/Oceans-Apart.aspx*)
- "Health Care Law Gives Women Control Over Their Care, Offers Free Preventive Services to 47 Million Women" (*http://www.hhs.gov/news/press/2012pres/07/20120731a.html*)

Health Services Research Information Center Portal (Goal 5, Objective 5.1). Health Services Research Information Center (HSRIC) (*http://www.nlm.nih.gov/hsrinfo/*), the portal for resources of interest to the health services research community, including datasets and reports, highlights many resources in such topic areas as health disparities and child health services research, both of which affect women's health. During 2012, some of the highlighted research that related specifically to women's health on this portal included:

- Veterans Health Administration Research & Development, Research Topics, Women's Health (*http://www.research.va.gov/research_topics/womens_health.cfm*)
- "Disparities in Use of Gynecologic Oncologists for Women with Ovarian Cancer in the United States" (*http://www.biomedcentral.com/bmchealthservres*)
- National Healthcare Disparities Report, 2011 (*http://www.ahrq.gov/qual/qrdr11.htm*)

HSRProj Database (Goal 5, Objective 5.1). The database HSRProj (*http://wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm*) contains detailed information on health services research projects in progress but not yet published; the database can be searched by researcher, funder, and topic. Health disparities and women's issues figure frequently in these research projects. Examples of such studies included in the database in 2012 include:

- Breast Cancer Screening and Outcomes: Role of Comorbidity (*http://wwwcf.nlm.nih.gov/hsr_project/view_hsrproj_record.cfm?PROGRAM_CAME=search_fields.cfm&NLMUNIQUE_ID=20122213&SEARCH_FOR=HSRP20122213*)
- Development of an Integrated Microfinance and Depression Care Program for Women (*http://wwwcf.nlm.nih.gov/hsr_project/view_hsrproj_record.cfm?PROGRAM_CAME=divide_string&NLMUNIQUE_ID=20123290&SEARCH_FOR=women%20OR%20woman%20OR%20female*)

- Meeting the Needs of Pregnant Women with Posttraumatic Stress Disorder (PTSD) in Healthy Start (*http://wwwcf.nlm.nih.gov/hsr_project/view_hsrproj_record.cfm?PROGRAM_CAME=divide_string&NLMUNIQUE_ID=20123138&SEARCH_FOR=women%20OR%20woman%20OR%20female*)

Women's Health Resources (WHR) Web Portal (Goal 5, Objectives 1, 2, and 6). NLM and ORWH have continued their innovative partnership that developed and implemented the WHR Web Portal. This portal, at *http://www.womenshealthresources.nlm.nih.gov*, uses the current NIH research priorities for women's health researches to identify overarching themes, specific health topics, and research initiatives in women's health. Within each section of the Web site are topics with links to relevant and authoritative resources and research initiatives for women's health. NLM has created specific user-friendly strategies for these topics to ease the searching of ClinicalTrials.gov and PubMed. Other Web resources used include AIDSinfo, American Indian Health, Arctic Health, Household Products Database, MedlinePlus, and NIH SeniorHealth. Search strategies for major studies related to women's health research also have been created. As with the topical search strategies, ClinicalTrials.gov and PubMed searches for each major report are included. In FY 2011, a user assessment and usability study for the portal was begun. The goal is to improve access and user satisfaction as well as to collect data about the information needs of women's health and sex and gender differences researchers. Five user groups were targeted for this study, including senior and junior researchers, advocates, media professionals, and consumers. The study consisted of holding multiple focus groups with each user group, developing and testing user-specific "research brief" templates, and conducting a usability audit of the WHR portal. The project team was awarded funds from the NIH Evaluation Set-Aside Program to supplement this work. The study will finish in FY 2013.

W**HR Web Portal Social Media Outreach (Goal 5, Objectives 1 and 6).** Through the use of social networking technologies, WHR increases the understanding and appreciation of women's health research. Twitter is used to disseminate new research finds, funding announcements, and health campaign messages. WHR has over 30,000 followers of @WomensHealthNIH, including many faculty, staff, and students at universities and university and college health centers as well as individual health care providers, researchers, and consumers. Facebook reaches college-aged women and university and college health center staff.

WHR Dissemination Outreach Projects (Goal 5, Objectives 2, 3, and 6). In FY 2011 and FY 2012, ORWH and NLM partnered to promote WHR and to support the NIH Strategic Plan for Women's Health Research Goals through information outreach dissemination projects. The pilot projects that were funded focused on information dissemination, information access, or resource development at a university, college, or community agency. Each project recipient was required to promote the NLM–ORWH WHR, create a library guide on sex and gender differences/research information resources at the university/college, and promote to students and faculty "The Science of Sex and Gender in Human Health" online curriculum. NLM used its existing network of historically Black colleges and universities and National Network of Libraries of Medicine partners to recruit eight project participants that developed seven projects targeting university/college students, faculty, and administrators, and five projects targeting community groups and consumers. A positive outcome of the project was situating the university library as the "go-to place" for sex and gender differences and inclusion research among the students and faculty. Based on the successful feedback from the universities, NLM–ORWH expects to continue support for this program in FY 2013.

Relationship to NIH Strategic Plan for Women's Health Research

NLM's informatics and molecular biology research projects address objectives within Goal 2 related to design and application of new technologies. Information system development and information outreach initiatives target objectives within Goal 5 related

to communication and social networking technologies.

The following molecular biology research projects address Objective 2.4:

- Gene Regulation in Metastasis and New Methods To Analyze Its Microarray Profiles, a project to study tumor metastasis in breast cancer by analysis of gene expression, transcription regulation, and DNA copy number variations. (Goal 2, Objective 2.4)
- Detecting Genome-Wide Epistasis with Efficient Bayesian Network Learning (Goal 2, Objective 2.4)
- Methods for Accurate and Efficient Discovery of Local Pathways (Goal 2, Objective 2.4)

The following informatics research projects employing clinical decision support, data-mining methods, and advanced imaging tools address Objective 2.5:

- Integrating Machine Learning and Physician Expertise for Breast Cancer Diagnosis (Goal 2, Objective 2.5)
- Bayesian Rule Learning Methods for Disease Prediction and Biomarker Discovery (Goal 2, Objective 2.5)
- Cervical Cancer Imaging Tools (Goal 2, Objective 2.5)

The following information systems development and information dissemination projects address Objective 5 related to communication and social networking technologies:

- Women's Health Resources Web Portal (Goal 5; Objectives 1, 2 and 6)
- Women's Health Resources Web Portal Social Media Outreach (Goal 5; Objectives 1 and 6)
- Women's Health Resources Dissemination Outreach Projects (Goal 5; Objectives 2, 3 and 6)

Fogarty International Center

Executive Summary

The Fogarty International Center (FIC) supports a range of programs designed to increase sustainable capacity in global health research. FIC programs cover communicable diseases such as HIV/AIDS and tuberculosis (TB); chronic, noncommunicable diseases such as cancer and brain disorders; and cross-cutting areas such as informatics and capacity in research ethics. These programs are often cosponsored by other NIH Institutes and Centers, including the Office of Research on Women's Health (ORWH). Although FIC programs are not designed specifically to address women's health, they do support research and research training related to this area. These programs include:

Global Research Initiative Program, Basic/Biomedical Sciences, and Social Science. The Global Research Initiative Program (GRIP) promotes the reentry of NIH-trained, low- and middle-income country (LMIC) investigators into their home countries as part of a broader program to enhance the scientific research infrastructure in LMICs and to stimulate research on local high-priority health issues. Examples of GRIP-supported research topics relevant to women's health include the effects of genetic predisposition and modifiable factors on the risks of hypertension and diabetes and counseling about breastfeeding for HIV-positive women.

International Tobacco and Health Research and Capacity Building Program (TOBAC). The TOBAC program supports transdisciplinary research and capacity-building projects that address the burden of tobacco consumption in LMICs by:

(1) Pursuing locally relevant observational, intervention, and policy research; and

(2) Building capacity in epidemiologic and behavioral research, prevention, treatment, communications, health services, and policy research.

TOBAC is supporting the development of a network for tobacco control among women in Parana, Brazil, that will establish community and institutional capacity to promote gender-relevant tobacco control efforts through community-based participatory research and training.

AIDS International Training and Research Program (AITRP). AITRP supports HIV/AIDS-related research to strengthen the capacity of institutions in LMICs to conduct multidisciplinary biomedical and behavioral research to address the AIDS epidemic in the collaborating country. AITRP-supported investigators are conducting epidemiologic studies on the attitudes of women toward highly active antiretroviral therapy, AIDS-related mortality and long-term survival rates, and a range of factors that may have a differential impact on HIV-infected women.

Global Infectious Disease Research Training Program (GID). GID addresses research training needs related to infectious diseases that are predominantly endemic in or affect people living in LMICs. The ultimate goal is to build a critical mass of researchers and support staff to conduct independent infectious disease research in LMIC institutions. GID-supported researchers are investigating the impact of P. vivax infection in pregnant women and establishing a center of excellence in Tanzania to focus on malaria in pregnant women and children, with an emphasis on research and intervention.

International Research Scientist Development Award (IRSDA). The IRSDA program supports U.S. postdoctoral biomedical, epidemiologic, clinical, social, and behavioral scientists in the formative stages of their careers to pursue careers in research on global health and prepare for independent research. These awards support 3–5 years of "protected time" for mentored research and career development experiences, leading to an independent research career focused on global health. A current award supported by the IRSDA program examines the use of midwives in Ghanaian maternity clinics.

FIC Research on Women's Health Report

(a) Given the size and budget of FIC, there is no position or office designated to focus on research on women's health and sex differences research.

(b) The following FIC-supported accomplishments contributed to women's health research in fiscal years (FYs) 2011 and 2012:

Biomass Fuel Cooking Increases Risk for Pulmonary TB in Women in Northern India. Smoke exposure from traditional cookstoves and open fires causes an estimated 4 million premature deaths every year, mainly among women and children who are either cooking or are most directly exposed to the smoke. Cooking smoke has been identified as a risk factor for several respiratory illnesses, but not TB. In order to investigate whether cooking smoke from biomass fuel is a risk factor for TB, a Fogarty-funded group of researchers conducted a case-control study among women in rural and urban slum areas in a territory of Northern India. The study results—when controlled for many confounding variables—indicated that cooking with biomass fuel increased risk for pulmonary TB in women in Northern India. These results are critically important not only for improving estimates of negative health effects of indoor cooking smoke for women (by including TB) but also for informing TB control.

Lakshmi, P. V., Virdi, N. K., Thakur, J. S., Smith, K. R., Bates, M. N., & Kumar, R. (2012). Biomass fuel and risk of tuberculosis: A case-control study from Northern India. *Journal of Epidemiology & Community Health*, *66*(5), 457–461.

Male Circumcision Reduces HR–HPV Transmission to HIV-Negative Female Partners. Human papillomavirus (HPV) is a significant health problem for women in LMICs. In East Africa, cervical cancer is the most frequent cause of cancer mortality among women (Ferlay et al., 2010). While male circumcision (MC) reduces high-risk HPV (HR–HPV) infection in men, the effect of MC on HR–HPV transmission and clearance

for female partners had not been studied. FIC provides laboratory and training support to researchers who demonstrated through a randomized case-control study of HIV-negative men that MC reduced prevalence and incidence of HR–HPV infection in HIV-negative female partners and also increased HR–HPV clearance. These results indicate that MC could have a significant role to play in HPV prevention efforts in low-resource settings and that as MC also appears to reduce the risk of multiple sexually transmitted infections for both men and women, this should be a consideration when setting public health policies.

Wawer, M. J., Tobian, A. A., Kigozi, G., Kong, X., Gravitt, P. E., Serwadda, D., … Gray, R. H. (2011). Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: A randomised trial in Rakai, Uganda. *The Lancet, 377*(9761), 209–218.

Prior Hormonal Contraception Use Does Not Affect HIV Viral Load Setpoint. In regions of the world with high-birth and high-maternal mortality rates, hormonal contraception (HC) is part of an effective and comprehensive family planning program. However, the effect of prior HC use on the HIV viral load (VL) setpoint in new seroconverters has not been adequately studied. In Rakai, Uganda, researchers cofunded by FIC studied blood samples of individuals participating in a community cohort study to determine if prior HC use affected the VL setpoint. The results indicated that prior HC use did not affect the VL setpoint. As the VL setpoint is a marker for HIV progression, these results indicate that HC use does not need to be considered a risk for rapid HIV progression if HIV seroconversion occurs.

Polis, C. B., Gray, R. H., Bwanika, J. B., Kigozi, G., Kiwanuka, N., Nalugoda, F., … Wawer, M.J. (2011). Effect of hormonal contraceptive use before HIV seroconversion on viral load setpoint among women in Rakai, Uganda. *Journal of Acquired Immune Deficiency Syndromes, 56*(2), 125–130.

Failure to Identify Predictors of CD4 Eligibility for ARV Initiation Among HIV-Positive Pregnant Women. Combination antiretroviral therapy (ART) for pregnant women is known to reduce vertical (mother to child) transmission of HIV. In resource-poor settings, this treatment is not always available. Recently, WHO policy prioritized women with CD4 counts ≤350 cells/uL for ART, based on the higher likelihood of vertical transmission in a treatment-limited setting. Given the limited availability of CD4 testing in many resource-poor settings, FIC supported training for a member of a research team that investigated the possibility of developing an algorithm that would predict CD4 levels among HIV-infected pregnant women in Lusaka, Zambia, using a retrospective study. As the results demonstrated poor predictability of the demographic and historical variables used, continuing to increase access to CD4 counts in low-resource settings remains critical.

Liu, K. C., Mulindwa, J., Giganti, M. J., Putta, N. B., Chintu, N., Chi, B. H., … Stringer, E. M. (2011). Predictors of CD4 eligibility for antiretroviral therapy initiation among HIV-infected pregnant women in Lusaka, Zambia. *Journal of Acquired Immune Deficiency Syndromes, 57*(5), e101–e105.

Understanding Perceptions of Antenatal Ultrasound in a Refugee Population. In developed countries, antenatal ultrasound is a standard and positively viewed part of antenatal care. As ultrasound is relatively inexpensive, versatile, and low risk, it has the ability to be more widely introduced in LMIC settings. FIC supported training for a member of a team that looked at the experience of routine antenatal ultrasound in a displaced Burmese population in Thailand. Quantitative and qualitative measures were obtained to provide a comprehensive understanding of four major themes: safety, emotions, information and communication, and unintended consequences of antenatal ultrasound. Women understood and appreciated the role of ultrasound in increasing childbirth safety, despite initial anxiety among some of them before the ultrasound; however, this could be overcome by improved patient information and staff communication. The study authors recommend that facilities introducing new technology in resource-poor settings assess acceptability of the technology through similar inquiries.

Rijken, M. J., Gilder, M. E., Thwin, M. M., Ladda Kajeechewa, H. M., Wiladphaingern, J., Lwin, K. M., … McGready, R. (2012). Refugee and migrant women's views of antenatal ultrasound on the Thai Burmese border: A mixed methods study. *PLOS ONE, 7*(4), e34018.

(c) While there were no significant plans to undertake sex/gender analysis or studies during FY 2011 and FY 2012, FIC has incorporated language in its research training announcements that encourages research training activities related to sex and gender differences:

> "Where appropriate, the design of training-related research projects should take into account potential sex and gender differences that may affect the questions asked and the analyses performed. These might include different responses to and impacts of health interventions, differences in physiology, and different behavioral bases for disease prevention strategies."

(d) In partnership with the Office of the Global AIDS Coordinator at the U.S. State Department, FIC, NIAID, NIMH, OBSSR, and ORWH, NICHD announced a new funding opportunity in 2012 called "NIH/PEPFAR Collaboration for Advancing Implementation Science in Prevention of Maternal-Child HIV Transmission (PMTCT)" (RFA-HD-12-210). The purpose of this announcement is to develop more efficient and cost-effective methods to deliver proven interventions for PMTCT. The Request for Application (RFA) incorporated an activity conducted by FIC's Center for Global Health Studies (CGHS): a forum will be established for a network of grantees, key collaborators, and PMTCT implementers to meet and enable cross-fertilization of ideas, insights, and experiences as the research progresses. To this end, CGHS will convene one meeting on the NIH campus each year and two regional meetings each year.

(e) In 2011, Fogarty and its NIH partners solicited applications (NOT-TW-11-018, "Administrative Supplements Funding for Planning Research in Support of the Global Health Initiative and Other Critical Health Interventions Focused on Women and Girls Health and/or Gender Equity") for 1-year administrative supplements to active NIH international research or research training grants. The supplements were intended to support implementation research focused on accelerating progress toward improved health for women and girls and/or the role of women and girls in the improvement of health. One FIC grantee at the University of California, San Francisco (UCSF) used the supplement to provide postdoctoral fellows and junior faculty from the health (e.g. medicine, nursing, public health) and empowerment (e.g. law, business, women's studies, anthropology, and sociology) sciences with an intensive 1-year, interdisciplinary, hands-on, mentored research experience at the intersection of women's health and empowerment. This curriculum will become the flagship postdoctoral fellowship program for the Women's Health and Empowerment Centers of Excellence at UCSF.

(f) FIC has nothing to report regarding health disparities among special populations of women during FY 2011 and FY 2012.

(g) No career development initiatives were undertaken during FY 2011and FY 2012 that specifically addressed career development for women in women's health research or other scientific fields.

(h) FIC programs support the NIH Strategic Plan for Women's Health Research Goal 6: "Employ innovative strategies to build a well-trained diverse and vigorous women's health research workforce." Specifically, FIC's support of NOT-TW-11-018, "Administrative Supplements Funding for Planning Research in Support of the Global Health Initiative and Other Critical Health Interventions Focused on Women and Girls Health and/or Gender Equity,"

maps to Strategic Plan Objective 6.2. (See Section E above for a more complete description of the Initiative.)

(i) FIC programs also contribute to the NIH Strategic Plan for Women's Health Research Goal 4: "Create strategic alliances and partnerships to maximize the domestic and global impact of women's health research." Specifically, FIC's support of the NIH/PEPFAR Collaboration maps to Strategic Plan Objective 4.2. (See Section D above for a more complete description of the Collaboration.)

References

Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D.M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer, 127*(12), 2893–2917.

National Center for Complementary and Alternative Medicine

Executive Summary

This executive summary is written in the context of the National Center for Complementary and Alternative Medicine (NCCAM) mission. NCCAM's mission is to define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative approaches and their roles in improving health and health care. NCCAM's goals (*http://nccam.nih.gov/about/plans/2011*) are to:

(1) Advance the science and practice of symptom management;

(2) Develop effective, practical, personalized strategies for promoting health and well-being; and

(3) Enable better evidence-based decision making regarding complementary health approaches and their integration into health care and health promotion.

NCCAM aims to achieve these goals by maintaining its focus on basic research while increasing its emphasis on translational, efficacy, and outcomes research.

Complementary and integrative medicine includes a range of therapeutic approaches and is defined by NCCAM within the National Institutes of Health (NIH) as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine." Complementary medicine is the use of complementary approaches in conjunction with conventional medicine, alternative medicine would be in lieu of conventional medicine, and integrative medicine combines conventional medicine with complementary modalities for which there is evidence of effectiveness and safety (*http://nccam.nih.gov/health/whatiscam*).

Complementary and integrative approaches can be divided into four broad categories that have substantial overlap:

(1) Natural product therapies encompass a variety of herbal medicines (botanicals), probiotics, vitamins, minerals, other natural products, and diet-based therapies;

(2) Mind-body therapies include practices that focus on interactions among the mind/brain, body, and behavior (meditation, biofeedback, deep-breathing exercises, guided imagery, progressive relaxation, hypnotherapy, yoga, qigong, tai chi, energy healing);

(3) Manipulative and body-based therapies focus on bodily structures (bones, joints, soft tissue) and systems (circulatory and lymphatic) and include spinal manipulation (chiropractic care), massage therapy, and movement therapies; and

(4) Alternative medical systems include ancient (Ayurveda, traditional healing, acupuncture) and more modern therapies (homeopathy, naturopathy).

The most current and comprehensive picture of Americans' use of complementary and integrative approaches has been developed under NCCAM leadership through the National Health Interview Survey (NHIS), conducted in 2007 by the National Center

for Health Statistics at the U.S. Centers for Disease Control and Prevention (Barnes, Bloom, & Nahin, 2008). NHIS data reveal that complementary therapies are used for a variety of diseases and conditions, most frequently for back pain, neck pain, anxiety, arthritis, and headaches. The complementary therapies used most often are natural products, deep breathing, meditation, and chiropractic and osteopathic manipulations. The use of complementary and integrative medicine in the general population peaks after age 50, and the prevalence of use is higher in adult women (70 percent) than adult men (59 percent). Non-Hispanic White women tend toward greater use than other racial/ethnic groups, and use rises as education increases. A recent report found that women are frequent users of vitamins and minerals, and they use movement therapies (yoga, tai chi, and qi gong) most specifically for wellness or health promotion (Edwards, Alekel, & Stussman, 2013). Chiropractic or osteopathic manipulation and acupuncture are the modalities used most specifically for treatment. Pain is the most common reason for use of complementary medicine, leading NCCAM to emphasize research on pain management.

NCCAM also funds five dietary botanical supplement research centers (*http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-09-001.html*), two of which are focused on women's health. The University of Illinois at Chicago/NIH Center for Botanical Dietary Supplements Research focuses on the safety of botanical dietary supplements and their impact on estrogenic hormones. The Botanical Research Center at the University of Illinois at Urbana-Champaign addresses the safety, efficacy, and mechanism of action of botanical estrogens consumed by women.

Accomplishments

Research

Presented below are highlights of FY 2011–FY 2012 NCCAM research relevant to women's health and/or sex differences. The author in **boldface** was the principal investigator of the project being described.

Breast Cancer

This preclinical study examined the effect of dietary genistein, an isoflavone from soybeans, on breast cancer patients who take tamoxifen, an antiestrogen treatment. The interaction of various doses of genistein with tamoxifen on the growth of estrogen receptor-positive breast cancer cells was investigated by subcutaneously injecting these cells into the flank of mice (they had their ovaries removed) without thymus (immune) function. Animals (10–13 per group) were randomized into 8 experimental groups, with estrogen (0.08 mg) and tamoxifen (3 mg) implanted and dietary genistein provided as low (250 ppm [parts per million]), medium (500 ppm) or high (1,000 ppm) doses: 1) control, 2) estrogen, 3) tamoxifen, 4) estrogen + tamoxifen, 5) tamoxifen + medium-dose genistein, 6) estrogen + tamoxifen + low-dose genistein, 7) estrogen + tamoxifen + medium-dose genistein, or 8) estrogen + tamoxifen + high-dose genistein. Tamoxifen significantly reduced estrogen-induced tumor prevalence and tumor size in breast cancer cells. This inhibitory effect of tamoxifen was significantly negated by both the low and medium doses of dietary genistein, whereas the high dose did not exert the same effect. Cells harvested from tamoxifen-treated tumors retained the estrogen responsiveness of their progenitor breast cancer cells. This indicates that the nullifying effect of genistein on tamoxifen-treated tumor growth was direct and was not caused by a diminished tamoxifen response. The low doses of genistein nullified the inhibitory effect of tamoxifen, potentially by acting on the tumor cell proliferation/apoptosis (programmed cell death) and mRNA expression of cyclin D1 (protein involved in cell cycle progression), as well as regulating mRNA expression of the progesterone receptor. Thus, data from this preclinical model suggest that caution is warranted regarding genistein intake by breast cancer patients who are taking tamoxifen.

Du, M., Yang, X., Hartman, J. A., Cooke, P. S., Doerge, D. R., Ju, Y. H., & **Helferich, W. G.** (2012). Low-dose dietary genistein negates the therapeutic effect of tamoxifen in athymic nude mice. *Carcinogenesis, 33*, 895–901.

Cognition

Soy foods are typically a major part of Asian diets, and some research has suggested that soy foods may exert health benefits for postmenopausal women. Soy protein contains isoflavones, which are compounds that exert estrogen-like effects in some but not all tissues. However, soy protein supplements containing isoflavones, in an amount within the upper range of traditional Asian diets, had no effect on global cognition in postmenopausal women. Nevertheless, this randomized, double-blind controlled trial found that soy protein supplements improved visual memory (memory for faces). Researchers randomly assigned 350 healthy postmenopausal women to receive the protein (25 g/day) as either isoflavone-rich soy protein (containing 91 mg of isoflavones as aglycone equivalents) or milk protein as the matched placebo for 2.5 years. Researchers monitored participants for a broad range of cognitive skills every month for the first 6 months and then every 2 months for the remainder of the trial. They observed that there was no significant difference in global cognition scores between the two groups. However, secondary analyses found that women in the soy protein group, compared with the placebo, had better visual memory. The researchers did not find significant differences between the groups on any other cognitive factors or individual test scores, or significant differences within a subgroup of younger postmenopausal women. The researchers concluded that long-term isoflavone-rich soy protein supplements did not improve global cognition but that they may improve the visual memory of healthy postmenopausal women.

Henderson, V. W., St. John, J. A., **Hodis, H. N.,** Kono, N., McCleary, C. A., Franke, A. A., & Mack, W. J.; WISH Research Group (2012). Long-term soy isoflavone supplementation and cognition in women: A randomized, controlled trial. *Neurology, 78*, 1841–1848.

Irritable Bowel Syndrome (IBS)

This prospective, randomized controlled trial explored the feasibility and efficacy of a group program of mindfulness training, a cognitive-behavioral technique, for women with IBS. The technique involves training in (a) intentionally attending to present-moment experience, and (b) nonjudgmental awareness of body sensations and emotions. Female IBS patients (N=75) were randomly assigned to 8 weekly and 1 half-day intensive sessions of either mindfulness group (MG) training or a support group (SG). Participants completed the IBS symptom severity scale (primary outcome), IBS-quality of life, brief symptom inventory-18, visceral sensitivity index, treatment credibility scale, and five facet mindfulness questionnaire before and after treatment and at 3-month follow-up. Women in the MG showed greater reductions in IBS symptom severity immediately after training (26 percent versus 6 percent; P = 0.006) and at 3-month follow-up (38 percent versus 12 percent; P = 0.001) relative to SG. Changes in quality of life, psychological distress, and visceral anxiety were not significantly different between the groups immediately after treatment, but there were greater improvements in the MG versus the SG at the 3-month follow-up. Mindfulness scores increased significantly more in the MG after treatment, confirming effective learning of mindfulness skills. Women's ratings of the credibility of their assigned interventions, measured after the first group session, were not different between groups. This randomized controlled trial found that mindfulness training had a substantial therapeutic effect on bowel symptom severity, improved health-related quality of life, and reduced distress, and these beneficial effects persisted at least 3 months after group training.

Gaylord, S. A., Palsson, O. S., Garland, E. L., Faurot, K. R., Coble, R. S., Mann, J. D., . . . Whitehead, W. E. (2011). Mindfulness training reduces the severity of irritable bowel syndrome in women: Results of a randomized controlled trial. American Journal of *Gastroenterology, 106*, 1678–1688.

Menopause

Hormone therapy is the most effective treatment for menopausal symptoms, including hot flashes and night sweats (vasomotor symptoms); however, its use has declined due to widespread concerns about health risks. Postmenopausal women express great

interest in finding safe, effective nonpharmacologic approaches with minimal side effects to relieve vasomotor symptoms, which affect as many as 80 percent of women. A promising approach is clinical hypnosis, a mind and body practice designed to facilitate a hypnotic state that promotes coolness to ameliorate symptoms. Researchers randomly assigned 187 postmenopausal women (ages 39 to 75 years) who reported at least 7 hot flashes/day or 50 hot flashes/week into 2 groups. Each group received five 45-minute weekly sessions of either (1) clinical hypnosis, combined with training in self-hypnosis and an audio recording for daily practice; or (2) a control intervention of structured attention plus an audio informational recording on hot flashes for daily listening. Measurements were taken at the beginning of the study and then at 6 and 12 weeks. Researchers assessed hot flash severity and frequency (hot flash score) subjectively with participant-recorded diaries, and they also monitored hot flash frequency objectively with a monitor (Biolog®) that sensed skin temperature. The researchers observed that participants in both groups improved on all outcomes, but the hypnosis group improved to a significantly greater extent than the control group. For example, from baseline to week 12, subjective weekly hot flash frequency decreased ($P < 0.001$) by 74 percent in the clinical hypnosis group compared with 17 percent in the attention control group. At the 12-week follow-up, the average reduction in objectively monitored hot flashes was 57 percent for clinical hypnosis compared with 10 percent for controls. At week 12, secondary outcomes also improved significantly ($P < 0.001$) in the hypnosis compared with the control group: These 3 outcomes were hot flash-related interference, sleep quality, and treatment satisfaction. The researchers found that clinical hypnosis resulted in significant reductions in both subjectively assessed self-reported and objectively assessed hot flash frequency and score compared with controls, although the researchers concluded that the mechanism by which clinical hypnosis works is unknown. No adverse effects were reported, except mild skin irritation for some women from the adhesive used with the monitoring device. Women in both groups expressed satisfaction with treatment, but women who practiced hypnosis had significantly greater levels of satisfaction. Funding is pending to extend the findings from therapist-delivered hypnosis to self-administered hypnosis.

Elkins, G. R., Fisher, W. I., Johnson, A. K., Carpenter, J. S., & Keith, T. Z. (2013). Clinical hypnosis in the treatment of postmenopausal hot flashes: A randomized controlled trial. *Menopause, 20,* 291–298.

Reproductive Health

Progesterone, the major naturally occurring steroid hormone progestogen, plays a central role in women's reproductive health. Synthetic progestins, such as medroxyprogesterone acetate, are often used in hormone therapy, oral contraceptives, and for the treatment of endometriosis and infertility. Although medroxyprogesterone acetate is clinically effective, it also promiscuously binds to androgen and glucocorticoid receptors, thereby leading to many undesirable side effects, such as cardiovascular diseases and breast cancers. Hence, identifying alternative progestins is clinically important. The purpose of this study was to biologically characterize nonsteroidal progestins from botanicals by investigating their interaction and activation of the progesterone receptor. Eight botanicals commonly used to alleviate menopausal symptoms were investigated using specific assays to determine whether they contain progestins. Red clover (a perennial plant) extract stimulated one of these receptors and bound to the progesterone receptor. A library of purified compounds isolated from red clover was screened using one of these assays. Kaempferol, a flavonoid found in a variety of plant-based foods, identified in red clover, and apeginin, a structurally similar flavonoid, bound to the progesterone receptor and induced progestegenic activity. Kaempferol and apigenin both stimulated progesterone-regulated genes in endometrial and breast tissue, demonstrating higher progestegenic potency in the endometrial compared with breast cells. Furthermore, progestins from these plant products activated progesterone signaling in breast cells without suppressing progesterone receptor

expression. These data suggest that botanical extracts used for women's health may contain compounds capable of activating progesterone receptor signaling.

Toh, M. F., Sohn, J., Chen, S. N., Yao, P., Bolton, J. L., & **Burdette, J. E.** (2012). Biological characterization of non-steroidal progestins from botanicals used for women's health. *Steroids, 77*, 765–773.

Initiatives

Dietary Supplement Research Centers: Botanicals (RFA-OD-09-001)

Through this research program, the NIH Office of Dietary Supplements (ODS), NCCAM, and the National Cancer Institute support research centers that:

(1) Promote collaborative integrated interdisciplinary study of botanicals, particularly those found as ingredients in dietary supplements; and

(2) Conduct research that has a high potential to be translated into practical benefits for human health.

This initiative is intended to advance the spectrum of botanical research activities, ranging from plant identification and characterization to early-phase clinical studies. Among the five centers that NCCAM funds, the two described below are focused on women's health.

University of Illinois at Chicago (UIC)/NIH Center for Botanical Dietary Supplements Research in Women's Health

This center at the University of Illinois at Chicago was established in 1999 to focus on research in botanical dietary supplements related to women's health. The Center's mission is to focus on the safety of widely available botanical dietary supplements, such as black cohosh and licorice. Investigators examine how multicomponent mixtures work together; how they are absorbed, distributed, and eliminated by the body; how they affect chemical, physical, and physiological processes; how they interact with drugs; and how they affect women's own estrogenic hormones.

Botanical Research Center at University of Illinois at Urbana-Champaign

This more recently created center at the University of Illinois at Urbana-Champaign was established in FY 2010. It is examining the safety, efficacy, and mechanism of action of botanical estrogens, such as wild yam, soy, and dong quai. The Center's projects are examining the biological effects of botanical estrogens on molecular mechanisms and cellular pathways as well as their actions on bone, uterus, breast tissue, breast cancer metastasis, and cognition

NIH-Institutes-and-Centers-Featured Activities Map to NIH Strategic Plan for Women's Health Research Goals

Hypnosis for Hot Flashes. (U01 AT004634: G. Elkins, highlighted above). Design an intervention to relieve hot flashes, using a skin conductance monitor (Biolog®) to objectively assess change in skin temperature in response to nonpharmacologic intervention.

- **Goal 2.** Incorporate findings of sex/gender differences in the design and application of new technologies, medical devices, and therapeutic drugs.
- **Goal 2, Objective 2.5 (Elkins).** Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.
- **Goal 2, Objective 2.7 (Elkins).** Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

Dietary Supplement Research Centers. (RFA-OD-09-001). UIC/NIH Center for Botanical Dietary Supplements Research in Women's Health (R21 AT005377-01A1 [cofunded by ORWH & NCCAM] & P50 AT00155: J.E. Burdette, highlighted above) and Botanical Estrogen Research Center at University of Illinois at Urbana-Champaign (5P50AT006268: W. Helferich, highlighted above).

- **Goal 1**. Increase sex differences research in basic science studies.
- **Goal 1, Objective 1.7 (Burdette).** Investigate the actions of steroid hormones and hormone-mimicking environmental agents on gene expression, cells, tissues, and organs. Apply this knowledge to sex differences in disease prevalence, symptoms, management, and outcomes in conditions such as lupus and cardiovascular diseases and to predominantly sex-specific diseases, such as breast cancer and uterine fibroids.
- **Goal 3, Objective 3.1 (Helferich).** Conduct developmental and developmentally framed research to understand the role of hormones, hormonal changes, and reproductive transitions on conditions affecting women and girls throughout the life span.

Reference

Barnes, P. M., Bloom, B., & Nahin, R. L. (2008). Complementary and alternative medicine use among adults and children: United States, 2007. *National Health Statistics Report, 12*, 1–23

Edwards, E., Alekel, D. L., & Stussman, B. (2013). Complementary, alternative, and integrative medicine and women's health. In M. B. Goldman, R. Troisi, & K. M. Rexrode (Eds.), *Women and health, 2nd ed.* (pp. 57–75). San Diego, CA: Elsevier.

Office of Behavioral and Social Sciences Research

Executive Summary

In 1993, the U.S. Congress established the Office of Behavioral and Social Sciences Research (OBSSR) at NIH. The office opened in July 1995. NIH already had a long history of supporting health-related behavioral and social sciences research, and the results of this earlier work have contributed significantly to the understanding of the basic underlying mechanisms of mental and physical health and illness. Establishing an office focused specifically on the behavioral and social contributions to health and well-being has enabled NIH to leverage existing efforts and develop synergy across multiple Institutes, Centers, and disciplines.

Situated within the Office of the Director's Division of Program Coordination, Planning, and Strategic Initiatives, OBSSR furthers the mission of NIH by emphasizing the critical role that behavioral and social factors play in health, health care, and well-being. With a budget of approximately $27 million, OBSSR serves as the focal point for the coordination and development of policies, goals, and objectives in the behavioral and social sciences at NIH. OBSSR's mission is to:

(1) Integrate a behavioral and social sciences perspective across NIH;

(2) Disseminate behavioral and social sciences research findings; and

(3) Provide advice to and communicate with the NIH Director, Congress, other Federal Government agencies, the research community, and the general public on matters regarding behavioral and social sciences research.

OBSSR's leadership is crucial at a time when exciting scientific opportunities, persistent public health needs, and emergent public health challenges face our Nation. The vision of the office is to bring together the biomedical, behavioral, and social science communities to work more collaboratively to solve complex, pressing health challenges. Notable areas of research in which OBSSR has led efforts include behavior change, adherence, social and cultural dimensions of health, community-based participatory research, health literacy, mind-body, mobile and wireless health, and systems science approaches to health. The four core elements of OBSSR's vision for the future are as follows:

(1) Next-generation basic science: OBSSR supports and facilitates the next generation of basic behavioral and social science research, which is informed by breakthroughs in complementary areas such as genetics, informatics, computer science, measurement, methods, and multilevel analyses.

(2) Interdisciplinary research: OBSSR facilitates collaborative research across the full range of disciplines and stakeholders necessary to elucidate the complex determinants of health and challenges to health systems. Such collaborations yield new conceptual frameworks, methods, measures, and technologies that speed the improvement of population health.

(3) Systems-thinking approaches to health: OBSSR stimulates systems thinking and modeling approaches to research that integrate multiple levels of analysis—from cells to society—that are required to understand the ways in which individual, contextual, and organizational factors interact over time to determine health status.

(4) Population impact: OBSSR works with its NIH partners to identify key problems in population health on which scientists, practitioners, and decision makers can work together to accelerate the translation, implementation, dissemination, and adoption of behavioral and social sciences research findings.

Initiatives

Since it opened its doors in 1995, OBSSR has worked to achieve the goals of its authorizing legislation by effectively highlighting and supporting the scientific opportunities that exist in basic and applied behavioral and social sciences research. OBSSR has been actively addressing its congressional mandate and has encouraged research in the behavioral and social sciences by developing ideas for initiatives and gaining support for them within the NIH community. Although OBSSR does not have grant-making authority, it has been active in organizing and funding (through transfers to NIH ICs) a variety of trans-NIH research programs. Therefore, the majority of its contributions to women's health research are in the form of cofunding grants administered by NIH ICs.

FY 2011

In 2011, OBSSR cofunded the following 20 grants with a women's health component:

Title: Advancement of Women in STEMM: A Multi-level Research and Action Project
PI (Principal Investigator): Marc Carnes
Grant: R01-GM-088477

The goals of this research are to develop, implement, and evaluate interventions designed to increase the participation and advancement of women in academic science, technology, engineering, mathematics, and medicine (STEMM).

Title: Center for Prevention Implementation Methods for Drug Abuse & Sex Risk Behavior
Grant: P30-DA-027828
PI: C. Hendricks Brown

This project is designed to accelerate research through the application and integration of system science methods for a wide-scale implementation of effective programs to prevent drug abuse and sexual-risk behaviors in communities across the country.

Title: Culture, Social Support and Quality of Life: Asian American Breast Cancer Survivors-Operationalizing Culture for Health Behavior and Social Science Research
PI: Marjorie Kagawa-Singer
Grant: R01-CA-158314

This study proposes to identify and define how culture may modify the definitions of self-integrity and quality of life for Asian-American breast cancer survivors.

Title: NPY, Neurovascular Niches, and Stress-Induced Remodeling of Adipose Tissue
PI: Zofia Kukoska
Grant: R01-HL-067357

The goal of this proposal is to test the hypothesis that intense or prolonged neurohormonal stress compromises protection

of neurovascular niches and affects resident adipose stem cells (epigenetically altering their neuropeptide Y [NPY] system).

Title: Development, Ecology, and Prevention of Adult Addictive Behavior
PI: Thomas Dishion
Grant: R01-DA-007031

This project tests genetically informed ecological models for the development of alcohol and other drug use and dependence, antisocial behavior, and high-risk sexual behavior in adulthood.

Title: Emotions Are Emergent Events Constrained by Affective and Conceptual Processes
PI: Lisa Barrett
Grant: DP1-OD-003312

This research uses a new systems-level model grounded in the neuroanatomy of the human brain that incorporates neuroscience findings from rats, primates, and humans and explains the mechanisms that produce the range and variety of behavioral and introspective instances that are called "emotion."

Title: Epigenetic Influence on Early Childhood Self-Regulation Capacities and Obesity
PI: Bernard Fuemmeler
Grant: R21-AG-041048

The purpose of this research is to determine the association that self-regulation capacities have with early-childhood caloric intake and weight and to identify epigenetic marks associated with these self-regulation phenotypes.

Title: Family Research Consortium V: Transdisciplinary Consortium on Mental Health, Co-occurring Disorders, and Families
PI: Suniya S. Luthar
Grant: R13-MH-082592

The grantee seeks to support continuing collaborative research efforts of the highly successful Family Research Consortium (FRC) in the Transdisciplinary Consortium on Mental Health, Co-occurring Disorders, and Families (FRC V).

Title: Flexible Work and Well-Being Center
PI: Erin Kelly
Grant: U01-HD-051256

This project seeks to design, implement, and examine the feasibility of a workplace intervention to improve the health of employees and their families.

Title: Genes, Prenatal Drug Exposure, and Postnatal Rearing Environment: An Adoption Study
PI: Jenae Neiderhiser
Grant: R01-DA-020585

This research study seeks to use and expand an existing prospective longitudinal adoption study, the Early Growth and Development Study, to better understand how genetic factors, prenatal drug exposure, and the postnatal rearing environment operate together to influence toddler development and, ultimately, an individual's risk of later drug use.

Title: Neurobiological and Behavioral Consequences of Cocaine Use in Mother/Infant Dyads
PI: Josephine Johns
Grant: P01-DA-022446

This research project seeks to elucidate neurobiological and biobehavioral consequences of cocaine use (by mothers) and prenatal exposure in infants that may underlie disturbances in mother-infant interactions

---

Title: Obesogenic Environment: Impact on Breast, Colorectal, and Prostate Cancer Risk
PI: Iona Cheng
Grant: R01-CA-154644

The goal of this proposal is to understand the effects of neighborhood-level obesogenic factors on risks of breast, colorectal, and prostate cancer, with careful consideration of individual-level health behaviors and genetic predisposition among African-Americans and Latinos.

Title: Oncofertility Consortium Annual Conference
PI: Teresa Woodruff
Grant: R13-HD-063248

Funding for this grant supports the annual meeting of the Oncofertility Consortium. The meeting is the only one of its kind and unites prominent researchers, scientists, clinicians, and patients in an interactive discussion about emerging technologies, research, and real-world options for cancer patients concerned about their fertility.

Title: Pregnancy and EARly Lifestyle improvement Study (PEARLS)
PI: Kaumudi Joshipura
Grant: U01-HD-072834

This project will conduct a randomized controlled trial of 400 overweight or obese, pregnant Puerto Rican women (free of diabetes) and their infants to improve metabolic health in mothers and infants.

Title: Reading Disabilities in Zambian Children
Grant: R01-TW-008274
PI: Elena Grigorenko

This study examines the development and etiology of specific reading disabilities in Zambian children and their siblings.

Title: Rush Center for Urban Health Equity
PI: Lynda Powell
Grant: P50-HL-105189-01

This study seeks to find ways to promote changes, all the way from policy to biology, to eliminate the health disparities affecting the residents of America's cities, in particular those who are low-income persons of color.

Title: The Aftermath of Rape on Mental Health
PI: Gail Wyatt
Grant: R03-TW-007964

This proposal seeks to eliminate some of the gaps in the scientific literature by examining the psychosocial sequelae of rape and treatment-related factors among treatment-seeking, rural, Black South-African rape survivors and to study the moderators and mediators in the relationship between psychosocial, cultural beliefs, and treatment factors and psychological distress.

Title: The Impact of Yoga Supplementation on Cognitive Function Among Indian Outpatients
PI: Triptish Bhatia
Grant: R01-TW-008289

This study will examine the impact of yoga supplementation on cognitive function among Indian outpatients with schizophrenia.

Title: Work, Family, Health, and Well-Being Initiative
PI: Mary Durham
Grant: U01-HD-051218

The proposed study aims to assess the effects of a workplace intervention designed to reduce work-family conflict and thereby improve the health and well-being of employees, their families, and their workplaces.

Title: Neighborhood and Family Effects on Disparities in Chronic Disease
PI: Anne Pebley
Grant: R01-HD-058514

The goal of this study is to significantly advance knowledge of the role played by specific family and neighborhood characteristics in observed disparities in the development of metabolic syndrome and chronic diseases, such as asthma and hypertension

---

FY 2012

In 2012, OBSSR cofunded the following 16 grants, all of which had a women's health component:

Title: Accountability for Cancer Care Through Undoing Racism and Equity (ACCURE)
PI: Eugenia Eng
Grant: R01-CA-150980

This grant seeks to specify structures built into cancer care systems that make such care vulnerable to institutional racism and to investigate how these structures can be changed to reduce racial inequity in the quality of care and completion of treatment for stage 1–2 breast and lung cancer patients.

Title: Enabling Family Communication About Cancer—Do You Know Your Kin Facts
PI: John Quillin
Grant: R01-CA-140959

This study proposes to develop and evaluate a clinically integrated intervention to improve patient-family communication about cancer risk and prevention.

Title: Exploring the Attitudes and Use of Family Cancer History and Biospecimen Collections
PI: Janet Kelly
Grant: R21-CA-163171

This pilot project will assess the acceptability and feasibility of collecting and storing biospecimens from Alaska Native people living in a rural community for the purposes of cancer research. The investigators anticipate that this research will provide a model approach for other Alaska Native communities to use family health history and the collection of biospecimens to reduce their risks of chronic disease, including cancer.

Title: Salud es Vida: Reducing Access Barriers to Cervical Cancer Screening Among Underserved Hispanic Women
PI: John S. Luque
Grant: R21-CA-163159

The overall objective of this study is to develop an effective, culturally appropriate cervical cancer prevention intervention for low-income, Mexican farmworkers in southeast Georgia.

Title: Understanding and Preventing Breast Cancer Disparities in Latinas—Annual Scientific Meetings of the Centers for Population Health and Health Disparities (CPHHD)
PI: Beti Thompson
Grant: P50-CA-148143

The overarching theme of this research is to understand and prevent precursors of breast cancer and to reduce breast cancer morbidity and mortality among Latinas.

Title: Developing an Intervention To Prevent Visceral Fat in Premenopausal Women: (CBID)
PI: Lynda Powell
Grant: U01-HL-097894

This study aims to develop a multilevel intervention targeting simultaneously the individual, the social network, and the community for the purpose of producing a sustained increase in physical activity and reduction in chronic stress.

Title: English Longitudinal Study of Ageing
PI: Michael Marmot
Grant: R01-AG-017644

The central objective is to provide data necessary for the exploration of the unfolding dynamic relationships between health and functioning, economic position, social participation/networks, and well-being as people plan for, move into, and progress beyond retirement.

Title: Epidemiology of Psychological Distress in a Chinese Aging Population
PI: Xin Qi Dong
Grant: R01-AG-042318

This project will conduct an epidemiologic study to elucidate the relationship between culture factors and psychological well-being in Chinese older adults.

Title: Health Disparities and Stress Hypothesis
PI: R. Jay Turner
Grant: R01-AG-34067

This research uses a lifespan perspective in an effort to understand potentially modifiable social factors implicated in health disparities that involve race or socioeconomic status. The study will use one or more operationalizations of allostatic load and the assessment of cell aging in combination with both clinical and subclinical assessments of psychiatric and substance use disorders/problems. The study will also provide an estimation of stress exposure in terms of lifetime exposure to major and potential traumatic events, recent life events, chronic stressors, discrimination, and other stressors.

Title: A Collaborative Workshop Across the Scientific Disciplines with the Goal To Begin To Develop a Comprehensive Data Collection and Evaluation System To Monitor the Success of Diversity Programs
PI: Sally Hillsman
Grant: U13-HD-010988

This workshop proposes to address the recommendations from a 2008 NIH-supported (additional funding provided by the National Science Foundation) leadership retreat, "Enhancing Diversity in Science: A Leadership Retreat on the Role of Professional Associations and Scientific Societies," regarding the need to establish a common standard for measuring and evaluating the success of diversity-enhancing programs.

Title: Mothers and Others: Family-Based Obesity Prevention for Infants and Toddlers
PI: Margaret Bentley
Grant: R01-HD-073237

This research proposes a randomized controlled trial among 468 non-Hispanic Black women, their families, and their child caregivers to test the efficacy of a multicomponent, tailored intervention versus an attention control (child safety) in promoting healthy weight gain patterns during infancy.

Title: Patient-Reported Outcomes in Routine Clinical Care of Patients Infected with HIV
PI: Heidi Crane
Grant: U01-AR-057954

This research seeks to improve medical care processes and patient outcomes in clinical practice settings using routine collection of patient-reported outcomes administered by computerized adaptive tests

---

Title: Population, Land Use, and Health Dynamics of Biomass Fuel Use in Sub-Saharan Africa
PI: Pamela Jagger
Grant: K01-HD-073329

This Mentored Research Scientist Development Award is focused on developing an integrated research program that addresses the determinants of fuel and technology use and their associated health and socioeconomic outcomes in sub-Saharan Africa.

Title: Neurobiological and Behavioral Consequences of Cocaine Use in Mother/Infant Dyads
PI: Josephine Johns
Grant: P01-DA-022446

This project seeks to elucidate the neurobiological and behavioral characteristics and responses of mothers who have used cocaine during pregnancy and of their offspring who were prenatally exposed to cocaine. It is thought that such exposure may have a negative impact on normal mother-infant interactions.

Title: Understanding Social Contributions to Disparities in Depression Care: U.S. and U.K.
PI: Debra Roter
Grant: R01-MH-086449

The proposed investigation is designed to contribute to the disentangling of physician-derived and patient-derived contributions to social bias that may exacerbate health disparities associated with the provision and receipt of depression care and assessment of suicide risk in the United States and the United Kingdom.

Title: Promoting Fruit and Veggies Among Pregnant Latinas: Intervention Development
PI: Amber Hromi-Fielder
Grant: R21-NR-013970

This research aims to gather data that will inform the design of a community-based intervention promoting appropriate gestational weight gain through increased fruit and vegetable consumption among overweight and obese, pregnant, low-income Latinas.

OBSSR Research Funding Opportunities

OBSSR led several funding opportunities in FY 2011 and FY 2012. Those that had a focus on women and trans-NIH support are listed below.

Practical Interventions To Improve Medication Adherence in Primary Care, (R01) PA-12-022; (R21) PA-12-023

Behavioral Interventions To Address Multiple Chronic Health Conditions in Primary Care, (R01) PA-12-024

Translating Basic Behavioral and Social Science Discoveries into Interventions To Improve Health-Related Behaviors, (R01) PA-11-063

Behavioral and Social Science Research on Understanding and Reducing Health Disparities, (R01) PAR-10-136; (R21) PAR-10-137

Understanding and Promoting Health Literacy, (R01) PAR-10-133; (R03) PAR-10-134; (R21) PAR-10-135

A full listing of the current OBSSR funding opportunities can be read here:

http://obssr.od.nih.gov/funding_opportunities/foas/foas.aspx.

Office of Disease Prevention—Office of Dietary Supplements

Executive Summary

The Office of Dietary Supplements (ODS) was created in 1995 in the Office of Disease Prevention, Office of the Director, NIH, to meet the requirements of the Dietary Supplement Health and Education Act (DSHEA) of 1994. DSHEA defined the purposes and responsibilities of ODS as follows:

Purposes

- To explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care.
- To promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions.

Responsibilities

- To conduct and coordinate scientific research within NIH relating to dietary supplements and the extent to which the use of dietary supplements can limit or reduce the risk of diseases.
- To collect and compile the results of scientific research relating to dietary supplements, including scientific data from foreign sources.
- To serve as the principal advisor to the Secretary and to the Assistant Secretary for Health and provide advice to the Director of NIH, the Director of the U.S. Centers for Disease Control and Prevention (CDC),

and the Commissioner of the U.S. Food and Drug Administration (FDA) on issues relating to dietary supplements. These issues include dietary intake regulations, the safety of dietary supplements, the claims characterizing the relationship between the use of dietary supplements and the prevention of disease or other health conditions and the maintenance of health, and scientific issues arising in connection with the labeling and composition of dietary supplements.

- To compile a database of scientific research on dietary supplements and individual nutrients.
- To coordinate funding relating to dietary supplements for NIH.

Subsequent congressional mandates directed ODS to develop a botanical research center initiative (1999), conduct evidence-based reviews of the efficacy and safety of dietary supplements (2001), and accelerate the validation of analytic methods and reference materials for dietary supplements (2004).

ODS developed its mission statement as part of its first strategic planning process in 1998. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

Initiatives

ODS Extramural Investments

ODS's guidelines and criteria for initiating, expanding, or otherwise modifying its extramural investments have reflected DSHEA and congressional mandates. These guidelines are a response to gaps in scientific knowledge, opportunities for research relevant to dietary supplements, requests for research support from investigators, requests for information, and available resources. ODS extramural investments are categorized into four broad areas:

(1) Research support;

(2) Research tools;

(3) Communications; and

(4) Science-policy interactions.

The Office's key activities are grouped into 15 programs under these 4 areas; these 15 programs capture most of ODS's activities. The budget allocation for each of the four areas is included in the descriptions below. In FY 2010, the extramural budget for grants, contracts, interagency agreements, and workshops was $21.7 million.

Communication and science policy efforts rely heavily on investments of ODS staff time and expertise rather than direct funding. An ODS staff member is responsible for overseeing each of the 15 ODS programs that support extramural research, and most ODS staff members are active in more than 1 program. Each program interacts with one or more stakeholder communities, including research investigators; educators and teachers; health practitioners; research and educational institutions; agencies of the Federal Government; dietary supplement, food, and related industries; media; consumer and public interest groups; and members of the public. The 4 areas and 15 programs are described briefly below.

Area 1: Research Support

Research Grant Portfolio. This portfolio consists of grants administered by NIH Institutes and Centers that receive funding from ODS for research components related to dietary supplements. This investment supports the development of new knowledge on the health effects of dietary supplements.

Botanical Research Centers (BRCs). ODS currently supports five centers in response to a congressional mandate. The Office administers the centers in partnership with the National Center for Complementary and Alternative Medicine and the National Cancer Institute. These centers expand the scientific base for botanicals used as dietary supplements and have participated in the Analytical Methods and Reference Materials Program.

Training and Career Development. These extramural investments consist primarily of cofunding for selected NIH research training and career grants. These grants enable junior

scientists to develop research programs related to dietary supplements. In addition, each year ODS organizes the Mary Frances Picciano Dietary Supplements Research Practicum. The Practicum offers a multi-day opportunity for faculty, students, and practitioners to acquire a broad, fundamental understanding of dietary supplements.

Conferences and Workshops. ODS funds research conferences and workshops primarily through NIH grant mechanisms, although it also supports conferences and workshops initiated by NIH. These conferences and workshops bring together key scientists to discuss and define the research needs for various dietary supplements.

Area 2: Research Tools

Analytical Methods and Reference Materials. ODS established this program in response to a congressional mandate and administers it primarily through contracts originated by ODS. Supporting the development of analytic methods and reference materials for dietary supplements has been key to making informative studies of these supplements possible.

Surveys of Dietary Supplement Use. ODS provides intellectual and financial support to Federal agencies conducting national nutritional surveys that include use of dietary supplements. As part of this effort, the Population Studies Program focuses on the evaluation of dietary supplement use, including the assessment of biological measures of supplement exposure and associated health effects in nationally representative populations, in order to evaluate nutrients of concern for inadequacy or excess use. In collaboration with other Government agencies and academia, the efforts of this program are building the capacity to analyze population data (including economic cost), such as data obtained through the National Health and Nutrition Examination Survey, and will serve as a training environment for postdoctoral fellows.

Dietary Supplement Databases. ODS provides intellectual and financial support and leadership to Federal agencies that are establishing databases to enable the interpretation of survey data on public nutrition habits and use of dietary supplements. ODS and its Federal partners at the U.S. Department of Agriculture, CDC, National Library of Medicine, and FDA have created a dataset of dietary supplement ingredients and a comprehensive database of information on supplement labels.

Evidence-Based Reviews. In response to encouragement from Congress, ODS provides intellectual and financial support, primarily to the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, to conduct reviews that are critical to determining the research needs for selected dietary supplements. These reviews are published on the AHRQ Web site and in peer-reviewed journals. Evidence-based reviews are key to identifying the status of scientifically validated knowledge about dietary supplements and the important gaps in research. ODS is currently sponsoring three evidence based-reviews with relevance to women's health through the AHRQ Evidence-Based Practice Center Program:

(1) Iodine Intake, Status, and Health in Vulnerable Population Groups;

(2) The Effects of Omega-3 Fatty Acids on Health Outcomes in Children; and

(3) An update of the 2009 evidence report "Vitamin D and Calcium: Systematic Review of Health Outcomes."

Area 3: Communications

Communications. ODS's communication activities include a broad spectrum of outreach activities, such as the ODS Web site; Twitter feed; exhibits; the MyDS app and MyDS Español, the Spanish-language counterpart; and public information pieces related to dietary supplements.

Computer Access to Research on Dietary Supplements (CARDS). ODS developed this consumer-friendly, Internet-based database in response to the DSHEA mandate to compile a database of scientific research on dietary supplements. CARDS contains information on federally funded research projects pertaining to dietary supplements.

International Bibliographic Information on Dietary Supplements (IBIDS). ODS developed this consumer-friendly, Internet-based database also in response to the DSHEA mandate to collect and compile the results of scientific research related to dietary supplements. IBIDS provides access to bibliographic citations and abstracts from the published, international, and scientific literature on dietary supplements.

Federal Dietary Supplement Working Group. ODS established the Federal Dietary Supplement Working Group in 2005 to share information and discuss issues related to dietary supplements among Federal agencies.

Area 4: Science-Policy Interactions

These programs reflect the philosophy that good policy is founded on good science. ODS furnishes expertise in nutritional sciences to address public health issues related to dietary supplements.

Nutrient Initiatives. The Vitamin D Initiative is an evolving partnership with NIH Institutes and Centers and other Federal agencies through the Vitamin D Federal Working Group to address the research gaps related to vitamin D. Through the folate and iodine initiatives, ODS and other Federal partners are examining the efficacy and safety of the relevant fortification programs in the United States.

Dietary Supplement Use in the Military. This partnership with the U.S. Department of Defense is evaluating the impact of the use of dietary supplements by military personnel.

Dietary Reference Intakes. ODS supports Federal programs to evaluate the reference standards for intakes of nutrients, including vitamins and minerals.

ODS Strategic Plan

Goal 1. Provide intellectual leadership by fostering research to analyze and evaluate the role of dietary supplements in promoting health and reducing the risk of disease.

Goal 2. Expand the general scientific knowledge base on dietary supplements by funding new research and training.

Goal 3. Support the development of research tools for the study of dietary supplements.

Goal 4. Make the most up-to-date scientific knowledge about dietary supplements publicly available.

Grant Funding—Research on Women's Health

Fiscal Year 2011: $3,862,577

- Botanical Dietary Supplements for Women's Health
- Botanical Estrogens: Mechanisms, Dose, and Target Tissues
- Domains of Inflammation and Risk of Dementia
- Identification of Natural Product Inhibitors of Breast Cancer Bone Metastasis
- Probiotics and Bone Health—Role of Gender and Intestinal Health
- Epigenetics and Nutrition: DNA Methylation, Dietary Intake, and CVD
- Does EPA or DHA Prevent Depressive Symptoms in Pregnancy and Postpartum?
- Training in Maternal and Child Nutrition
- VITamin D and Omega-3 triaL (VITAL)
- Vitamin D and Osteoporosis Prevention in Elderly African Americans
- Vitamin D and Immunosenescence in Older Long-Term Home Residents
- Treatment of Vitamin D Insufficiency
- Determinants and Consequences of Low Vitamin D in Populations of African Descent
- Dietary and Serum Phytoestrogens and Women's Health Conditions in Midlife
- Established Investigator Award Anti-Inflammatory Exposures in Cancer Prevention
- Building Interdisciplinary Research Careers in Women's Health (BIRCWH)
- BIRCWH Program at the University of California, Davis

- Musculoskeletal Benefits of Bicarbonate in Older Adults—A Dose-Finding Trial
- Supplementation and Pregnancy Outcome
- Prenatal Iron Supplements: Safety and Efficacy in Tanzania
- BIRCWH Program at Tulane University

Fiscal Year 2012: $3,916,764

- Botanical Dietary Supplements for Women's Health
- Domains of Inflammation and Risk of Dementia
- Botanical Estrogens: Mechanisms, Dose, and Target Tissues
- Prevention of Estrogen-Mediated Mammary Carcinogenesis by Mixtures of Tocopherols
- VITamin D and Omega-3 triaL (VITAL)
- Vitamin D3 Effects on Musculoskeletal Symptoms with Use of Aromatase Inhibitors
- Established Investigator Award Anti-Inflammatory Exposures in Cancer Prevention
- Epigenetics and Nutrition: DNA Methylation, Dietary Intake, and CVD
- Obesity and Asthma: Genetics and Nutrigenetic Response to Omega-3 Fatty Acids
- Vitamin D and Osteoporosis Prevention in Elderly African Americans
- Vitamin D and Immunosenescence in Long-Term Care Residents
- Dietary and Serum Phytoestrogens and Women's Health Conditions in Midlife
- Treatment of Vitamin D Insufficiency
- Optimizing Vitamin D in the Elderly
- Determinants and Consequences of Low Vitamin D in Populations of African Descent
- Musculoskeletal Benefits of Bicarbonate in Older Adults—A Dose-Finding Trial
- Long-Term WIFS and Malaria Risk in Early Pregnancy: A Randomized Controlled Trial (Liverpool School of Tropical Medicine, reproductive health)
- Long-Term WIFS and Malaria Risk in Early Pregnancy: A Randomized Controlled Trial (Harvard University, infectious disease)
- BIRCWH Program at the University of California, Davis
- Training in Maternal and Child Nutrition

NIH Strategic Plan: A Vision for 2020 for Women's Health Research

Many of the awards cofunded by the ODS in FY 2011 and FY 2012 further the NIH Strategic Plan for Women's Health Research Goal 2, in particular, objectives 2.1, 2.2, 2.3, 2.5, and 2.7.

2.1. Encourage the development of technologies that will address sex-based differences at all scales of detail, from the nanometer to the whole person

2.2. Develop novel animal, in vitro, and computational (virtual) models to study sex differences in diseases and conditions.

2.3. Develop the information systems needed for collecting, sharing, and comparing clinical data for diseases and conditions of women and girls.

2.4. Develop computational models that will utilize multiple levels of analyses to address both qualitative and quantitative outcomes of clinical research related to women.

2.5. Work toward devising minimally invasive technologies for rapid and accurate screening, diagnosis, and treatment of diseases and conditions of women and girls.

2.7. Design drugs, biologics, and devices to diagnose, prevent, and treat diseases and conditions affecting women and girls.

APPENDIX A

ORWH-Cofunded Research Summaries, FY 2011

National Cancer Institute

Title: **Advanced Glycation End Products and Colorectal Cancer Risk in Women**
P.I.: **Li Jiao**
Institution: **Baylor College of Medicine**
Grant No.: **CA156626-01**
Award: **$98,397**

Advanced Glycation End-products (AGEs) are a heterogeneous group of compounds formed via the nonenzymatic glycation of lipids, proteins and nucleic acids. AGEs form endogenously during normal metabolism, and exogenously from foods processed at a high temperatures and tobacco smoking. N5-(carboxymethyl)-lysine (CML)-AGE is one of the best characterized AGEs. The accumulation of AGEs in the human tissues accelerates under hyperglycemia. AGEs trigger oxidative stress and inflammation by interacting with the receptor for AGEs (RAGE). Soluble RAGE (sRAGE) neutralizes the reactions mediated by the RAGE and therefore, acts as an anti-inflammatory factor. We recently reported that levels of sRAGE significantly predicted a lower risk of colorectal cancer (CRC) in Finnish male smokers. The role of AGEs and sRAGE in CRC development has not been investigated in women. We hypothesize that AGEs contributes to CRC development while sRAGE exerts a protective effect. We propose a case-cohort study that builds upon three NIH-funded studies conducted within the Women's Health Initiative (WHI) Observational Study of a cohort 93,676 postmenopausal women. The proposed study includes 425 incident CRC cases and 791 randomly selected subcohort participants. The study has three specific aims: 1) To examine the association between baseline fasting circulating levels of CML-AGE, sRAGE, and the sRAGE/CML ratio and risk of subsequent development of CRC; 2) to examine the independent predictors of circulating levels of CML-AGE and sRAGE among the subcohort participants, including age, body mass index, alcohol use, daily average intake of nutrients (e.g., carbohydrate nutrients and fatty acids), and tobacco smoking; and 3) to explore the inter-relationships among circulating levels of CML-AGE, sRAGE and serological markers of insulin resistance, inflammation and estradiol on the risk of CRC. The availability of pre-diagnostic bio-specimens and exposure information, as well as previously measured analytes, makes this study highly feasible and efficient. The long-term goal of this research is to elucidate a modifiable pathway, AGEs/RAGE, that may connect environmental exposure (e.g., dietary intake), inflammation, and insulin resistance with CRC etiology and prognosis.

Title: **Cancer Center Support Grant: Cancer Institute of New Jersey**
P.I.: **Robert S. Dipaola**
Institution: **University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School**
Grant No.: **CA072720-13S9**
Award: **$15,000**

The Cancer Institute of New Jersey (CINJ) is a matrix style, basic, clinical and population research center under the auspices of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School. The Director serves as Associate Dean for Oncology Programs and is responsible for integrating research at the medical school with the Robert Wood Johnson University Hospital, School of Public Health, and several schools and departments of Rutgers University. CINJ was awarded its first P30 Cancer Center Support Grant (P30 NCI 072720) on March 1, 1997. CINJ has a current membership of 155, whose peer reviewed, funded research projects, as defined by the CCSG guidelines, total more than $50 million in

direct costs, nearly $15 million of which is from the NCI. The research base of CINJ is organized into eight programs: Breast Cancer Research; Cancer Pharmacology/Developmental Therapeutics; Carcinogenesis and Chemoprevention; Cytokines, Cytokine Signaling and Cancer; Molecular Mechanisms of Tumor Growth; Prostate; Population Science, and Transcriptional Regulation and Oncogenesis. This application requests support for the following: Administration; Data Safety and Monitoring; Developmental Funds; Planning and Evaluation; Program Leaders; Protocol Review and Monitoring System; Protocol Specific Research; and Senior Leadership. In addition, we are requesting funds for the following shared resources of CINJ: Analytical Cytometry/Image Analysis; Biometrics; Centralized Education and Training for Clinical Research Personnel; DNA Sequencing; Immunohistochemistry; Laboratory Support Services; Office of Human Resource Services; Research Pharmacy; Tissue Retrieval Service; Transcriptional Profiling; and Transgenic/Knock-out Mouse Service.

Title: **Cancer Center Support Grant: Hollings Cancer Center**
P.I.: **Andrew S. Kraft**
Institution: **Medical University of South Carolina**
Grant No.: **CA138313-03S1**
Award: **$15,000**

The Hollings Cancer Center (HCC) at the Medical University of South Carolina (MUSC) seeks National Cancer Institute (NCI) designation via the P30 Cancer Center Support Grant mechanism to support its mission to reduce the cancer burden in South Carolina and beyond. As South Carolina's leading academic medical center, MUSC has been charged and supported over the past decade to build clinical, basic, translational and population-based research programs that address the state's significant cancer morbidity and mortality. Through the support of an NCI P20 Planning Grant (2001-2007), the HCC has recruited and organized 97 cancer scientists, representing six MUSC Colleges—Medicine, Pharmacy, Dental Medicine, Nursing, Health Professions and Graduate Studies—into productive and collaborative cancer research programs. These programs are: Lipid Signaling in Cancer, Cancer Genes & Molecular Regulation, Developmental Cancer Therapeutics and Cancer Immunology. A Cancer Prevention & Control program is in development. The HCC has expanded and continues to expand its research facilities and resources to enhance further growth. In 2006, the HCC completed a seven story tower adjacent to its original 85,761 feet building adding more than 116,000 feet in research, clinical and administrative space, and MUSC has committed an additional 62,000 feet of research space to the HCC in two new buildings starting construction in summer 2008. As part of this P30 application, five shared research resources will be presented: Lipidomics, Flow Cytometry & Cell Sorting, Cell & Molecular Imaging, Biostatistics and Clinical Trials. The HCC has invested $1.6 million since 2004 into enhancing these five essential and critical resources. Given the rapid and ongoing development of research in the programs, the HCC has also invested another $6 million in initiating the development and optimizing the function of seven other shared resources that will greatly impact on HCC's current and future programmatic-based research initiatives. These investments have resulted in a doubling of the HCC's extramural research funding base since 2003, currently $31.2 million with NCI funding representing $12.1million. Accrual to therapeutic clinical trials has quadrupled in the same time period. This application demonstrates that HCC scientists have made significant contributions to the understanding of cancer biology and the development of novel approaches to prevent, diagnose and treat cancer.

Title: **Cancer Center Support Grant: Ohio State University Comprehensive Cancer Center**
P.I.: **Michael A. Caligiuri**
Institution: **Ohio State University**
Grant No.: **CA016058-35S1**
Award: **$5,000**

The Ohio State University Comprehensive Cancer Center (OSUCCC) is currently in its 35th year as an NCI designated CCC and is now requesting continued federal support for the next five years. Dr. Caligiuri currently continues in his seventh year as the OSUCCC Director and has since been named CEO of OSU's freestanding James Cancer Hospital. The overall goal remains to reduce cancer morbidity and mortality through continued basic, translational and clinical research. The 239 OSUCCC full, associate or introductory members are currently served by 18 shared resources and are distributed among the our six Research Programs which remain unchanged: Cancer Control, Experimental Therapeutics, Innate Immunity, Molecular Biology and Cancer Genetics, Molecular Carcinogenesis and Chemoprevention, and Viral Oncology. Since the last competitive renewal, the OSUCCC has shown significant growth as demonstrated by: 1) the recruitment of 159 faculty focused in basic, translational and clinical cancer research and medicine; 2) more than a 80% increase in patient accrual to investigator-initiated trials; 3) the addition of 5 new shared resources at an institutional investment of over $4.2 million; 4) a 96% increase in total NCI funding despite a period of relatively flat federal funding; 5) an 85% increase in publications, 51% of which were collaborative (i.e., inter-, intra-programmatic, or both); 5) discovery, preclinical development and administration of two new anti-cancer agents into man, along with additional important advances in basic and clinical cancer research. The OSUCCC has also seen tremendous growth in institutional commitment since 2004 as demonstrated by 1) a ten-fold increase in annual financial support (now approximately $50 million) for the OSUCCC under the control of the Director; 2) an additional $7.0 million of cash annually from OSU for research and infrastructure expansion; 3) a formal direct reporting relationship to the Executive Vice President and Provost with complete oversight of the University-wide cancer funding initiatives, opportunities and cancer grant submissions; 4) A seat on the University President's cabinet providing representation of the CCC at the highest level of the University; 5) a six-fold increase in space currently under the sole control of the Director, including new additional dry and wet laboratory and office space for recruitment of additional faculty; 6) a written commitment and approval by the OSU Board of Trustees for the expansion of the Cancer Program facilities that will more than double the current square footage under control of the OSUCCC Director in the next five years at a cost of approximately $800 million. With these new resource commitments in place, the OSUCCC is poised for continued significant growth and expansion in the next 5 years.

Title: **Cancer Center Support Grant: University of Pittsburgh Cancer Institute**
P.I.: **Nancy E. Davidson**
Institution: **University of Pittsburgh**
Grant No.: **CA047904-23S1**
Award: **$15,000**

This Cancer Center Support Grant application from the University of Pittsburgh Cancer Institute, an NCI-designated Comprehensive Cancer Center, seeks support for years 23-27. The UPCI is organized as a matrix center that integrates cancer research, clinical care, and cancer outreach across the University of Pittsburgh and its affiliated health system, UPMC. The UPCI includes 348 members from 37 academic departments who have come together to work to reduce the burden of cancer through cancer-related basic, translational, clinical, behavioral, epidemiological, prevention and control research. Total annual extramural cancer research funding (direct costs) to UPCI was $109.5 million (peer-reviewed $95M, non-peerreviewed $14.5M) on October 1, 2009 of which $42.5M was received from the National Cancer Institute. The

commitment of UPCI to transdisciplinary cancer research is exemplified by the fact that its members lead three SPORE grants (lung, head and neck, and skin cancers), eight cancer-focused POIs, two Early Detection Research Network grants, and a phase I UOl. The impact of the cancer research driven by UPCI and its members can be seen in the more than 4,400 unique publications by UPCI investigators from 2004-2009 of which 45% represent collaborative efforts (17% intra-programmatic, 20% inter-programmatic, and 8% both). The integration of investigators at the main University of Pittsburgh campus with clinicians from a unique clinical care network encompassing about 40 UPMC community cancer centers across Western Pennsylvania has enabled enhanced patient access to clinical trials throughout our catchment area in a highly productive way. In 2008 a total of 11,484 patients were entered in the cancer registry. During that same year 1,158 and 2,508 patients entered interventional and non-interventional clinical trials, respectively. It is noteworthy that in 2008 30% of accruals to interventional trials were to investigatorinitiated trials and 40% of accruals to interventional trials took place at UPMC community cancer centers. This renewal application requests support for twelve scientific research Programs, fifteen Shared Facilities, Protocol-Specific Research Support, Protocol Review and Monitoring System, planning and evaluation activities, developmental funds, senior leadership, staff investigators, and administration.

Title: **Cancer Center Support Grant: Yale Cancer Center**
P.I.: **Thomas James Lynch**
Institution: **Yale University**
Grant No.: **CA016359-33S1**
Award: **$15,000**

The Yale Cancer Center (YCC) was designated as an NCI Comprehensive Cancer Center in 1974. YCC has elected to profoundly alter its structure to better facilitate clinical translation of its abundant scientific strengths. A particularly important component, taken in consultation with the NCI, was relocation of operational control of Medical Oncology to YCC, to augment Center influence over the Clinical Trials Program. An administrative 3-year extension from the NCI enabled these changes. The new Director, Richard Edelson, an accomplished translational scientist, has led the Center since these pivotal changes were initiated in 2003. Over $68 million of institutional support permitted YCC to enhance facilities and recruit 60 external faculty members, including leaders of 5 of the 8 Research Programs, 6 of the 11 interdisciplinary cancer disease site teams and both the Clinical Research Services Core and Protocol Review Committee. Strategic scientific recruitments include Joseph Schlesinger (pioneer in the design of inhibitors of receptor tyrosine kinases and now Co-Leader of the Signal Transduction Program) and Jeffrey Sklar (a leading innovator in molecular diagnosis of cancer and now Co-Leader of the Gene Regulation and Functional Genomics Program). Preserving continuity by reappointing the Deputy Director, the Director appointed new Associate Directors of Basic and Clinical Sciences. All Research Programs now thematically stress mechanistic themes, and the Clinical Division has been organized around the three main cancer treatment modalities (small molecules/anticancer agents, radiation therapy, and biological/ immunological agents), rather than being confined to single disease sites. Due to these collective YCC structural and functional changes, the number of investigator initiated clinical trials, based on YCC science, have dramatically increased. Construction has begun on a $460M new Clinical Cancer Tower, proximal to the YCC scientific laboratories. The 210 YCC members come from 27 Yale Departments and 4 Schools. Since the last CCSG submission, total peer-reviewed, annual direct costs of cancer-relevant research support increased by 42%, from $43 million to $62 million, inclusive of $15.3 million from the NCI. Integration of the new scientific and clinical investigators has permitted the YCC to target 8 sets of grouped research projects for focused development. Last approved in 1998, YCC continues to satisfy guidelines for Comprehensiveness. Based on the NCI total cost funding base of $25.6 million, YCC is requesting a budget of $3.8 million in total costs.

Title: **Cancer Health Disparities Research Among Appalachian Women**
P.I.: **Michael Caligiuri and Electra Paskett**
Institution: **Ohio State University**
Grant No.: **3-P30-CA-016058-35S1**
Award: **$5,000**

Women in Appalachia Ohio suffer a disproportionate burden of cancer, including higher cancer incidence and mortality rates for cervical, colon, and lung cancer compared to cancer rates for women in Non-Appalachian region of Ohio. The proposed supplement would support a Conference to strengthen the existing community and academic infrastructure to increase community-based participatory research (CBPR) capacity within Appalachia Ohio to address the cancer health disparities among women in Appalachia Ohio. Plans for this proposed Conference have been developed in collaboration with established community partners and identified needs among women in this community. The Conference will consist of two related educational efforts: a Seminar designed to build upon our past efforts to increase knowledge about cancer health disparities among women in Appalachia, and a Workshop to support the development of joint research efforts between academic researchers and community partners to address these disparities. The Seminar will feature presentations about CBPR programs conducted to address cancer in Appalachian women by scientist/academic researchers, as well as evidence-informed interventions conducted by community partners. The agenda for the Workshop will help build academic-community partnerships through interactive sessions on the important components of CBPR and strategies to ensure academic-community partnerships effectively address cancer health disparities and cultural barrier among underserved women in Appalachia Ohio. Collectively, this conference will maximize learning, group interaction and networking among academic researchers at the Ohio State University and established community partners through the Appalachia Community Cancer Network (ACCN) to enhance joint CBPR efforts through academic-community partnerships with a goal of reducing cancer health disparities among women in Appalachia. The proposed conference will strengthen the academic-community infrastructure at the OSUCCC to increase CBPR capacity within Appalachia to address defined cancer health disparities including elevated rates of cervical, colon and lung cancers among women in Appalachia. OSUCCC will plan, implement and evaluate this conference with a clear vision of the needs and values of this community.

Title: **Characterization of Novel Viruses from Human Genitals**
P.I.: **Christopher B. Buck and Diana V. Pastrana**
Institution: **National Cancer Institute Intramural Research and Center for Cancer Research**
Grant No.: **OD-11-302**
Award: **$25,000**

Next-generation sequencing projects characterizing the ribosomal genes of bacterial species have revealed that humans are stably colonized by a staggering diversity of distinct microbial species. Since viruses lack universally conserved gene products, such as ribosomal sequences, comprehensive elucidation of the diversity of the viral constituents of the human "metagenome" has been more challenging. This proposal is aimed at developing a more detailed catalog of viral sequences chronically shed into the human genital tract. By expanding our knowledge of the human genital virome, we hope to gain insight into several diseases. For example, about a dozen known species of human papillomavirus (HPV) are thought to play a role in essentially all cases of cancer of the uterine cervix, as well as roughly 20-60% of vulvar and vaginal cancers. Several known HPV species have also been suggested as possible causal factors underlying a fraction of miscarriages. The fraction of gynecological cancers and miscarriages that are not attributable to known HPVs might theoretically be linked to previously unidentified members of the papillomavirus family or to other unidentified viruses that may commonly inhabit the female genital tract. Our laboratory has previously utilized a method known as rolling circle amplification (RCA) to identify previously unknown HPVs and other viral families that are common

constituents of skin virome of healthy human subjects. This previous work also revealed a wide variety of DNA sequences with little or no homology to any sequences available in GenBank. For the current project, we have obtained genital swab specimens from HIV infected individuals, who might be expected to harbor a higher burden of genital viral flora. Next-generation sequencing of these samples has revealed an overwhelming number of sequence fragments with no clear homologs, as well as sequence fragments with distant homology to known HPV genera. Several intriguing classes of sequence show limited resemblance to viral families that have previously only been found in plants or fungi. These preliminary data warrant continuation of the project, which will involve cloning and sequencing the complete genomes of unidentified new genera of HPVs, as well as full-length sequencing of candidate novel human virus families.

Title: **Comparison of the Impact of Vaccination with Gardasil and Cervarix**
P.I.: **Allan Hildesheim**
Institution: **National Cancer Institute Intramural Research**
Grant No.: **N01-CP11005**
Award: **$50,000**

Two vaccines are currently licensed for the prevention of HPV-infections and their associated cancers—Gardasil and Cervarix. While both vaccines are based on HPV virus-like particles, they differ with respect to the HPV types included in the vaccine, the adjuvant used, and potentially by the ability to protect against infections with HPV types other than those included in the vaccine formulation. Given these differences, it is currently unclear whether the overall impact afforded by use of these two vaccines will be similar or not, and to the extent that they differ by how much. Support from ORWH will be used for analyses aimed at addressing this question.

Title: **Confirmation Studies of Blood-Based Biomarkers of Risk for Breast Cancer**
P.I.: **Samir Hanash**
Institution: **Fred Hutchinson Cancer Center**
Grant No.: **1R21CA161713-01**
Award: **$229,680**

There is a substantial need to identify biomarkers of risk for breast cancer. An in-depth quantitative proteomics approach was applied to the analysis of plasmas that were collected prior to a diagnosis of breast cancer in search for candidate markers of risk for this disease. The samples were obtained from the Women's Health Initiative (WHI) cohort and consisted of women diagnosed with breast cancer within seven years of blood collection and controls matched for age, self-reported ethnicity, hysterectomy status and enrollment date. In parallel studies proteomic profiling was applied to blood specimens obtained at baseline and following one year of hormone therapy (HT) with conjugated equine estrogen (CEE) or CEE/MPA (medroxyprogesterone acetate). Extensive proteomic analyses identified a large subset of circulating proteins that were affected by HRT, and has also yielded a set of breast cancer risk marker candidates that merit additional validation studies. Interestingly some of the risk candidates were also affected by HRT and thus may contribute to elucidation of breast cancer risk associated with CEE/MPA therapy. In aim 1, we propose to conduct a confirmation study of risk markers identified using an independent set of WHI participants from the WHI hormone therapy trials who developed breast cancer and matched controls. Of the 14 candidates to be subjected to confirmation studies, eight have ELISAs available that would allow their assay. The remainder of the candidates would be subjected to confirmation using Multiple Reaction Monitoring mass spectrometry. A second aim consists of evaluating the identified risk markers as mediators of hormone therapy effects on breast cancer. To that effect plasmas collected at baseline and at 1-year of HT in the CEE and CEE/MPA trials will be utilized to determine changes in concentration of risk marker candidates in cases and in matched controls. The proposed project has the potential to contribute clinically relevant breast cancer biomarkers to identify women at increased risk and to clarify breast cancer

risk associated with postmenopausal hormone therapy. PUBLIC HEALTH RELEVANCE: There is a substantial need to identify women at increased risk for developing breast cancer. Prior studies by the applicants using in-depth quantitative technology to profile circulating proteins in the blood for potential risk markers have identified many potential markers of risk among post-menopausal women that subsequently developed breast cancer. These novel candidate risk markers for breast cancer require additional studies for their verification. The objectives of this proposal to do additional verification studies of the candidate biomarkers in an independent set of women from the Women's Health Initiative and to determine the relevance of these markers as mediators of the risk for breast cancer associated with post-menopausal hormone therapy.

Title: **Decisional Aid Intervention for Women Considering Breast Reconstruction**
P.I.: **Sharon L. Manne**
Institution: **University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School**
Grant No.: **CA149531-01A1**
Award: **$200,000**

The decision whether to pursue breast reconstruction (BR) can be challenging. Women must weigh the importance of potential benefits of the procedure and their personal values and preferences against the risks associated with the procedure and decide what type of reconstruction to have should they pursue it. The decision is typically made in a stressful circumstance, which is immediately after the initial diagnosis of breast cancer. Complicating matters is the fact that there is evidence to suggest that there are variable rates of satisfaction with the cosmetic outcomes of BR. Outcomes may not be in line with what the patient initially expected. BR can be a difficult decision made under stressful circumstances and women may not be as well-informed about the long-term effects as they could be. When patients are faced with treatment decisions for which personal values and quality of life issue play a role and there are multiple treatment choices, decision support in the form of decision aids can be helpful to the process of making a well-informed choice. Decision support aids are a strategy used as an adjunct to practitioners' counseling to facilitate their understanding of the treatment options, the advantages and disadvantages of each option, consideration of the personal importance they attach to the benefits and risks of each alternative, and to encourage active participation with the care provider in deciding which option to pursue. We propose to develop a web-based DA for women being offered BR. We will accomplish this in three phases. Phase 1 is a developmental phase where the basic DA content is developed by the study team with input from patients who have undergone BR, were offered BR and decided against it, or are considering BR. We will include input from minority women, women over 65 years of age, and less educated women, who have less access to BR. Phase 2 consists of gathering feedback terms on the DA prototype from women who have undergone BR, women who were offered BR and chose not to have it, and women who are considering BR. Again, feedback from minority women, women over 65 years of age, and less educated women will be included. The BR Decision Aid (BRDA) will then be finalized. Phase 3 will be a usability and feasibility pilot test of the DA with a sample of women considering BR. The study has one primary aim and two secondary aims. The primary aim is to evaluate the usability and feasibility of a decisional aid to assist women with making the decision to undergo BR. The secondary aims are to examine the acceptability of the BRDA and to provide preliminary data on the impact of BRDA on BR knowledge, values, decisional conflict, preparedness, BR interest, and anxiety.

Title: **Disruption of Ceramide Synthesis by CerS2 Depletion as a Tool to Increase Breast Cancer Sensitivity to Taxane Therapy**
P.I.: **Stefka D. Spassieva and Lina M. Obeid**
Institution: **Medical University of South Carolina**
Grant No.: **3-P30-CA-138313-03S1**
Award: **$15,000**

Paclitaxel is widely used for breast cancer treatment, but the success of the chemotherapy can be hindered by patients not responding or developing resistance; therefore, it is important to discover new strategies to increase sensitivity or to overcome the resistance to taxane therapy, which will improve the chances of breast cancer patients to become diseases-free. With our pilot project proposal, we address the possibility of developing such a new strategy by investigating breast cancer sensitization and resistance to paclitaxel in the context of the ceramide pathway. The potential of the ceramide pathway to sensitize to paclitaxel treatment was recently shown in a functional genomics screen. In that screen, several members of ceramide pathway are shown to alter the response of chemotherapy resistant cancer cell lines (including a breast cancer cell line) to paclitaxel treatment. Of particular interest for our current study is one member of the ceramide pathway, ceramide synthase 2 (CerS2), which when down-regulated by siRNA was shown to increase the sensitivity of cancer cells to paclitaxel. Moreover, our recent study showed that depletion of CerS2 resulted in alteration of ceramide metabolism, activation of the Unfolded Protein Response (UPR), and induction of autophagy. In addition to the findings from our laboratory, the functional genomics screen showed that paclitaxel treatment of cancer cells can activated the UPR as well. Moreover, a very recent study found that the elevation of 78-kDaglucose-regulated protein (GRP78), an UPR marker, can serve as a predictor for the effectiveness of the taxane treatment in breast cancer patients. Accordingly, our working hypothesis is that aberrant ceramide synthesis in CerS2 depleted breast cancer cells disrupts ER homeostasis, which when combined with paclitaxel treatment, enhances ER stress and leads to cell death.

Title: **Efficacy of HPV-16/18 Vaccine Against Oral HPV Infections**
P.I.: **Aimee Kreimer**
Institution: **National Cancer Institute Intramural Research**
Grant No.: **N01-CP11005**
Award: **$50,000**

With support from ORWH, we previously expanded specimen collection in our Costa Rica trial to permit the evaluation of vaccine efficacy at sites other than the cervix. It is now known that HPV causes a subset of H&N cancers, cancers of the oropharynx in particular. Given this, we are now in the process of evaluating efficacy of the vaccine to protect against HPV infections in the oral cavity. Testing of oral specimens for HPV DNA using sensitive methods is ongoing and expected to be completed in FY11. Once testing is completed, data preparation and analysis will follow. ORWH support could be used to support the analytical efforts associated with this evaluation.

Title: **Estrogen and Skin Cancer**
P.I.: **Tatiana M. Oberyszyn**
Institution: **Ohio State University**
Grant No.: **5R21CA135570-02**
Award: **$160,869**

Americans live in a culture that glorifies youth. According to market researcher FIND/SVP, the anti-aging products market is expected to hit $56 billion by 2007. Studies in post-menopausal women have found that hormone replacement therapy is effective at reversing the dryness and wrinkling that affects aging skin. Based on these studies, there is increasing interest in the use of topical creams containing hormones such as estrogen to prevent or reverse some of the

normal cutaneous aging processes in younger pre-menopausal women. While exposure to these creams may be beneficial cosmetically, the effect of applying estrogen to sun exposed sites for prolonged periods of time, on skin cancer development is not known. Our preliminary studies using female Skh-1 hairless mice found a significant increase in the number of tumors in mice treated topically with estrogen immediately following UVB exposure compared to mice treated with vehicle control. These data indicate that increased levels of estrogen in the skin combined with UV exposure may act to enhance initiation and promotion of UV-induced skin cancers. These findings also suggest that the use of lotions and creams containing estrogenic compounds on sun exposed sites by younger women may be contributing to the increase in the number of skin tumors being diagnosed in women under the age of 40. Most studies have examined the effects of topical or systemic estrogen on the skin in post-menopausal women; however, the reality is that younger pre-menopausal women are applying topical estrogen containing creams on their faces previously exposed to UV light to prevent/reverse the signs of aging. Two specific aims are proposed to test the hypothesis that topical estrogen application to previously UVB exposed skin accelerates skin carcinogenesis. Studies in specific aim 1 will use the Skh-1 hairless mouse murine model of UVB induced skin carcinogenesis to determine the effects of clinically used topically applied estrogen (Estrogel$^{(R)}$) on UVB induced skin tumor development in previously UVB exposed female skin of intact (pre-menopausal) and ovariectomized (post-menopausal) mice. Studies in specific aim 2 will determine the effects of topically applied estrogen (Estrogel(R)) on UVB induced skin tumor progression in female Skh-1 skin of intact and ovariectomized mice. The studies carried out in these aims will determine whether topical estrogen increases the number of UVB induced skin tumors that develop and also whether it differentially enhances the progression of benign UVB-induced tumors to malignant squamous cell carcinomas in intact (pre-menopausal) and ovariectomized (post-menopausal) mice. PUBLIC HEALTH RELEVANCE: There is an increase societal pressure in the US to remain young looking. Several studies carried out in post-menopausal women demonstrate the effectiveness of topical estrogen in reversing the signs of aging including thinning, dryness and wrinkling. As a result younger pre- and peri-menopausal women are turning to topical creams containing estrogen as anti-aging lotions. Our preliminary studies using female Skh-1 hairless mice found a significant increase in the number of tumors in mice treated topically with estrogen immediately following UVB exposure compared to mice treated with vehicle control. These data indicate that increased levels of estrogen in the skin combined with UV exposure may act to enhance initiation and promotion of UV-induced skin cancers. These findings also suggest that the use of lotions and creams containing estrogenic compounds on sun exposed sites by younger women may be contributing to the increase in the number of skin tumors being diagnosed in women under the age of 40. The current studies are designed to determine the effect of topical estrogen treatment of previously UVB exposed skin on tumor development and progression from benign lesions to frank malignant squamous cell carcinomas.

Title: **Gallbladder Cancer Pilot Study**
P.I.: **Ann Hsing and Jill Koshiol**
Institution: **National Cancer Institute Intramural Research**
Grant No.: **N01-CP11005**
Award: **$150,000**

Gallbladder cancer is one of the few non-gynecological tumors known to occur with higher frequency in women than in men. The highest rates of this cancer (particularly in women) are observed in Chile. Investigators in the Infections and Immuno-epidemiology Branch (IIB) are evaluating the feasibility of conducting a case-control study of gallbladder cancer in Chile to better understand the causes of this disease. As currently envisioned, the initial pilot effort will define whether such a study would be successful at identifying and enrolling cancer cases, controls with gallstones (an important precursor for this cancer) and controls form the general population. We are working with well established investigators in the region with a proven track

record of conducting epidemiological investigations to maximize the likelihood of success. A case-control study of gallbladder cancer in Chile would permit us to elucidate the role of obesity (and metabolic syndrome more generally), diet, infections, immunological responses, and genetic susceptibility factors in the etiology of this tumor. This study could have important public health implications, since cholecystectomies are currently being recommended for women for the prophylaxis of gallbladder cancer in this high risk area. A better understanding of the causes of this disease could lead to the development of better and less aggressive preventative measures against this disease.

Title: **Immune Markers of Protection by HPV Vaccination**
P.I.: **M. Safaeian and A. Hildesheim**
Institution: **National Cancer Institute Intramural Research**
Grant No.: **N01-CP11005**
Award: **$100,000**

One of the stated aims of the publically-funded HPV vaccine trial in Costa Rica is to investigate potential immunological markers and mechanisms of protection by the HPV vaccine that might assist in the identification of minimal levels required for protection and also assist in the generation of second generation and/or other vaccines in the future. At the HPV Immunology Laboratory affiliated with our group, we have developed assays to help monitor vaccine immune responses after vaccination in our cohort. Support from ORWH will help activities at the laboratory to evaluate immune responses and to evaluate markers of protection against both homologous and non-homologous HPV types. It will also assist in our immunological follow-up of individuals receiving different numbers of doses, to further understand our recent finding that vaccine efficacy is observed when fewer than three doses are administered.

Title: **The Influence of Gender on the Relationship Between Mental Health and Smoking**
P.I.: **Cristine D. Delnevo**
Institution: **University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School**
Grant No.: **3-P30-CA-072720-13S9**
Award: **$15,000**

Individuals with past-month mental health problems are approximately twice as likely to smoke as other persons and suffer a greater burden from tobacco-related morbidity and mortality, including cancer. In addition, women are overrepresented among smokers with poor mental health and preliminary data from our research team suggests that relationship between smoking and poor mental health may differ by gender. We propose analyses of three public health surveillance data systems to explore the issue of smoking and mental health by gender. The Behavioral Risk Factor Surveillance System (BRFSS), the National Survey on Drug Use and Health (NSDUH), and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) all address both tobacco use and mental health. Accordingly, we will conduct secondary data analyses to achieve these specific aims: 1) document the prevalence and demographic correlates of tobacco use and nicotine dependence among individuals with poor mental health and 2) evaluate whether there is an interaction effect by gender for smoking and poor mental health. We hypothesize that women with mental health problems, particularly certain psychiatric disorders, will be at higher risk for current smoking and nicotine dependence than men. More research is needed to examine gender disparities in the context of mental health and smoking. Thus, the significance of this proposed research is its potential to generate a better understanding of smoking and mental health by gender to inform and direct tobacco control efforts which are vital to reducing tobacco-caused cancers in women.

Title: **National Health and Nutrition Examination Survey (NHANES): Survey of Physical Activity Measures**
Institution: **In partnership with the National Cancer Institute**
Award: **$170,000**

The importance of the NHANES physical activity, sleep, and strength data have been repeatedly highlighted recently. The First Lady continues to promote her Lets Move! campaign. HHS provided support for the NHANES Youth Fitness Study, which will explore the feasibility of expanding and extending measures of physical activity and fitness down to age 3 years. The National Collaborative on Childhood Obesity Research has received tremendous response to the release of the Measures Registry and Catalogue of Surveillance Systems. The Strategic Plan for NIH Obesity Research notes the need for research to explore how complex behaviors, such as sleep, patterns of sedentary behavior, and exercise can influence eating behavior, energy balance, and metabolic health. The NHANES data will support exploration of these and other research questions.

The value of the NHANES accelerometer data to the extramural research community is evident, judging by the more than 35 (and increasing) publications resulting from the 2003-2006 data in just over 3 years. A presentation on the NHANES accelerometer data at the American College of Sports Medicine this month attracted a large audience and generated many appreciative comments from researchers.

NCHS has provided us with status reports that summarize some aspects of the current data collection, and the results are very exciting. As valuable and appreciated as the 2003-2006 accelerometer data have been, the current data collection promises to be even better, providing rich and very complete data on physical activity and sleep, as well as body strength.

Physical Activity and Sleep:

The plots below are based on data from the first 678 participants in the Physical Activity and Sleep component. Earlier data from the first 458 participants showed that component participation rates were about 96%, with about 1/3 of those who did not participate missing the component because they were late or left early (i.e., they missed because of lack of time, not refusal). The plots show:

- Wear compliance is very high. The protocol requests wear for 24 h/d for 7 days. The 25th percentile of mean wear time per day is about 20 hours and the median is about 22 hours.
- Compliance is much higher than in the 2003-2006 cycles (note that only wear during wake time was requested then). In 2003-2004, the proportion of participants meeting the criterion of 10 h wear/d on 6 or more days ranged from about 40% (for younger ages) to 70% (for older adults). Currently, nearly 70% to more than 80% of participants of all ages are providing 6 or more days with at least 18 h wear/d.

Title: **Natural History and Clinical Implications of Anal HPV Infections**
P.I.: **Aimee Kreimer**
Institution: **National Cancer Institute Intramural Research**
Grant No.: **N01-CP11005**
Award: **$200,000**

HPV is known to be involved in the development of the majority of anal cancers. Anal cancers are more common in women than in men, and are increasing in the United States. We previously noted that anal HPV infection is common (about 30%) among young adult women in our population in Costa Rica. Understanding of the natural history of anal HPV infections and the clinical significance of anal HPV positivity is limited. In particular, information on rates of persistent HPV given infection and the clinical implications of these persistent infections and any associated lesions is lacking. We have the opportunity to evaluate these issues within our cohort of women in Costa Rica. ORWH support could be used for activities associated with the follow-up and testing of women in our cohort previously found to have an HPV infection.

Title: **Nuclear Pore Complex Architecture and Drug Resistance in Ovarian Carcinomas**
P.I.: **Donald Stave Kohtz**
Institution: **Mount Sinai School of Medicine**
Grant No.: **CA141318-02**
Award: **$82,208**

While ovarian carcinomas initially respond well to treatment with platinum drugs, the majority relapse and acquire resistance. In ovarian carcinomas, we have observed reductions of NUP62 in resected tumor tissue from ovarian carcinomas, and redistribution of NUP62 among subnuclear fields of nuclear pore complexes (NPCs). Further, enrichment of NUP62-depleted NPCs renders ovarian carcinoma cells resistant to cisplatin in culture. The studies suggest the hypothesis that survival advantages conferred by the enrichment of NUP62- and/or NUP214+ NPCs may be exploited by tumor cells. To advance this hypothesis, we propose: 1) To investigate alterations in the accumulation and distribution of NUP62 and NUP214 in ovarian carcinomas, and to decipher how these factors correspond to tumor parameters; and, to investigate how changes in expression or accumulation of either NUP62 or NUP214 influences distribution of the other nucleoporin among NPCs. 2) To investigate how knockdown of NUP62 confers resistance to cisplatin; specifically, to decipher how altering the distribution and prevelance of NUP62+/NUP214- and NUP62-/NUP214+ NPC populations influence survival signaling through NF-:B signaling pathways. The proposed studies impact the basic biology of epigenetic regulation and may also illuminate a new approach to improving the prognosis of ovarian carcinomas treated with platinum drugs. As the patterning and architecture of NPC populations influences the sensitivity of ovarian carcinoma cells to cisplatin, small molecules may be developed that modify NPC architecture to enhance its therapeutic effectiveness. These agents may be employed to reduce the number of cells that survive and/or become latent in response to therapy, and also to chemosensitize relapsed tumors that have acquired platinum resistance.

Title: **Pilot Study of Somatic Mutations and Gene Fusions in Ovarian Cancer**
P.I.: **Adrian V. Lee, Aleksandar Milosavljevic, and Xiaosong Wang**
Institution: **University of Pittsburgh**
Grant No.: **3-P30-CA-047904-23S1**
Award: **$15,000**

Ovarian cancer is the largest cause of death from female reproductive tract cancers. In 2010, there were an estimated 21,880 new cases and 13,850 deaths. The high rate of mortality from ovarian cancer is in part due to diagnosis at an advanced stage. Indeed, up to 70% of ovarian cancers have metastasized at diagnosis, and only 30% of women with this diagnosis can expect to live 5 years. In stark contrast, 20% of ovarian cancer is detected at an early stage (and within the ovary) resulting in an excellent 90% survival rate (2). While the last 30 years has seen dramatic reductions in mortality rates from several cancers (e.g. a 30% reduction in breast cancer mortality), the mortality rate from ovarian cancer has seen only a modest improvement. We propose a pilot analysis of ovarian cancer data publicly available from the Cancer Genome Atlas to: 1) Identify novel fusion genes which might serve as novel diagnostic, prognostic, and therapeutic targets, and 2) identify patterns of somatic mutations which may highlight novel pathways for therapy. This pilot project will involve a unique collaboration between investigators in the newly developed Women's Cancer Research Center (a collaboration between the University of Pittsburgh Cancer Institute (UPCI) and the Magee Women's Research Institute), and bioinformaticians in the Dan L Duncan Cancer Center at Baylor College of Medicine. TCGA is a rapidly providing an outstanding wealth of information on molecular alterations in many cancers (*http://cancergenome.nih.gov*). However, similar to most other studies, this information (data) needs translation into knowledge, particularly the clinical relevance of the identified changes. The ovarian cancer dataset at TCGA is one of the most mature (*http://tcga-data.nci.nih.gov/tcga*). 587 matched and tumor tissues have been analyzed. Assays have included expression arrays (mRNA and miRNA), DNA copy number and SNP arrays,

methylation marks, and massively parallel sequencing. UPCI is a major contributor to TCGA. For ovarian cancer, UPCI provided approximately 120 matched normal and tumor tissue, and about 62 passed QC and are in the final dataset. Our goal is to perform an initial pilot analysis of molecular changes in the ovarian cancers and validate them in the index cases we have here at UCPI. Validated somatic alterations will then be examined in larger data sets and correlated with clinical features and outcomes.

Title: **Regulatory T Cell Function in Ovarian Cancer**
P.I.: **Kirsten B. Moysich**
Institution: **Roswell Park Cancer Institute Corp.**
Grant No.: **CA126841-03**
Award: **$15,000**

Etiologic and prognostic factors in ovarian cancer remain poorly understood, although emerging evidence suggests that factors related to immune response play important roles in the development and clinical treatment of this disease. Recent evidence has revealed that a subset of T cells with immunosuppressive properties, referred to as regulatory T cells (Treg), are essential for the development and maintenance of self-tolerance. There is a very consistent body of literature that points to an important role of these Treg cells in human health. These studies have shown that lower peripheral Treg cells expression is associated with autoimmune disease, allergy, and adverse transplantation outcomes, indicating that insufficient Treg cell stimulated immune suppression might lead to the development of these auto reactive health conditions. On the other hand, elevated Treg cell expression has been consistently reported in patients with a wide variety of malignancies, suggesting that Treg cell-mediated suppression might interfere with an adequate immune response to tumor associated antigens. Our group and others also provided direct evidence linking elevated Treg cell expression to greater risk of ovarian cancer and poorer prognosis. Thus, the role of Treg cells in cancer etiology and prognosis is an area of emerging interest, as high Treg activity might a) prevent an adequate immune response at the time of cancer initiation and progression, b) prevent an adequate immune response after initial treatment of the tumor; and c) result in lower responsiveness to tumor immunotherapy. To date, we are unaware of any comprehensive epidemiological study that has focused on the role Treg cells in human cancer in general or ovarian carcinogenesis in particular. Thus, we propose to evaluate the role of Treg cell burden as well as a panel of candidate genetic polymorphisms, directly relevant to Treg cell activity, in the etiology and prognosis of ovarian cancer. We hypothesize in Aim 1 that women with ovarian cancer will have higher blood Treg cell levels than healthy controls. We also expect in Aim 2 that women with a genetically determined high activity Treg cell profile will be less effective in mounting an immune response toward tumor cells in the initiation and progression phase of ovarian carcinogenesis. We further hypothesize in Aim 3 that ovarian cancer patients with a genetically determined high activity Treg cell profile will be less effective in battling residual disease. We also seek to determine in Aim 4 if genetic variability in Treg cell function can predict Treg cell expression in ovarian tumors. We propose to utilize data and specimens from core resources at our institute and from a population-based case-control study of ovarian cancer. For Aim 1, we will newly recruit 100 ovarian cancer patients and 100 controls via our institute's Biorepository to collect fresh blood samples required for Treg cell measurements. In the case-control study we recently recruited over 900 ovarian cancer patients and 1800 community controls (Specific Aim 2) from the Buffalo, NY, Pittsburgh PA, and Cleveland, OH areas. We propose to follow-up the ovarian cancer patient group and assess relevant clinical outcomes (recurrence, survival; Specific Aim 3). We will also select 630 patients with advanced stage disease with available blood and tumor samples from our institute's Ovarian Cancer Specimen Bank (Specific Aim 4). For the laboratory analyses, we will utilize Illumina Golden Gate assays and flow-cytometry techniques for the genotype and Treg cell assessment, respectively. Our statistical and genetic analyses will be carried out by a trained geneti epidemiologist.

Title: **Role of the Fractalkine Signaling in Epithelial Ovarian Carcinoma (EOC)**
P.I.: **Maria V. Barbolina**
Institution: **University of Illinois at Chicago**
Grant No.: **1R21CA160917-01**
Award: **$202,968**

Epithelial ovarian carcinoma (EOC) is a leading cause of death from gynecologic malignancies. Peritoneal metastasis is an unsolved clinical problem in treatment of EOC. Currently used therapeutic approaches are not specific to EOC metastasis and are inefficient at keeping patients in remission. Thus, targeting the pro-metastatic pathways could provide improved opportunities to increase survival. In our approach to find new targets we searched among pathways that satisfy the following criteria: 1) play a major role in EOC progression; 2) have proven to be effective targets for treatments of other diseases. Chemokine signaling is essential for cancer cell migration, proliferation, adhesion, and invasion, i.e., properties that are necessary for a successful development of metastasis. In this application we will characterize fractalkine pathway as crucial for the development of metastasis in EOC and determine potential usefulness of its main players, chemokine fractalkine (CX3CL1) and its receptor, fractalkine CX3CR1, as novel targets for future therapies aimed at prevention and retardation of metastatic spread. Our preliminary data show that primary and metastatic specimens of human EOC are highly positive for CX3CR1, while normal ovarian surface epithelium in non-diseased control subjects is CX3CR1-negative. Moreover, we show that EOC cells can migrate in CX3CR1-dependent manner to CX3CL1. Furthermore, in our pilot experiments increase of CX3CR1 expression in EOC cells led to formation of more tumors of larger size in a xenograft EOC mouse model. Chemokines are promising drug targets. Moreover, chemokine receptors are the G protein coupled receptors, a class of proteins that are effective drug targets covering an estimated 30% of FDA approved drugs. Such drugs have been proven to work in the clinic, and new drugs against CX3CL1 and CX3CR1 are currently under development. CX3CL1/CX3CR1 is a uniquely suitable drug target because the interaction between the chemokine and its receptor is very specific, and there are no other chemokine ligands activating CX3CR1, in contrast to other chemokine/receptor pairs that display high cross-reactivity. Thus, drugs directed at either CX3CR1 or CX3CL1 will likely to affect only the CX3CL1/CX3CR1 axis. Based on our preliminary data and published literature our hypothesis is that CX3CL1/CX3CR1 axis is required for homing metastatic EOC cells to the peritoneum and facilitation of metastatic spread by supporting cell adhesion and migration. To test this hypothesis we propose two aims. In Aim 1 we will determine the requirement of CX3CL1/CX3CR1 in adhesion to peritoneal mesothelial cells and underlying extracellular matrix using cell culture models and previously developed by us EOC metastasis-specific culture conditions. Adhesion is one of the main initial steps of the metastatic colonization of the peritoneum. In Aim 2 we will characterize the requirement for CX3CL1/CX3CR1 in development of EOC metastasis in vivo using a xenograft mouse model. PUBLIC HEALTH RELEVANCE: Epithelial ovarian carcinoma is the deadliest gynecologic malignancy mainly due to metastasis and is an unsolved problem in public health. In this proposal we will characterize the requirement for chemokine signaling in progression of ovarian carcinoma, because 1) according to our preliminary data it could play a major role in all stages of the ovarian carcinoma metastatic cascade, and 2) chemokines and their receptors are effective drug targets proven to work in the clinic in treatments of other diseases.

Title: **Single Nucleotide Polymorphisms (SNPs) in the Anti-inflammatory Cortisol Pathway and the Risk of Ovarian Cancer**
P.I.: **Kirsten Moysich**
Institution: **Roswell Park Cancer Institute Corp**
Grant No.: **5-R01-CA-126841-03**
Award: **$15,000**

Ovarian cancer remains the most lethal gynecological cancer, due to the fact that the majority of patients present with advanced disease at diagnosis. The established risk factors such as parity,

use of oral contraceptive (OC) pills, use of NSAIDS, and talc exposure, suggest a role of ovulation and inflammation in the etiology of ovarian cancer. More than 90% ovarian tumors arise from the surface epithelium[1] lined by a single layer of squamous to cuboidal cells covering the entire ovarian surface[2]. This epithelium is breached during each ovulation leading to an inflammatory reaction [3-4]. Persistence of inflammation associated with ovulation can cause genetic damage and trigger carcinogenesis. Cortisol, a major anti-inflammatory steroid plays a significant role in attenuating inflammation, thereby reducing the risk of ovarian carcinogenesis. Levels of cortisol in the ovarian epithelium rise significantly prior to ovulation. Ovarian tumor cells have significantly reduced expression of genes in the cortisol pathway compared to those in normal ovarian epithelial cells [5]. We, therefore, hypothesize that single nucleotide polymorphisms (SNPs) in genes involved in the cortisol pathway are associated with the risk of ovarian cancer due to potential variation in anti-inflammatory cortisol response. SNPs in these candidate genes have not been adequately captured in a recent GWAS of ovarian cancer. Thus a thorough investigation of genetic variability in this highly biologically plausible pathway is warranted. We propose to utilize data and samples from an existing study of 800 incident epithelial ovarian cancer cases and 800 population-based controls recruited in Pennsylvania, Ohio, and New York between 2003 and 2008. Our first aim is to evaluate the association of SNPs in the cortisol pathway and the risk of ovarian cancer. We will identify functional and tag SNPs using public databases (Hapmap, Genome Variation Server, dbSNP). Logistic regression models will be used to estimate the associations between these SNPs and risk of ovarian cancer. Our second aim is to evaluate the association of SNPs in the cortisol pathway with the severity of disease (grade and stage of ovarian cancer) at diagnosis. Finally, in our exploratory aim, we propose to conduct a preliminary analysis on a subset of patients to evaluate the associations of SNPs in the cortisol pathway and disease-free and overall survival. We have substantial follow-up time (at least five years) on a large subset of the study sample. We will use Cox proportional hazards ratios and Kaplan-Meier survival probabilities to analyze the data. Dr. Moysich maintains active national and international collaborations with ovarian cancer researchers and will have access to a number of study samples for replicating significant genetic associations. The results of this study will provide a valuable insight into the etiology of ovarian cancer by uncovering an important anti-inflammatory pathway. It could also potentially help to direct therapeutic research and develop strategies to screen high risk women for prognosis.

Title: **Stress, Immunity, and Cervical Cancer: Biobehavioral Outcomes of a Randomized Trial**
P.I.: **Lari Wenzel**
Institution: **University of California, Irvine**
Grant No.: **CA118136-05S2**
Award: **$15,000**

The incidence and mortality rates for invasive cervical cancer in minority, low-income, and less educated women exceeds that for white, higher income, and better educated women. In southern California the incidence and mortality rates for cervical cancer are nearly twice that of non-Latina white women. Our preliminary work supports and extends the extant literature, noting that quality of life can be significantly disrupted among cervical cancer survivors, with qualitative differences in how Latina women experience cancer survivorship. However, there is a paucity of literature on interventions designed to assist cervical cancer survivors manage illness-specific stress and improve health behaviors. Our preliminary NCI-funded study provides strong data indicating that a six session psychosocial telephone counseling (PTC) intervention can improve QOL, with accompanying intervention-induced neuroendocrine and immune parameter modulations which may be related to disease endpoints. Specifically, we demonstrated a significant association between the improvement in QOL elicited by PTC and a shift to a more pronounced Th1 immunologic stance. In primary support of these significant biobehavioral findings, the project herein proposes to accomplish the following Specific Aims: 1) Test the

efficacy of PTC for cervical cancer survivors, compared to usual care. 2) Evaluate the longitudinal immune and neuroendocrine parameters in cervical cancer patients who have received PTC, compared to usual care. 3) Examine the longitudinal relationship between PTC associated modulations of QOL measures and biologic parameters (immune and neuroendocrine). To achieve these aims we will randomize patients ascertained through the two SEER cancer registries to PTC (N=125) or usual care (N=125), stratifying on English or Spanish language preference. Assessments will occur at baseline (9-20 months post diagnosis), and three and nine months post enrollment/baseline. Assessments will include evaluation of QOL (overall QOL, psychological distress, coping, social support, sexual functioning), health behaviors, neuroendocrine parameters (DHEA-S, cortisol, GH) and immunologic parameters (NK cell activity, IL-5, interferon, HPV E6/E7 peptides, IL-15, IL 10). This project has significant public health relevance for an important unstudied cancer survivor population, many of whom are poor and underserved. If effective, an intervention which could improve quality of life (QOL) and health behaviors, and enhance neuroendocrine and immune responses for women with cervical cancer could have significant implications toward disease recurrence or survival.

Title: **Survivorship Care Planning and Communication for Rural Breast Cancer Survivors**
P.I.: **Ann M. Geiger**
Institution: **Wake Forest University Health Sciences**
Grant No.: **CA155932-01A1**
Award: **$160,950**

The Institute of Medicine and others have strongly recommended survivors exiting active treatment receive a comprehensive survivorship care plan addressing surveillance, late effects symptoms, psychosocial needs, and general health maintenance, as well as indicating which providers will handle which components of the plan. Despite this recommendation, survivorship care planning and communication are often inadequate, leaving survivors confused and uncertain about their care. In addition, little is known about communication-related barriers to survivorship care, which may be of particular concern for rural-residing survivors who often live at some distance from their oncology specialist(s) and have limited primary care access. To reduce confusion and uncertainty, and to avoid duplication of medical effort, we envision a formal planning and communication process that integrates patient preferences with recommendations from multiple providers to generate a comprehensive survivorship care plan. [We believe effective implementation of this process requires a clinically-oriented individual like a nurse, nurse practitioner, physician assistant, or physician to facilitate and coordinate communications between survivors and their primary care and oncology specialty providers.] Our goal is to generate information needed to create and evaluate a process designed specifically to accommodate the needs of rural-residing survivors while also meeting the needs of suburban and urban survivors. Thus we aim to: (1) describe breast cancer survivors' knowledge about, perceived importance of, and barriers to survivorship care planning and communication; (2) assess survivors' current and preferred communication with oncology specialists and primary care providers about their survivorship care plans; and (3) explore the relationship between current survivor and provider survivorship care planning and communication with survivors' cancer-related uncertainty and quality of life. All data will be collected via a survey relying heavily on questions drawn from previously validated instruments and administered via hard copy mail, on-line or telephone interview. Our analytic approach will include descriptive statistics, correlation, and regression modeling. Both this proposal and the resulting testable intervention of a clinical model of survivorship care planning and communication will substantially advance our understanding of cancer survivorship care, particularly for rural-residing breast cancer survivors.

Title: **Symposium: Opportunities and Changes in Cancer Research Among Women in Developing Countries**
P.I.: **Bu-Tian Ji and Wong Ho Chow**
Institution: **National Cancer Institute Intramural Research, Division of Cancer Epidemiology and Genetics**
Grant No.: **OD-11-302**
Award: **$5,000**

Studies of cancer risks and survival in different populations with diverse exposures, cancer surveillance and care, and varying incidence and mortality patterns broaden the opportunities for discoveries of cancer causes and prognostic factors. With rapid changes in economic conditions and industrial development in Asia, particularly in countries such as China, South Korea, and Japan, lifestyle and environmental exposures in this region have also undergone substantial changes over the past few decades. These changes are reflected in the cancer incidence patterns of these countries. For instance, in Shanghai, China, incidence rates of cancers that are traditionally high in developing countries, such as esophageal squamous cell carcinoma, and cancers of the stomach and liver, have declined precipitously over the past few decades. In contrast, cancers of the colon and breast have increased substantially. In fact, among women under age 50 years, breast cancer is the most rapidly rising malignancy in Shanghai. Similar cancer incidence patterns are being reported in other areas of Asia. Changes in lifestyle such as fewer number of children and later age at first child birth, decreased physical activity both at work and at home, and increasing intake of meat, fat, and processed foods are believed to have contributed to the upward trends of colon cancer and breast cancer among women in Shanghai and some other areas in Asia. Likewise, the relatively high and perhaps worsening air pollution in many Chinese cities have kept the lung cancer incidence rates relatively high among women in these areas, despite an extremely low rate (<5%) of cigarette smoking among Chinese women. Occupational exposure to industrial agents also tends to be higher than similar industries in the United States. Furthermore, almost all women have held jobs outside the home, with the majority being employed in blue collar jobs with greater chance for exposure to industrial carcinogens. The changing environment and cancer occurrence in Asia provide an unparalleled opportunity for collaborative research into cancer causes and gene-environment interaction in cancer development. Since the early 1980s, the pioneering efforts of several investigators in DCEG and other NCI Divisions have led to many fruitful collaborations in China. With more rapid changes in recent years in China and other parts of Asia, there are enhanced opportunities for further collaboration. The purpose of the proposed workshop is to review current status of collaborative cancer research, to discuss research ideas and identify new opportunities for research, and to plan future collaborative research directions. The proposed workshop will invite investigators from the U.S., China, and other Asian countries who have conducted collaborative research in Asia to share their research results, with the goal of identifying gaps and opportunities for further collaboration. The proposed location for this one-day workshop is Shanghai, China, in order to minimize travel by most invited investigators from Asia. The workshop is tentatively planned for June 28, 2011, and will be opened to local academic participants. The workshop is to be jointly sponsored by the NCI and the Shanghai Cancer Institute. The requested funding from the Office of Science Planning and Assessment will support meeting arrangements (i.e., meeting site, technical support, and refreshments) and travel for a limited number of invitees from Asia. A summary report and abstract of presentations will be delivered after the workshop. However, the ultimate achievement will be the continuing dialogue and new research collaborations among some meeting participants.

Title: **Testing the Feasibility of a Nurse Patient Navigation Intervention in Lung Cancer**
P.I.: **Ruth McCorkle**
Institution: **Yale University**
Grant No.: **3-P30-CA-016359-33S1**
Award: **$20,000**

This single blind, randomized clinical trial is designed to 1) describe the feasibility of implementing a Nurse Patient Navigation (NPN) intervention that addresses patient and caregiver questions, symptoms, psychosocial needs, and facilitates timely, coordinated care, and 2) compare the impact of the NPN Intervention with an attention control group at Smilow Cancer Hospital with newly diagnosed advanced lung cancer patients on quality of life outcomes, utilization of health care services, and perceptions of care transitions. Thirty-two women newly diagnosed with advanced lung cancer will be randomized to either the NPN intervention or attention control groups. The 14 contact NPN intervention includes provision of information, problem-solving strategies, coordination of care, and support for patients that will enhance their QOL and increase their perception of care transition. Outcome data will be collected on patient quality of life outcomes, health care utilization, and care transition at baseline, 1, and 3months post diagnosis. The primary goal of this application is to assess the feasibility of implementing a Nurse Patient Navigation (NPN) intervention for newly diagnosed advanced lung cancer patients. The intervention will be implemented and evaluated with women undergoing diagnostic and staging procedures, including surgery, at Smilow Cancer Hospital (SCH).

Title: **Understanding the Cervical Cancer Health Gap for Women in Jail**
P.I.: **Megha Ramaswamy**
Institution: **University of Kansas Medical Center**
Grant No.: **CA162869-01**
Award: **$80,361**

Women in the criminal justice system are four-five times as likely to have cervical cancer compared to non-incarcerated women. Some have attributed this disparity to difficulty in follow-up of abnormal Paps, but little is known empirically about why women involved in the criminal justice system have low abnormal Pap follow-up rates. The objective of this application is two-fold: to understand the interpretation of abnormal Pap events and their subsequent follow-up from the perspective of incarcerated women; second, to interpret women's abnormal Pap events and follow-ups based on a review of their medical records. The validation of women's accounts of abnormal Pap follow-up (or lack thereof) with medical chart review will provide an understanding as to why some women do not gain access to follow-up care. Thus, we will be able target interventions to address this documented gap in women's understanding of abnormal Pap events versus actual events. To meet this objective, first we will conduct focus groups and in-depth interviews with 40 women in a Kansas City county jail about abnormal Pap screening and subsequent follow-up events. Studying women's experiences with abnormal Paps and follow-up may provide clues as to their cervical cancer screening knowledge and the processes by which women actually seek out cervical cancer prevention services given their movement in and out of jails. Second, we will ask the 40 women previously interviewed for permission to access their medical records, in order to investigate whether incarcerated women's self-report of abnormal Pap and follow-up events matched actual medical records of these events. This aim will allow us to gauge women's understanding of Pap events, validate the medical barriers that women faced in trying to gain access to follow-up care, and demonstrate the feasibility of assessing health care access through medical chart review for this high-risk population. This project has significance for public health impact by providing insight into how to address the cervical cancer burden for women involved in the criminal justice system. This project is innovative in its goal of assessing incarcerated women's understanding of abnormal Pap events and validating their understanding with medical record review. Study findings will contribute to the

development of an intervention that attempts to close the cervical cancer health gap between women involved in the criminal justice system and their sisters in the "free" world.

Title: **Urinary Estrogens and Estrogen Metabolites in Relation to Objective Measures of Physical Activity Among Controls in the NCI Polish Breast Cancer Study**
P.I.: **Cher Dalla and Gretchen Gierach**
Institution: **National Cancer Institute Intramural Research, Division of Cancer Epidemiology and Genetics**
Grant No.: **OD-11-302**
Award: **$15,000**

The prevalence of obesity remains elevated in the United States, particularly among women. According to data from the National Health and Nutrition Examination Survey, 35% of women in the United States were classified as obese in 2007-2008 with a BMI of ≥ 30 kg/m2. More specifically, the prevalence of obesity among women ages 40-59 was 38.2% during this time period. This is of particular importance given the consistent association between obesity and an increased risk of cancer among postmenopausal women, including cancers of the breast, endometrium, and colon. Additionally, numerous epidemiological studies suggest that higher levels of physical activity may reduce postmenopausal breast cancer risk. However, the mechanisms underlying these observed associations and the relationship between energy balance and biomarkers, such as estrogens and their metabolites, remain unclear. Promoting physical activity may have important implications for reducing breast cancer risk and other cancers, but to date, our understanding of the underlying mechanisms is limited in several respects: 1) lack of objective measures of physical activity in studies of sex steroid hormones; 2) incomplete assessment of estrogen metabolites, which are suggested to differentially contribute to breast cancer risk and 3) small sample sizes and limited covariate information in previous studies. We aim to better define relationships between physical activity and estrogen metabolites among postmenopausal women by leveraging the existing resources of the population-based NCI Polish Breast Cancer Study. We propose a novel approach to examine the association between accelerometer measured physical activity and a more comprehensive estrogen hormone profile among population-based controls (n=685) from the Warsaw site of the Polish Breast Cancer Study. Objective physical activity measures, collected through the use of an accelerometer, quantify the duration and intensity of activity on a minute-by-minute basis, without the limitation of self-report bias. This study addresses health behaviors and their interaction with biology and their role in cancer prevention, two areas of scientific priority outlined by the Institute of Medicine (IOM). Findings from this study will extend our biological understanding of the effects of physical activity, a modifiable health behavior, on estrogen metabolism and may contribute to translational efforts to improve cancer prevention and risk prediction for women.

Title: **Videoconference CBT for Rural Breast Cancer Survivors with Cognitive Complaints**
P.I.: **Robert J. Ferguson**
Institution: **Eastern Maine Medical Center**
Grant No.: **CA143619-01A1**
Award: **$170,338**

Cognitive dysfunction associated with cancer chemotherapies can have a dramatic effect on cancer survivor quality of life and is recognized as a growing survivorship problem. However, the etiology of chemotherapy-related cognitive change is unknown, with no current broadly validated treatment. The PI is developing a brief cognitive-behavioral therapy (CBT; Memory and Attention Adaptation Training; MAAT) designed to help cancer survivors self-manage and cope with daily memory failure. Preliminary research suggests MAAT may improve self-reported daily cognitive failures and verbal memory performance, and survivors rate it with strong satisfaction, but more

research is needed. The proposed research aims to evaluate a revised and more intense version of MAAT (increase from 4 to 8 visits) delivered through videoconferencing technology to aid rural breast cancer survivors with chemotherapy-related cognitive complaints-individuals with geographic and cost barriers to survivorship services. MAAT will be compared to a videoconference supportive therapy (ST). Thus, this study seeks to evaluate feasibility of MAAT delivered through videoconference technology. Participants. 48 women treated for stage I, II, or IIIa breast cancer with chemotherapy-related cognitive complaints, 6 months past last chemotherapy and who do not have other neurologic or psychiatric histories, or untreated anxiety or mood disorders will be enrolled. Intervention. MAAT-Video (MAAT-V) will consist of 8 weekly one-hour group sessions consisting of 2-4 members each linked by videoconferencing devices at up to 6 rural outreach clinics. Multiple participants can be seen by the clinician and participants can also see each other from different sites. ST is identical in length and time of sessions (8 one-hour sessions), but is more passive and less instructional than MAAT. Design. Breast cancer survivors will be randomized to either MAAT-V or ST. Survivors will be evaluated for self-reported impact of cognitive problems on quality of life, anxiety about cognitive problems, functional wellbeing, and on brief telephone-based neuropsychological tests of memory at 3 time points: pre-treatment, post-treatment and 2-month follow-up. Statistical analyses will consist of a 2 X 3 (baseline, post-treatment and follow-up), repeated measures analysis of variance with dependent measures listed above and a planned comparison approach to reduce risk of spurious findings. Type of chemotherapy, age, education, estimated IQ, fatigue, and other factors will be evaluated as possible covariates. Clinically significant change on outcome measures will be evaluated using the reliable change index (RCI). Satisfaction will be assessed with 0-8 Likert-type ratings. A qualitative analysis of 20 randomly selected participants will be completed to assess practicality of MAAT-V. Significance. Study results will advance knowledge of the feasibility of MAAT delivered through videoconference to improve breast cancer survivor quality of life, especially in rural, underserved areas.

Title: **Vitamin D Status, Gene Polymorphism, and Breast Cancer Progression/Prognosis**
P.I.: **Tsogzolmaa Dorjgochoo**
Institution: **Vanderbilt University Medical Center**
Grant No.: **CA156648-01**
Award: **$77,710**

Project Summary/Abstract) The association of vitamin D deficiency, or low levels of circulating vitamin D, with increased risk for cancers, including breast cancer (BC), has received extensive attention. Experimental studies have shown that vitamin D has many anti-cancer properties, including anti-proliferative, anti-angiogenic, pro-apoptotic, and immunomodulation effects. Less attention has been paid to the role of vitamin D deficiency on BC prognosis and survival outcomes. Studies have shown that circulating vitamin D and polymorphisms in genes regulating vitamin D metabolism and signaling are both associated with BC risk, however, we know less about associations with BC prognosis. A few studies have linked low circulating vitamin D levels with prognostic factors for BC outcome, such as advanced disease or metastasis. Only one study directly evaluated the association between vitamin D status and BC survival, and no study has investigated this association in relation to vitamin D polymorphisms. We propose to address these questions in a prospective cohort of Chinese women with BC and test three hypotheses: 1) Circulating vitamin D level will predict BC progression and prognosis (recurrence, metastasis, overall or disease-specific death) after cancer treatment; 2) Genetic polymorphisms in vitamin D metabolism and signaling pathway genes affect circulating vitamin D level and its bioavailability in BC survivors; and 3) Circulating vitamin D and vitamin D gene polymorphisms together affect BC progression and prognosis. The proposed study will use resources from the Shanghai Breast Cancer Survival Study (SBCSS) and the Shanghai Breast Cancer Genome-Wide Association Study (GWAS). We will include 2,073 women newly-diagnosed with invasive BC and aged 20-74 years at the time of diagnosis, who have both blood samples for assessing circulating 25(OH)D and genotype information. Information on cancer diagnosis and

conventional treatment, breast cancer recurrence, and causes of death will be verified through medical chart reviews. We will evaluate the effect of circulating vitamin D level and its combined effect with polymorphisms in the vitamin D pathway genes on BC progression and prognosis using appropriate statistical methods and controlling for known prognostic factors. The Mendelian Randomization (MR) method will be used to re-assess this association. Breast cancer survivorship is recognized as a critical component of cancer-related public health programs. The proposed study aims to fill a gap in our knowledge by evaluating the associations of circulating vitamin D and vitamin D pathway gene polymorphisms with breast cancer prognosis. This study will expand our understanding of the role of "Vitamin D status" and related pathway gene polymorphisms in BC prognosis. The study results could potentially lead to the development of new preventive and therapeutic strategies that can be applied to BC patients. In addition, the research could help determine if chemoprevention clinical trials with vitamin D should be considered for BC patients at high-risk for disease progression.

Title: **Workshop: Postpartum Breast Remodeling, Lactation, and Breast Cancer Risk: Toward Improved Assessment and Prevention**
P.I.: **Mark Sherman**
Institution: **National Cancer Institute Intramural Research, Division of Cancer Epidemiology and Genetics**
Grant No.: **OD-11-302**
Award: **$5,000**

The goal of this workshop is to critically assess key questions related to postpartum events and the pathogenesis of breast cancer. The postpartum period is an important focus of research related to promoting child health. In contrast, comparatively few studies have taken advantage of the repeated medical contacts during this period to conduct research on maternal health, and in particular, to develop strategies for reducing breast cancer mortality. The postpartum period is temporally related to pregnancy and breastfeeding, two poorly understood factors related to breast cancer risk. In addition, this window offers the unique opportunity to collect and analyze breast milk, which may enable non-invasive analyses of breast cells and fluids among young healthy women. Therefore, this time in the life course represents a promising interval for investigating the pathogenesis of early onset breast cancer and for developing strategies for risk assessment and prevention of these tumors. Accordingly, the objective of this workshop is to assemble experts to critically assess our current understanding of postpartum re-modeling of the breast, lactation, and breast cancer and to identify gaps in knowledge and resources that would be required to advance research on this topic. A recent comprehensive review of breastfeeding in developed countries produced by the AHRQ (Ip et al Breastfeeding Medicine (2009) concluded that breastfeeding reduces maternal risks for breast cancer and for type 2 diabetes mellitus, which elevates breast cancer risk. Risk stratification of young women may allow the development of evidence-based screening intervals at later ages or identification of candidates for prevention interventions.

National Heart, Lung, and Blood Institute

Title: **Cardiovascular Disease Biomarkers and Mediation of Hormone Therapy Effects**
P.I.: **Ross L. Prentice**
Institution: **Fred Hutchinson Cancer Center**
Grant No.: **1R21HL109527-01**
Award: **$352,000**

Confirmatory analyses of novel plasma protein associations with the risk of coronary heart disease and stroke will be carried out by applying enzyme-linked immunosorbent assays to baseline plasma specimens from cases and controls in the Women's Health Initiative postmenopausal hormone therapy trials. Candidate proteins were highly ranked in recent in-depth

proteomic discovery research. For CHD these are alpha-1-acid glycoprotein 1, thrombospondin 1, complement factor D preprotein, glutathione peroxidase 3, and insulin-like binding protein 1 (IGFBP1). For stroke the candidate biomarkers are IGFBP2, IGFBP6, insulin-like growth factor 2, hemopexin, and beta 2 microglobulin. Specimen analyses will be carried out for 349 CHD cases and for 1-1 matched controls, and for 326 stroke cases and matched controls. Data analyses will control for traditional cardiovascular disease risk factors, and for available biomarkers of inflammation, thrombosis, and lipids. Women developing CHD or stroke following their first year of hormone therapy trial enrollment, and their matched controls, will also have plasma concentrations assessed in 1-year blood specimens for the subset of these proteins found to be affected by estrogen-alone or by estrogen plus progestin in discovery work using the same proteomic platform. The baseline and 1-year protein concentrations will be jointly analyzed to assess the extent to which treatment-related changes in these protein concentrations can mediate hormone therapy effects on CHD and stroke. These analyses will incorporate a novel correction for biomarker measurement error. The project has a high probability of confirming some new biomarkers of CHD and stroke risk, and for providing additional insight into observed hormone therapy effects on these diseases. PUBLIC HEALTH RELEVANCE: This project will evaluate novel blood proteins as potential risk markers for coronary heart disease and stroke in postmenopausal women, and will evaluate the extent to which changes in these biomarkers as a result of postmenopausal hormone therapy can help to explain the observed effects of postmenopausal estrogen and estrogen plus progestin on the risk for these major diseases.

Title: **Clinical Research United in Successful Enrollment—Workshop on Clinical Trials**
Institution: **In partnership with the National Heart, Lung, and Blood Institute**
Grant No.: **OD-11-287**
Award: **$9,964**

As our health care system moves to expand access, evidence based-medicine and the need for well designed and conducted clinical trials become paramount. The goal of this workshop was to provide recommendations to NHLBI and co-sponsors in three key areas that impact clinical trial enrollment: 1) Public and professional awareness and acceptance of clinical trials, 2) Human subject research policies, guidelines, and reimbursement, and 3) clinical trial enrollment experience and practice, in order to optimize enrollment in clinical trials.

Title: **Endogenous Cardiac Repair in Humans**
P.I.: **Kenneth Ber Margulies**
Institution: **University of Pennsylvania**
Grant No.: **HL089847-03S1**
Award: **$40,000**

Until recently, the heart has been viewed as a terminally differentiated organ with no capacity for new cardiac myocyte (CM) formation. This view appears to be incorrect, in that we and others have been able to isolate cardiac-derived progenitor cells (CDPCs) from human myocardium. Extending these results, our recent studies indicate that cells expressing the stem cell surface marker c-kit can be isolated from human hearts immediately after explantation and subsequently induced to differentiate into CM via short-term co-culture with neonatal rat ventricular myocytes (RVMs). Though we typically find more c-kit+ cells usually in failing vs. nonfailing hearts, the need to replace these failing hearts via transplantation highlights the inadequacy of native cardiac repair mechanisms. Based on these findings, our broad working hypothesis is that increased c-kit+ CDPCs in failing human hearts include both lineage-negative c-kit+ and c-kit+/CD45(dim-moderate) cells that are each capable of new myocyte formation in vitro. In this context, the objective of this proposal is to quantify and characterize these distinct subpopulations of stem/progenitor cells within human hearts with an emphasis on elucidating their functional

capacity for replication and CM differentiation. Our first aim is to identify what types of stem/progenitor cells are present in normal and failing human hearts. We will define distinct stem/progenitor subpopulations based on immunotyping of disaggregated myocardial cells with fluorescence microscopy and flow cytometry and perform complementary studies in tissue sections from the same hearts to define their distribution. Our second aim is to characterize replicative capacity of the selected CDPC subpopulations based on a combination of static assays (telomere length, telomerase activity and and p16INK4a expression) and functional assessment of proliferation rates. Our third aim is to characterize the cardiac myogenic potential of selected CDPC subpopulations derived from human hearts. These studies will define the rates and frequency of CM differentiation for sorted subpopulations under stardardized co-culture conditions, define whether cell contact is required for induction of CM differentiation by neonatal rat myocytes and identify secreted factors (chemokines or growth factors) that promote or augment rates of in vitro CM diffentiation in selected CDPC subpopulations. The clinical/therapeutic significance of this proposal is based on the premise that insights into the proliferative and cardiomyogenic potential of endogenous cardiac stem/progenitor cell subpopulations will promote progress towards therapeutic cardiac regeneration with or without cell therapy per se.

Title: **Metabolism During Mechanical Circulatory Support in the Developing Heart**
P.I.: **Michael A. Portman**
Institution: **Seattle Children's Hospital**
Grant No.: **HL060666-12**
Award: **$20,000**

Extracorporeal membrane oxygenation (ECMO) remains the primary method of long term support after myocardial stunning caused by cardiac surgery in infants and children. ECMO often provides a bridge to recovery in these young patients. However, ventricular unloading as occurs with ECMO also promotes cardiac atrophy. Therefore, this therapy can be counterproductive in initiating reparative processes leading to restoration of normal cardiac function. Substantial abnormalities in hormonal homeostasis, such as decreases in circulating levels of thyroid hormones, occur during both shorter term cardiopulmonary bypass (CPB) and longer term ECMO. Disruptions in thyroid hormone homeostasis can alter substrate utilization, deplete citric acid cycle intermediates, possibly effecting net protein turnover. Additionally, we have noted that pyruvate supplementation can improve cardiac function after CPB in immature pigs. Thyroid hormone supplementation promotes pyruvate entry into the citric acid cycle, and promotes citric acid cycle intermediate conversion to amino acids. These findings suggest that appropriate substrate supplementation can improve protein synthesis and functional recovery after protracted mechanical circulatory support. We will study a prolonged period of mechanical circulatory support (ECMO) in the immature pig, an appropriate translational model for children undergoing these procedures. We will test the primary hypothesis: in the developing heart cardiac dysfunction due to ventricular unloading (ECMO)-is a consequence of impaired substrate utilization due at least in part to disruptions of thyroid hormone homeostasis. Targeted metabolic interventions in combination with thyroid hormone supplementation will minimize the adverse effects of ECMO and thereby improve longer term functional recovery and survival. Using NMR and GC-MS, we will determine if metabolic abnormalities, which lead to cardiac dysfunction and atrophy can be treated by supplementing the citric acid cycle with pyruvate. We will determine if pyruvate combined with thyroid hormone supplementation (T3) a) accelerates pyruvate flux, b) reduces oxidation of amino acids, c) stimulates transamination to amino acids and d) improves cardiac function and protein synthesis after a prolonged period of ventricular unloading. We will also determine if supplementation of medium chain fatty acids with and/or without thyroid hormone similarly supports the heart.

Title: **Phytoestrogens, Insulin Resistance, and Endothelial Function**
P.I.: **Nina Stachenfeld**
Institution: **John Pierce Laboratory, Inc.**
Grant No.: **1R21HL109822-01**
Award: **$238,669**

With the goal of reducing the age-associated vasomotor symptoms and decreasing the risk of cardiovascular disease, many women choose over the counter phytoestrogens in favor of estrogens prescribed by their physicians. Genistein is the best studied and most common of the soy-derived phytoestrogens. Genistein is structurally similar to 172-estradiol and has high affinity for the ER2 receptor present in the human vasculature, but low affinity for the ER1 receptor present in reproductive organs. Studies support beneficial effects of soy-derived phytoestrogens on vascular reactivity and endothelial function. However, during genistein treatment the expected improvement in endothelial dependent dilation is attenuated in individuals with insulin resistance. This project is designed to study the impact of genistein on microvascular reactivity both in healthy women and in women with insulin resistance. Our general hypothesis is that genistein improves endothelial function through a nitric oxide mechanism in healthy women, but that this mechanism is ineffective in women with insulin resistance. We will use the cutaneous vasculature as a model to study endothelial function, and will infuse estradiol and genistein directly into the skin using microdialysis while measuring microvascular blood flow with laser Doppler flowmetry. Our first Aim will use dose-response curves to determine the 172-estradiol and genistein effects on the peripheral microvasculature in women with and without insulin resistance. We hypothesize that both hormone infusions will increase blood flow in both groups of women, but the vasodilation will be attenuated in women with insulin resistance. Our second Aim tests the hypothesis that nitric oxide mediates the estradiol and genistein-induced vasodilation in healthy women, but is not a factor in the more moderate vasodilation seen in women with insulin resistance. Women take genistein and other phytoestrogens assuming a level of cardiovascular protection, but data have not definitively demonstrated these benefits. Our studies will directly assess the extent to which genistein impacts vasodilation and examine the mechanism for its effects. Moreover, our findings will provide a basis to study the impact of genistein and other phytoestrogens on other conditions associated with compromised peripheral circulation such as Reynaud's disease and hypertension. The proposed studies will not only provide mechanistic information on the interaction between estradiol, genistein, insulin resistance and endothelial function, but will serve as a basis for future studies in older women and men with insulin resistance. PUBLIC HEALTH RELEVANCE: With the goal of reducing vasomotor symptoms and protection against the age-associated increase in cardiovascular disease risk, women are increasingly choosing over the counter phytoestrogens (such as genistein) in favor of estrogens prescribed by their physicians. Genistein may improve vascular function but not carry with it the increased breast cancer risks that have been associated with estrogen exposure. Insulin resistance increases cardiovascular disease risk, and may also interfere with the actions of genistein on cardiovascular function. Therefore, these studies have broad public health implications because it is important that women not have a false sense of cardiovascular protection while taking genistein.

Title: **Sex Differences in Molecular Heterogeneity of Cardiac Repolarization**
P.I.: **Glenna C.L. Bett**
Institution: **University at Buffalo, The State University of New York**
Grant No.: **1R21HL093631-01A1**
Award: **$231,240**

This proposal is a revised application in response to an RFA for R21 applications to advance Novel Science in Women's Health Research. Although heart disease is the #1 killer of both Men and Women in the US, only 27% of participants in cardiac clinical trials are women. In basic research, most experiments are performed on male animals only. It is therefore not surprising that little is known about the basic molecular mechanisms even for such clinically important

fundamental factors such as why female cardiac action potentials are longer than male action potentials. Even less is known about why 70% of congenital Long QT syndrome patients are women, and why women are at particular risk for drug induced arrhythmias. This application proposes to advance science in women's health research by determining the molecular basis for sex dependence and hormonal regulation of IKr and IKs, the two major repolarizing currents in heart. This research is strongly hypothesis driven, and the overall guiding hypothesis is that differences in the electrophysiological and pharmacological profile of IKr and IKs are responsible for sex differences in cardiac repolarization. This is a departure from the current concept that it is purely the action potential duration that is the key determinant of arrhythmia susceptibility. We are proposing that the important factor is not the absolute action potential length, but the relative contribution of IKr and IKs, combined with their pharmacological sensitivities that are a critical factor in arrhythmogenesis. The alpha subunits of IKr and IKs are HERG and KCNQ1 respectively. However, their relative expression, electrophysiological and pharmacological profiles are determined by the presence of KCNE ancillary subunits. Our hypothesis is that hormonal regulation of these subunits is the major factor in determining differences between male and female myocytes. We will test this hypothesis by determining IKr and IKs electrophysiological profile in human cardiomyocytes derived from male and female induced Pluripotent Stem Cells (iPSCs) from skin cells, as well as ventricular myocytes from male, female and ovariectomized (OVX) guinea pigs. We will also expose myocytes to estradiol and testosterone to test the direct effects of hormones on currents and use molecular interventions to determine subunit specificity. We will use the experimental data to develop mathematical models of human and guinea-pig action potentials which contain hormonal regulation of IKr and IKs. We will use these models to make predictions about the dynamic behavior of repolarization (e.g., restitution, QT prolongation and pharmacological sensitivity) which can be tested in our experimental human and guinea pig models. These innovative simulation studies will provide testable hypotheses which are readily applicable to electrophysiological studies in humans. PUBLIC HEALTH RELEVANCE: This proposal seeks to understand the basis of sex-differences in the electrical activity and pharmacological sensitivity of the heart. Sex is an often overlooked fundamental clinical variable, which can have a significant impact on health outcome. Understanding the basis of cardiac sex differences offers the opportunity for translational advances in the identification of therapeutic targets with the potential to improve patient outcomes and improve healthcare for both men and women.

Title: **Sexual Dimorphism of Skeletal Muscle**
P.I.: **Virginia H. Huxley**
Institution: **University of Missouri, Columbia**
Grant No.: **5R21HL093068-02**
Award: **$186,684**

Skeletal muscle (SKM) microvasculature has been studied extensively with respect to respiratory gas and nutrient exchange, volume distribution, and blood flow control, into and within the organ, in health and disease. This R21 is in response to a PFA requesting development of models for the study of function in males and females. This is terribly important as most studies of SKM have been conducted in males (animals and humans) with the presumption that the data apply equally to both sexes. Evidence from multiple studies accumulated over the last decade is making it clear that this assumption in error. One model used widely for in vivo study is the rodent cremaster, a thin muscle derived from the abdominal wall that raises and lowers the testes. Surprisingly, no microvascular skeletal muscle preparation of equivalent metabolic and fiber type substitutes presently for the cremaster that facilitates study of both males and females. This proposal aims to rectify this lack by validating the abdominal wall skeletal muscle preparation in males and female rodents. The hypothesis is that microvascular skeletal muscle functions do not differ between age-matched males and females of the same species. Accordingly, 3 aims will be carried out in in situ and isolated abdominal muscle microvessels from age- and strain-matched

female and male mice: Aim 1 will assess whether sexual dimorphism exists with respect to blood flow regulation from measures from microvascular diameter to selected endothelium-dependent and -independent agents. Given recent data we expect to reject our hypothesis as we anticipate that a) arterioles from males will develop greater basal tone and b) the dose-response relationship for the endothelium-dependent dilation will differ between males and females. Aim 2 will assess whether sexual dimorphism exists with respect to exchange regulation from measures from measures of microvessel solute permeability (Ps). Given our data, we expect to reject our hypothesis as we anticipate that a) venules from males will be leakier than those from females, b) basal arteriole and capillary barrier properties will not differ by sex, and c) the vasoactive agents will produce a variety of exchange responses reflecting differences in sex-specific mechanisms regulating solute distribution between the vascular and tissue compartments of males and females. Aim 3 will compare the sex, age, organ and species matched diameter (Aim 1) and exchange data (Aim 2) from microvessels as they lay in the living tissue and following isolation from the tissue. This is an incredibly opportunity to make these comparisons as not all tissues are amenable to study in situ and it is assumed that the data from the isolated vessels reflect the behavior in the tissue. Data from this project will form the foundation for future genetic, biochemical, and physiologic studies of microvascular function in males and females. It is imperative that we validate a model for study of microvascular function in both sexes to understand intelligently the sex-dependent mechanisms regulating vascular function in health and dysfunction in disease. With the knowledge the foundation, and provide rational means for prevent and treating vascular disease specific to the needs of males and females.) PUBLIC HEALTH RELEVANCE: This project is to develop and validate a skeletal muscle model for the study of the primary functions of the smallest blood vessels in age-matched male and female animals of the same species, the mouse. The 2 primary functions of the microcirculation 1) blood flow to metabolizing tissue, and 2) the movement of nutrients from blood to tissue as well as the removal of wastes from tissue to blood, appear to differ between males and females in health and cardiovascular disease including hypertension and secondary to type 2 diabetes. As materials distribute themselves between blood and tissue, so too will fluids move between compartments; thus if exchange regulation differs between males and females it is likely that volume distribution will also differ. Therefore it is imperative to have access to a model to learn the differences and similarities between the sexes as the data from males, disease incidence and severity and subsequent treatment strategies will not apply equally to females.

Title: **Uterine-Specific Genetic Modification and Lymphangioleiomyomatosis**
P.I.: **Jose M. Teixeira**
Institution: **Massachusetts General Hospital**
Grant No.: **HL109935-01**
Award: **$50,000**

Lymphangioleiomyomatosis (LAM) is a rare disease primarily found in females and is characterized by a diffuse interstitial infiltrate of atypical smooth muscle cell lesions in the lung parenchyma resulting in airway restriction. The etiology of the disease is unknown but is thought to involve hormonal regulation because it usually presents between menarche and menopause. Additionally, LAM is often found in patients with mutations in tuberous sclero-sis complex (TSC), suggesting that inactivation of TSC can contribute to its development. We are studying uterine development and associated pathologies by conditionally deleting and/or activating candidate genes in pathways critical for normal differentiation and function. We have created mice with uterine-specific leiomyomas (fibroids) by either constitutively activating β-catenin or by expressing a truncated allele of adenomatous polyposis coli (APC) and we have shown preliminary evidence that the leiomyomas develop as a result of vascular hemorrhaging and subsequent hypertrophic scarring. The Mullerian duct-derived internal female reproductive tract organs (uterus, oviduct, cervix, and cranial portion of the vagina) are the only structures from the bipotential mammalian embryo not found in males, suggesting that the hormonally

responsive mesenchymal stromal cells of the uterus might be the source of the cells for pulmonary fibrosis and account for the female-specificity of LAM. We hypothesized that pulmonary LAM might be caused by uterine vascular pathologies that allow intravasation of uterine stromal cells that can subsequently lodge and proliferate in the lungs. Histological analysis of the lungs from our mouse models with uterine hemorrhaging and leiomyomas showed fibrotic lung plaques similar to that observed in human LAM that were also HMB45-, aSMA- and desmin-positive, markers for human LAM. We propose to investigate this hypothesis further with the following Specific Aims: (1) confirm that cells in the lung lesions are derived from the uterus, (2) determine whether uterine mesenchymal cells can be detected in peripheral blood, (3) test the hormone responsiveness of the smooth muscle cells in the lung lesions, and (4) assess the marker profile of lung lesions for comparison with human LAM. The results from these studies will lay the foundation for continued investigation of the triggers and signaling pathways involved in the development of the LAM lesions as well as provide an in vivo model system for preclinical studies of therapeutics targeting those pathways.

National Institute on Aging

Title: **A Biopsychosocial Investigation of Women's Health at Midlife**
P.I.: **Dawn M. Upchurch**
Institution: **University of California, Los Angeles**
Grant No.: **AG038467-01A1**
Award: **$200,000**

Midlife is a time of significant change in women's personal and professional lives. Moreover, health increasingly deteriorates, setting the stage for quality of life in later years. The purpose of the proposed research is to identify and investigate the longitudinal explanatory pathways that impact 3 important health outcomes. We target outcomes that are common and that have high personal and social costs: 1) Vasomotor Symptoms; 2) Depressive Symptoms; and 3) Allostatic Load. A distinguishing feature of this research is its use of an innovative biopsychosocial model that incorporates multiple domains of women's lives and acknowledges the multidimensionality of women's health. Specifically, we investigate the impact of: 1) Social Stressors and Social Support; 2) Psychological Factors; and 3) Lifestyle Behaviors on each health condition over a 10-year period using latent growth curve analysis, longitudinal structural equation models, and longitudinal random effects, as appropriate. In so doing, we will identify the specific pathways for both level and change over time for each woman for each health outcome. Because we propose that multiple aspects of health are linked in complex ways, we will also examine the interrelationships between the intervening variables, between the health outcomes, and investigate possible feedback between health outcomes and intervening variables. Data are from the Study of Women Across the Nation (SWAN) a community-based, 10-year longitudinal study of midlife women (aged 42-52 at baseline) designed to characterize the physiological and psychosocial changes that occur during the menopause transition. By emphasizing characteristics that are potentially modifiable, the proposed research will provide new information relevant to clinical and programmatic intervention that may serve to reduce health differentials and promote well-being among midlife women.

Title: **Epigenetics of the Aging Astrocyte: Implications for Stroke**
P.I.: **Farida Sohrabji**
Institution: **Texas A&M University Health Science Center**
Grant No.: **AG042189-01**
Award: **$100,000**

Stroke is the leading cause of disability in the US and, with heart disease, the leading cause of death. The risk for stroke with consequent functional disability is increased with age, and in women this risk is elevated after the menopause. Paradoxically, hormone therapy at menopause increases the risk for stroke. Animal models of stroke confirm that stroke severity is worse in aged animals as compared to younger animals. In middle age, our recent data shows that female rats sustain a greater degree of tissue damage in the cortex and striatum as compared to younger females. Middle aged males, on the other hand, do not differ significantly from younger males in the extent of cortical infarction. This age difference in cortical cell loss is also paralleled by functional changes in astrocytes, a specific brain support cell. Astrocytes play a key role in normal and pathological conditions. Following stroke, astrocytes are rapidly mobilized to the peri-infarct area, detoxify the injured brain via glutamate uptake and fluid efflux and secrete growth factors known to promote angiogenesis and neuronal survival and neurogenesis. Astrocytes culled from the ischemic cortex of middle aged female rats show profound loss of protective functions including a reduced ability to sequester glutamate, decreased growth factor release, increased release of chemokines and increased ability to recruit leukocytes. These changes are consistent with increased infarct volume observed in older females. Hence in this proposal we will determine age and sex-specific epigenomic changes in astrocytes obtained from the ischemic cortex, to determine critical translational and transcriptional modulators. In Specific Aim 1 we will determine age-related changes in the expression of small non-coding RNA. MicroRNA, a key translation regulatory element, regulates large gene networks, and have been shown to play a central role in cell senescence and injury (stroke). In Specific Aim 2 we will determine age-related changes in DNA and histone methlyation patterns. Methylation patterns of specific leucines associated with activation (H3K4me3 and H3K9ac) or repression (H3K9me3 and H3K27me3) of gene transcription will be targeted. These complementary approaches will allow us to develop a molecular fingerprint of the aging astrocyte. Finally, in Specific Aim 3, select molecular targets will be manipulated using (1) miRNA mimetics or antagomirs and (2) demethylases to reverse age-specific patterns in astrocytes. Data gathered from these studies is expected to aid in the eventual identification of epigenomic changes that predict disease severity and facilitate discovery of therapeutic targets.

Title: **Exploring Factors Influencing Gender Disparities in Access to Transplantation**
P.I.: **Dorry Segev**
Institution: **Johns Hopkins University**
Grant No.: **AG034523-02**
Award: **$205,000**

In the modern era, kidney transplantation is a safe and effective treatment for many patients with kidney failure. However, choosing the right patients for kidney transplantation is difficult, especially among older patients. Although older patients who receive transplants survive longer than if they had stayed on dialysis, still very few older patients are placed on the transplant waiting list. This is because no tools exist for determining risk in older patients undergoing transplantation, so clinical decision making has to be based on subjective perceptions of a patient's strength and reserve. Misclassification of these factors by the patient or provider likely results in decreased access to transplantation in a population that stands to greatly benefit from this treatment. Although transplant outcomes and survival benefit are similar in men and women, it has been well established that women have significantly less access to transplantation than men. We recently showed that this disparity is strongest in older patients, with older women having 30-60% less access than their male counterparts. However, it remains unclear

whether patient or provider level factors contribute to this disparity. In this study we will explore differences by gender and age in factors influencing a patient's decision and ability to pursue transplantation. We will then use a new technique to explore the potential role of gender and age biases in a provider's choice to refer a patient for transplantation. Understanding the root causes of this gender/age disparity is crucial to developing interventions to improve access to transplantation, and healthcare in general, for women and older adults.

Title: **Gonadotropins in a Female Model of Age-Induced Hypertension**
P.I.: **Kathryn L. Sandberg**
Institution: **Georgetown University**
Grant No.: **AG039779-01**
Award: **$230,250**

This project addresses the PA-10-015 by proposing to investigate the role and mechanisms of follicle stimulating hormone (FSH) and leutinizing hormone (LH) in the age-induced increase in blood pressure (BP) and body weight (BW) observed in the female Dahl salt-sensitive (DS) rat. We have previously shown that ovariectomy accelerates the age-induced increase in BP and BW in this model and that 172-estradiol (E2) prevents these effects. Aging and ovariectomy, however, also result in a marked rise in FSH and LH. Though some studies implicate these pituitary hormones in BP regulation, their mechanisms of action are poorly understood. These proposed studies will provide key insight into this experimental model of female aging and postmenopausal hypertension. Aim 1 will determine if preventing the rise in FSH & LH that occurs as a result of ovarian hormone deficiency during normal aging from 4 months old (mo) to 12 mo in the female DS rat will attenuate the age-associated increase in BP, BW, insulin insensitivity, endothelial dysfunction, renal oxidative stress and activation of the vasoconstrictor arm of the renin angiotensin system (RAS) in vascular, renal and adipose tissues. We will also investigate the E2 and progesterone (P4) dependency of these pituitary hormone effects. Aim 2 will serve as the corollary to Aim 1 and will determine if increasing FSH & LH in young (3-4 mo) female DS rats will result in an increase in BP, BW, insulin insensitivity, endothelial dysfunction, renal oxidative stress and activation of the vasoconstrictor arm of the RAS in vascular, renal and adipose tissues. The clinical significance of this research is the insight it will provide into the mechanisms underlying the marked rise in the prevalence of hypertension in women as they age and after their transition into menopause.

Title: **Menopausal Symptoms Initiative—Finding Lasting Answers for Sweats and Hot Flashes**
P.I.: **Andrea Z. LaCroix**
Institution: **Fred Hutchinson Cancer Research Center**
Grant No.: **AG032699-04**
Award: **$200,000**

The long-term objective of NIA's RFA-AG-08-004 entitled, "New Interventions for Menopausal Symptoms (U01)" is to accelerate progress in identifying effective remedies for vasomotor symptoms (VMS) in women going through the menopausal transition. We have created a network of scientists who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials to fulfill this mission. This Data Coordinating Center (DCC) application is being submitted in conjunction with the network entitled, "The Menopausal Symptoms Initiative-Finding Lasting Answers to Sweats and Hot Flashes (MSI-FLASH)". Our DCC will be jointly led by Andrea LaCroix and Garnet Anderson who have served together as Co-Principal Investigators of the Women's Health Initiative Clinical Coordinating Center (Seattle) for more than a decade. The MSI-FLASH network has five clinical sites located in Boston (Lee Cohen and Hadine Joffe, PIs), Indianapolis, IN (Janet Carpenter, PI), Oakland, CA (Barbara Sternfeld and Bette Caan, PIs), Philadelphia (Ellen Freeman, PI) and Seattle

(Katherine Newton and Susan Reed, PIs). This multidisciplinary investigator group proposes five randomized controlled trials testing a range of behavioral, mind-body, hormonal and pharmacologic interventions to treat hot flashes. The specific objectives of the DCC are to: 1) Provide and coordinate all necessary leadership activities to facilitate collaboration and productivity among network scientists during all phases in the lifecycle of VMS clinical trials from hypothesis formulation to publication, dissemination, and data sharing; 2) Build upon 15 years of experience and well established human and operational resources to coordinate 5 or more multi-site randomized trials including support of protocol development, recruitment, intervention, data collection and management, and statistical analysis; and 3) Create the infrastructure to involve an expanded network of scientists from the US and worldwide to facilitate the development and use of common methodologies and measurements for VMS trials inside and outside of this trial network so that emerging new treatments for hot flashes can be rapidly identified and rigorously tested for efficacy and safety with comparable results.

Title: **Metabolic Syndrome as Women Undergo Menopausal Transition: A Multi-ethnic Study**
P.I.: **Jennifer Shuwen Lee**
Institution: **University of California, Davis**
Grant No.: **AG040568-01**
Award: **$195,983**

Young women have much lower rates of cardiovascular disease (CVD, including stroke) than men. However, as midlife women transition to post-menopause, they lose this 'cardiovascular protection,' and CVD is most common in post-menopause than any other stage of a woman's lifespan. Metabolic Syndrome (MetS) is a clustering of 5 metabolic abnormalities and is a major predictor of CVD and type 2 diabetes. MetS is clinically diagnosed as having any, and at least, 3 of the 5 components. MetS occurrence increases during the menopausal transition (MT). Reasons for this are unclear; however this may be due to androgen excess, relative to estrogen, during the MT. The proposal's goal is to establish basic aspects of how the constellations of the MetS components evolve during the course of the MT, a key 5- to 10-year biological stage in a woman's lifespan. In turn, this is intended to identify customized ways of preventing MetS early and related CVD and diabetes, with effective intervention strategies during the MT. The proposal incorporates a shift in our thinking of menopause and sex hormones in midlife women, namely, that the increase in MetS occurrence may be due more to androgen gain (and less to estrogen loss), in the MT. Our starting hypothesis is that mapping the constellations of MetS components, and the number of MetS components satisfied, in the midlife will provide a window into bridging the MT, its changing sex hormones, and loss of CV protection in women. If correct, this would shift our clinical focus to individualize hormone strategies against characteristic MetS constellations and related CVD and diabetes in midlife and early post-menopausal women. Aim 1. To characterize the constellations of MetS components satisfied over time in women, of 5 race/ethnicities, who develop MetS as they undergo the MT. Aim 2. To determine the hormonal and inflammatory factors that predict the course of MetS constellations in midlife women as they undergo the MT. We propose an efficient study that analyzes unique, existing longitudinal data from the largest U.S. study of the MT, the Study of Women Across the Nation (SWAN), a multi-ethnic cohort of 3302 women. Our long-term objective is to prevent the dramatic increase in CVD in older women by implementing, in midlife, individualized preventative strategies. Both our aims bear directly on this wider objective. These would impact 60+ million midlife and older U.S. women.

Title: **National Social Life, Health, and Aging Project**
P.I.: **Linda J. Waite**
Institution: **National Opinion Research Center**
Grant No.: **AG030481-04**
Award: **$200,000**

The primary objective of the National Social Life, Health and Aging Project (NSHAP) is to establish an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally-representative sample of 3,005 community-dwelling adults ages 57-85 in 2005/6. We propose to collect a second wave in NSHAP to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. We propose to revisit respondents four years after their initial interview. Using these data, we can describe and model the distribution of changes in health, well-being, social networks, social participation and social context. In each case, we shall examine the distributions both for the entire sample and within subgroups defined by key sociodemographic characteristics such as gender, race/ethnicity, and socioeconomic status. We also propose to augment the sample by interviewing the spouse/cohabitating romantic partner. These data will allow us to characterize the impact of marital and romantic relationships on health by examining the effects of one person's characteristics and behaviors on the health of the other. We will also analyze the partnerships themselves, and assess the relationship between characteristics of the partnership, such as support, closeness and mistreatment, and the health of each of the partners. In sum, we will explore our overarching hypothesis that older adults with strong functioning intimate relationships will show more positive (or less negative) health trajectories that those who have weaker relationships or lack such relationships altogether.

Title: **Ovarian Hormone-Independent Sex Chromosome Effects in Menopause**
P.I.: **Hong Ji**
Institution: **Georgetown University**
Grant No.: **AG037832-02**
Award: **$153,500**

Postmenopausal women have a higher incidence of diseases such as metabolic syndrome, cardiovascular and renal disease than premenopausal women. To begin to uncover genes and pathways that contribute to these adverse effects of aging in the postmenopausal woman, we propose two distinct strategies for discovering novel genes and pathways that may contribute to the increased risk postmenopausal women face towards these diseases. We will take advantage of the "four core genotypes" mouse model in which sex chromosome effects can be separated from the gonadal sex thus enabling comparisons among XX and XY animals independently of whether they were born with ovaries (e.g., XX- vs. XY-females) or testes (XX- vs. XY-males). While recent microarray studies in mice have demonstrated that thousands of genes are regulated by gonadal hormones, the number of genes regulated by the sex chromosome complement independently of the gonadal hormones is far more limited. Thus, we expect to discover a handful of genes (<10) that are differentially regulated by the sex chromosome complement (SCC) in the ovarian hormone deficient female during over activity of the renin angiotensin system (RAS). Aim 1 will use a tightly focused microarray approach leveraging our ability to differentiate SCE from gonadal sex to identify genes in the kidney that are differentially regulated by the SCC in the Ang II infused E2-deficient female. Aim 2 will use a candidate gene approach to test the hypothesis that the regulation of the tissue-specific renin angiotensin system (RAS) in the kidney by ovariectomy and hypertension is sex chromosome dependent. We hypothesize that

the interaction between the XX SCC with the E2-deficient state of ovariectomy tips the vasoconstrictor/vasodilator balance of the renal RAS towards vasoconstriction to a greater extent than in the XY-Female by increasing plasma and renal levels of Ang II, the ratio of the Ang II synthetic enzyme, angiotensin converting enzyme (ACE) to the catabolic enzyme, angiotensin converting enzyme 2 (ACE2) and the ratio of the type 1 angiotensin receptor (AT1R) to the vasodilator type 2 angiotensin receptor (AT2R).

Title: **STRAW+10: Addressing the Unfinished Agenda of Staging Reproductive Aging**
P.I.: **Sioban D. Harlow**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **AG039961-01A1**
Award: **$3,500**

We propose a multi-disciplinary symposium "STRAW+10: Addressing the Unfinished Agenda of Staging Reproductive Aging" to update the 2001 Stages of Reproductive Aging Workshop (STRAW) recommendations. The menopausal transition is a period of critical change, including loss of fertility, increased bone resorption, change in lipid profiles and temporal increases in symptoms, sleep disturbances and depression. STRAW proposed nomenclature, a staging system, and menstrual and endocrine criteria to define stages of ovarian aging. It has become the gold standard for characterizing reproductive aging, as the Tanner Stages characterize puberty. In the past decade, understanding of the critical junctures in hypothalamic and ovarian function before and after the final menstrual period and their implications for women's health has advanced considerably. We will convene 30 investigators from key research groups in the United States and worldwide. The specific aims are to refine criteria for the early menopausal transition given new population-based data relating to follicle-stimulating hormone, antral follicle count, anti-mullerian hormone and inhibin-B; to assess how to include women with higher body-mass-index and who smoke in staging algorithms; to provide recommendations regarding staging of women following gynecological surgery, chemotherapy, and hormone therapy and in women with polycystic ovarian syndrome and chronic diseases such as HIV/AIDS; and to assess potential criteria for staging the post-menopause. The Day 1 public scientific sessions will present recent advances and discuss implications of new data for staging. On Day 2, small working groups will propose modifications to the STRAW criteria. Following discussion, final recommendations will be adopted and research priorities defined. The expected outcome will be a set of recommendations for modifying the STRAW criteria that characterize the end stages of reproductive life including their extension to be more broadly applicable to the range of women's experience. Short- and long-term research priorities will be specified including studies needed to replicate and validate proposed criteria as well as to address gaps in knowledge. The meeting, co-sponsored by The North American Menopause Society (NAMS), The American Society for Reproductive Medicine, The International Menopause Society and The Endocrine Society, will be held September 20-21, 2011 prior to the NAMS Annual Meeting in Washington D.C. STRAW+10 recommendations will be presented at the NAMS meeting. A peer-reviewed executive summary will be published simultaneously in the co-sponsors' journals, Climacteric, Menopause, Fertility and Sterility; with a non-technical version published on their websites. The STRAW+10 staging system will facilitate consistent classification of menopausal status, ensuring comparability of research studies and clinical trials. Once specified, a staging system can be developed into a clinical tool to guide assessment of fertility and contraceptive choices, and healthcare decision-making. Funds will be allocated to support participation of 4 trainees/new investigators.

Title: **Study of Women's Health Across the Nation—Coordinating Center**
P.I.: **Kim Sutton Tyrrell**
Institution: **University of Pittsburgh**
Grant No.: **AG012553-17**
Award: **$125,000**

The Study of Women's Health Across the Nation (SWAN) is a 7-center multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition. SWAN has amassed ten years of data about endocrinology of the transition and other factors relevant to midlife health and aging. As SWAN requests its fourth competing renewal, the study itself proposes to transition from a study of the menopause to a study of aging in women. The average age of participants at the beginning of the SWAN IV project will be 59 years (54 to 65) and SWAN IV will follow these women through the age range of 59 to 70. SWAN has the unprecedented capability to link the expansive biological, medical, social, behavioral, and demographic data it has collected during mid-life and the menopausal transition to the development of both positive and adverse health states in early oldage. The primary objectives of SWAN IV are to: 1) Characterize the endocrinology and symptomotology of the post-menopause (2 to 12 years after final menses); 2) Ascertain additional health outcomes (such as measured physical performance) that are relevant to the early old age range and that may be affected by the factors that we have studied in mid-life and 3) Understand the relations between the mid-life and menopausal transition experience of women and subsequent positive and negative health outcomes. To accomplish this, the investigators propose annual phone contact to closely track menopausal status, menopausal symptoms and selected health events. In addition, two in-person clinic visits are proposed to accomplish detailed physical measures of early disease. The major thematic areas of SWAN IV include 1) Physical Functioning; 2) Bone/Osteoporosis; 3) Cognitive Function/ Symptoms/ Mental Health and 4) Cardiovascular. New areas for SWAN include physical performance and osteoarthritis, history of major depression, and carotid wall thickness. SWAN will continue to monitor symptoms, cognition, cardiovascular risk factors, endocrinology, bone density and fractures. SWAN IV will advance our understanding of how modifiable risk factors related to the menopause transition are linked to sub-clinical disease measures and hard outcomes. This may lead to improved strategies for the primary prevention of disease in women. RELEVANCE: SWAN has compiled the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. Of particular public health importance is that the continuation of SWAN will permit the study to increase understanding of the effects of these menopause-related changes on subsequent health and risk factors for age-related diseases.

Title: **SWAN Repository III**
P.I.: **Daniel S. McConnell**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **AG017719-12S1**
Award: **$200,000**

This competing renewal application is to provide for continued maintenance of and activities associated with the SWAN Repositories of serum, plasma, urine, DNA and transformed cells generated from a 10-year study of a population of 3302 women from 5 ethnic groups who have been evaluated annually prior to, during and following the menopausal transition. These Repositories, an arm of the Study of Women's Health Across the Nation (SWAN), are meant to support, facilitate and extend the Core SWAN; additionally, the Repositories provide a mechanism for opening the resources of SWAN to the greater scientific community. Implementing activities associated with three proposed specific aims of this competing renewal will 1) provide for the continued management of the current 1.7 million Repository specimens and the additional specimens that will accrue as a result of fielding SWAN IV in 2009 to 2014; 2) expand the DNA Repository, the most frequently requested specimen type that is uniquely renewable because of our investment in cell

immortalization; 3) promote effective information interchange about the SWAN Study, its data and the Repository resources through development of a 2-level web-based "data warehouse"; 4) provide for continued administration of the application review process for specimen utilization and administrative management of specimen distribution including Material Transfer Agreements; 5) engage in strategies to promote utilization of specimens; and, 6) expand the scope of the genetics studies associated with the SWAN study and its Repository.

Title: **SWAN: Study of Women's Health Across the Nation**
P.I.: **Joel S. Finkelstein**
Institution: **Massachusetts General Hospital**
Grant No.: **AG012531-18**
Award: **$75,000**

The Study of Women's Health Across the Nation (SWAN) is a multi-center, multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. The goals of the original RFA were to answer the following questions: How do hormones change with the menopausal transition? What factors affect the timing of the transition? What are the symptoms that accompany menopause and who is at risk? How do cardiovascular risk factors change with the transition and is there ethnic variation? What are the rates of bone loss with the transition? When does bone loss begin and what are the risk factors? What are the health consequences of menopause and who is at risk? SWAN is compiling the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. SWAN is now poised to study the effects of these menopause-related changes on subsequent healthy aging and on age-related diseases in the post-reproductive period. SWAN I was first funded in September 1994 by the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the Office of Research on Women's Health (ORWH) in response to RFA AG-94-002, Menopause and Health in Aging Women. The first competing continuation of SWAN (SWAN II) was funded in 1999 and the second (SWAN III) in 2004. SWAN I, II and III have been supported by a cooperative agreement mechanism, with 9 funded components: 7 clinical centers, a central reproductive hormone laboratory (CLASS), and a coordinating center. A second central laboratory (MRL) was originally funded as a subcontract to the Coordinating Center (CC). In addition, a Core Repository of serum, plasma, and urine specimens and a DNA Repository were established in June 2000 under separate funding (U01 AG 17719, PI: Dr. MaryFran Sowers). For non-study-related reasons, site operations at New Jersey Medical School stopped in April 2004. The basis of this action was allegations made by two study employees who resigned abruptly. The SWAN PI and study coordinator were subsequently exonerated from these allegations. Please see Appendix 12 for a more complete report. The grant was transferred to the Albert Einstein College of Medicine in 2005. Since that time, the New Jersey PI and project director have worked tirelessly to overcome the obstacles to re-implement the study. As of June 1, 2008, a total of 155 women have successfully completed their clinic visit and five more visits are scheduled. We project that by the end of SWAN III, data will be available for 250 women. This has been very encouraging and thus Nanette Santoro, PI of the New Jersey SWAN site has been approved by the NIA to prepare a U01 application to cover further contacts for the Hispanic women. Please note that the SWAN IVproject applications pertain to the remaining six sites only. Information relative to the New Jersey site is covered in the separate application submitted by Dr. Nanette Santoro. From over 16,000 women aged 40-55 years who were screened during 1995-1997, 3302 women aged 42-52 years were enrolled in SWAN's longitudinal cohort (approximately 450 at each of 7 clinical centers). They completed their baseline clinic visit during 1996-1997. Of the 3302 women enrolled, 1550 were Caucasian, 935 African American, 286 Hispanic, 250 Chinese, and 281 Japanese. A subset of 880 menstruating women was enrolled in the Daily Hormone Study (DHS) started in 1997, which is designed to examine cyclical daily hormone and symptom patterns during the menopausal transition.

Title: **Ultra-Low-Dose Estrogen Gel for Vasomotor Symptoms in Women Failing Placebo or a Behavioral Intervention: A Randomized Trial (MSI-FLASH)**
P.I.: **Andrea Lacroix**
Institution: **Fred Hutchinson Cancer Research Center**
Grant No.: **5-U01-AG-032699-04**
Award: **$200,000**

The long-term objective of NIA's RFA-AG-08-004 entitled, "New Interventions for Menopausal Symptoms" (U01) is to accelerate progress in identifying effective remedies for vasomotor symptoms (VMS) in women going through the menopausal transition. They have created a network of scientists who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials to fulfill this mission. This Data Coordinating Center (DCC) application is being submitted in conjunction with the network entitled, "The Menopausal Symptoms Initiative-Finding Lasting Answers to Sweats and Hot Flashes (MSI-FLASH)." Their DCC will be jointly led by Andrea LaCroix and Garnet Anderson who have served together as Co-Principal Investigators of the Women's Health Initiative Clinical Coordinating Center (Seattle) for more than a decade. The MSI-FLASH network has five clinical sites located in Boston (Lee Cohen and Hadine Joffe, PIs), Indianapolis, IN (Janet Carpenter, PI), Oakland, CA (Barbara Sternfeld and Bette Caan, PIs), Philadelphia (Ellen Freeman, PI) and Seattle (Katherine Newton and Susan Reed, PIs). This multidisciplinary investigator group proposes five randomized controlled trials testing a range of behavioral, mind-body, hormonal and pharmacologic interventions to treat hot flashes. The specific objectives of the DCC are to: 1) Provide and coordinate all necessary leadership activities to facilitate collaboration and productivity among network scientists during all phases in the lifecycle of VMS clinical trials from hypothesis formulation to publication, dissemination, and data sharing; 2) Build upon 15 years of experience and well established human and operational resources to coordinate 5 or more multi- site randomized trials including support of protocol development, recruitment, intervention, data collection and management, and statistical analysis; and 3) Create the infrastructure to involve an expanded network of scientists from the US and worldwide to facilitate the development and use of common methodologies and measurements for VMS trials inside and outside of this trial network so that emerging new treatments for hot flashes can be rapidly identified and rigorously tested for efficacy and safety with comparable results.

National Institute of Alcohol Abuse and Alcoholism

Title: **Mechanisms for Estrogen-Dependent Myocardial Depressant Effect of Ethanol**
P.I.: **Abdel A. Abdel-Rahman**
Institution: **East Carolina University**
Grant No.: **AA014441-06A1**
Award: **$200,000**

Contrary to conferring cardioprotection in male animals, acute ethanol causes estrogen (E2)-dependent myocardial depression in females. Despite progress made during the previous award, the molecular mechanisms for this health related problem remain unresolved. We hypothesize that E2-mediated accumulation of ethanol-derived acetaldehyde (ACA) creates environment conducive to paradoxical transformation of E2 into a pro-inflammatory hormone. We will focus on myocardial catalase and mitochondrial aldehyde dehydrogenase 2 (mit-ALDH2) because E2 enhancement of their physiological activity confers cardioprotection and both enzymes regulate myocardial ethanol-derived ACA balance; catalase catalyzes ethanol oxidation to ACA and mit-ALDH2 detoxifies ACA. We hypothesize that E2 enhancement of myocardial catalase activity could result in higher ethanol-derived ACA. Subsequently, competition of higher ACA level with more cytotoxic substrates for mit-ALDH2 leads to accumulation of cytotoxic aldehydes (oxidative stress and myocardial dysfunction). We further hypothesize that E2 mediates these cellular effects

via nongenomic estrogen receptor (ER) signaling. To test our novel hypotheses, we will employ a multidisciplinary approach that encompasses integrative, cellular, molecular and pharmacological studies to address the following specific aims. Aim 1 studies will test the hypothesis that enhancement of nongenomic rapid ER signaling mediates ethanol-evoked oxidative stress and myocardial depression in female rats. Aim 2 studies will elucidate the role of ACA generating (ADH, catalase) and aldehyde detoxifying (mit-ALDH2) enzymes in the E2-dependent oxidative stress and myocardial depression caused by ethanol. Aim 3 studies will test the novel hypothesis that ethanol/ACA-evoked eNOS/nNOS uncoupling plays pivotal role in the paradoxical transformation of E2 into proinflammatory hormone in the myocardium and vasculature. These studies will further our understanding of the molecular mechanisms for the E2-dependent myocardial dysfunction caused by acute alcohol and will allow identification of novel targets for new interventions for the treatment/prevention of cardiovascular anomalies caused by alcohol in females.

National Institute of Allergy and Infectious Diseases

Title: **Airway Inflammation and Airway Remodeling**
P.I.: **David H. Broide**
Institution: **University of California, San Diego**
Grant No.: **AI070535-06**
Award: **$12,500**

Airway remodeling is the term applied to the structural changes observed in the airway in asthma. Although current NIH guidelines recommend maintaining a goal of normal lung function in asthma, current therapeutic strategies do not specifically target airway remodeling as the cellular and molecular mechanisms that result in remodeling are not well defined and thus therapeutic targets are not well understood. Thus, there is an important need to identify mechanisms by which airway remodeling is mediated so that potential novel therapies could be directed at these pathways. In addition, characterization of these pathways could lead to the development of non-invasive blood or sputum biomarkers to identify, monitor, and perhaps subset, patients with asthma and remodeled airways. This UCSD AADCRC proposal will be directed by David Broide (Professor of Medicine) and include three projects (Broide, Croft, Zuraw) that will investigate mechanisms of airway remodeling in asthmatics exposed to allergen and rhinovirus common triggers of asthma. Thus, the overall hypothesis that will be explored in all three projects is that exposure to allergen triggers expression of inflammatory and remodeling pathways in allergic asthmatics that are exacerbated by exposure to respiratory viruses such as rhinovirus. The specific hypothesis that will be explored in each project and that will be driven by samples from asthmatics, is that the innate immune response (airway epithelium, macrophages, natural helper cells) play an important role in initiating and perpetuating the inflammatory and airway remodeling response to environmental triggers in allergic asthmatics. The three interrelated projects will focus on "Innate inflammation and airway remodeling" (Broide, Project 1), "TNF-R family members, inflammation and remodeling" (Croft, Project 2), and "Epithelial GILZ inflammation and remodeling" (Zuraw, Project 3) and be supported by Administrative Core A, and "Asthma Clinical Core B" which will be a source of sputum, BAL, endobronchial biopsy, and blood samples from asthma and control subjects provided by investigators in Core B (Ramsdell, Harrell, and Thistlethwaite, UCSD; Proud and Leigh, University of Calgary; and Hamid, McGill University). An lOFM Core is also proposed as requested by the RFA.

Title: **Airway Inflammation and HLA-G in Asthma**
P.I.: **Steven R. White**
Institution: **University of Chicago**
Grant No.: **AI095230-01**
Award: **$12,500**

Our program seeks to clarify cellular and molecular mechanisms that lead to chronic asthma in order to identify novel, more effective therapies. We concentrate on immune mechanisms that underlie chronic airway inflammation with a clear focus on one immune tolerance molecule, the class I major histocompatibility complex protein human leukocyte antigen (HLA)-G, that we believe has an important role in modulating airway inflammation that is critical to chronic asthma. The key premise of our AADCRC proposal is that understanding the role of HLA-G will lead to new and better therapies to alleviate the suffering caused by asthma. To this end we propose three highly integrated and related projects: in Project 1, we will examine the presence and regulation of expression of HLA-G in asthmatic airways and in the airway epithelium, and relate presence to asthma severity and to the expression of regulating microRNA. We will examine the regulation of HLA-G expression by key Th2 cytokines such as IL-13 that are important to chronic asthma and relate expression back to airway cytokine concentrations in chronic asthma. In Project 2, we will exploit naturally occurring genetic variations in HLA-G and its LILRB receptors to understand how signaling through HLA-G and its receptors regulate the transition of CD4+ lymphocytes to the Th2 phenotype in mild/moderate asthma and to the Th17 phenotype in severe asthma. This project also will examine how genetic variation in the LILRB receptors modulate the effects of HLA-G on both T cell phenotype and on the SHP1 and SHP2 signaling pathways that modulate airway smooth muscle hypertrophy in chronic asthma. In Project 3, we will elucidate mechanisms that account for the higher risk of asthma among children of asthmatic mothers compared to children of non-asthmatic mothers. Using HLA-G as a model of the interactions of genotype and asthma status in mother and child, we will identify differentially expressed genes and the mechanisms for their differential expression in airway epithelium, CD4+ T cells and airway smooth muscle in subjects with chronic asthma. To complete these projects, each will interact with a robust Patient Recruitment and Data Analysis Core that will recruit 100 carefully phenotyped and genotyped asthmatic subjects and additional control subjects, and collect blood and airway biological specimens to be used in each project through a Lung Biological Specimens Core that will provide analytical and long-term storage. We believe that our current levels of productivity and collaboration combined with new, exciting and cutting-edge questions in this proposal will allow us to be successful in achieving our overall goal—identifying novel therapeutic targets for chronic asthma.

Title: **Autoimmunity Center of Excellence (ACE) at Stanford**
P.I.: **Charles Garrison Fathman**
Institution: **Stanford University**
Grant No.: **AI082719-03**
Award: **$30,000**

The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The major theme of the Stanford Autoimmunity Center of Excellence (the Center) is the study of the regulation of CD4 T cells in pathogenesis and treatment of autoimmune diseases. The Center will support and be supported by other ACE groups across the United States; and will take advantage of Stanford's documented leadership in basic and clinical research, technology development, and education in clinical immunology. Success of the Center will be supported by the interrelationships previously established at Stanford among clinician scientists from multiple departments studying autoimmune diseases in multiple organs and tissues. The Stanford ACE will be composed of outstanding basic and clinical investigators from multiple disciplines at Stanford Medical School and proposes both a basic Research Project, centered on CD4 T cell

unresponsiveness, and a translational Research Project to study a new T cell lineage (termed Th17 cells) that is characterized by the ability of these lymphocytes to secrete high levels of the proinflammatory cytokine interleukin-17 (IL-17). Proposed clinical research projects encompass three different autoimmune diseases [diffuse systemic sclerosis (SSc), psoriatic arthritis and systemic juvenile idiopathic arthritis (SJIA)] that afflict adults and children, as well as organ systems including joints, skin, blood elements, and blood vessels, and will both test efficacy of therapy and develop tests to characterize the mechanisms of action of these therapeutics. The proposed Pilot and Feasibility Project proposes a two year research plan in Systemic Juvenile Idiopathic Arthritis (SJIA) patients to identify and validate urine peptide biomarkers that predict (a) response to TNF inhibition; (b) response to IL-1 inhibition; and (c) impending disease flare. In addition, this proposal will provide other ACE groups access to cutting edge reagents and technology platforms for studying human autoimmune diseases, and dissemination of Educational Materials that can be used by other ACEs to teach clinical immunology concepts to high school, undergraduate, graduate, postgraduate, and clinical fellows and faculty. The Stanford ACE proposes to support integrated basic, pre-clinical and clinical research by proposing and then conducting basic and translational research into the mechanism of CD4 T cell unresponsiveness; two clinical trials that include novel therapies and mechanistic studies of these therapies for autoimmune diseases; and a pilot proposal that intends to develop new bi omarkers of disease. PROJECT 1A: Clinical Component (Genovese, M) CLINICAL COMPONENT DESCRIPTION: Stanford University Medical Center (SUMC) has an extraordinary tradition of medical, translational, and basic science research. An outstanding array of resources, faculty, and facilities will be available to support the proposed ACE site at Stanford University. This proposal brings together a skilled group of translational researchers with a track record of productivity in both laboratory and clinical research focusing on human autoimmune mediated diseases. Stanford has brought together various disciplines to demonstrate both accomplishment and ability to work together with the following fields represented: Adult Rheumatology, Dermatology, Pulmonary Medicine, and Pediatric Rheumatology. The projects chosen for this submission highlight the significant collaborations that exist between Rheumatology (Adult and Pediatric), Dermatology and Pulmonary Medicine. Both clinical trials projects explore dermatologic and rheumatologic manifestations of diseases such as Psoriatic arthritis and Systemic Sclerosis. Clinical Trial Concept 1: The use of an anti-IL-17 mab in the treatment of active Psoriatic Arthritis Primary Hypothesis: The proportion of patients achieving the ACR 20 response from Baseline to Week 14 among active Psoriatic Arthritis (PSA) subjects treated with IL-17 mab is larger than the proportion achieving ACR 20 response from Baseline to Week 14 among active PSA subjects treated with placebo Objectives: The goal of this study is to determine the safety and efficacy of a monoclonal antibody to lnterleukin-17 (IL-17 mab) in the treatment of PsA with active skin and joint disease. Clinical Trial Concept 2: The use of CTLA-4lg (abatacept) in subjects with diffuse systemic sclerosis Primary hypothesis: Given several lines of evidence supporting the role of activated T cells in affected skin, we hypothesize that inhibiting T cell activation may lead to significant clinical improvement in skin manifestations in patients with diffuse systemic sclerosis (dSSc), and that changes in tissue and blood autoantibody and cytokine profiles will be associated with clinical response. Objectives: The primary goal of this study is to determine the safety and efficacy of CTLA-4lg (Abatacept) for the treatment of cutaneous manifestations of dSSc. RELEVANCE: The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune (Al) disease. The Stanford ACE proposes clinical research projects that encompass three different autoimmune diseases (SSc, psoriatic arthritis and SJIA), and proposes to study the MoA of therapeutics for preventing or treating different Al diseases.

Title: **Cervical/Vaginal Mucus and Microbicides**
P.I.: **Thomas Hope**
Institution: **Northwestern University, Feinberg School of Medicine**
Grant No.: **AI094584-01**
Award: **$18,750**

To develop a functional microbicide it is critical to know how it will interact within HIV in the context of the female genital tract. This is a critical issue as previous clinical trials have indicated that microbicides do not function as expected in the presence of semen. Likewise, other factors, such as cervical/vaginal mucus, might also modulate microbicide function. To date, little is known about how HIV interacts with these fluids and how the interaction of these fluids changes the local environment. Even less is known about how microbicides interact with HIV within this milieu. For example, the vehicle delivering the microbicide might interact with the biological fluids of sexual transmission to either increase or inhibit HIV acquisition or microbicide potency. The Hope laboratory has recently developed methods that allow the transport of HIV with cervical and cervical/vaginal mucus to be analyzed and quantified. These studies have revealed that mucus can perturb HIV transport and is pH sensitive. At acidic pH, as is found in the lactobacilli influenced environment of the vaginal vault, HIV transport is greatly reduced. At neutral pH, such as when semen is introduced into the system, HIV transport is reduced 10-15 fold relative to what is observed in media (water). Additionally, we have found, but not yet published, that virus-binding antibodies can further reduce transport in neutral pH cervical mucus. These antibodies do not need to be neutralizing as any antibody binding to the virus can decrease virus transport. Semen also contains mucins and other components that have the potential to alter HIV transport as we have observed in cervical mucus. How HIV is transported within semen and how this changes when mixed with mucus or microbicides is not defined. How this process influences HIV transport and interaction with mucosal barriers is not understood. In the first phase (R21) of this proposal we will define how HIV is transported in semen alone and mixed with mucus and/or microbicide vehicles such as carbopol gel and hydroxy ethyl cellulose (HEC). In the second phase (R33) of this proposal we will extend our studies into the environment of the rhesus macaque female genital tract to determine how biological fluids and microbicide vehicles alter the way that virus interacts with the mucosal barriers of this environment and how these changes can increase or decrease SIV acquisition. These studies will lead to a better understanding of how virus interacts with biological fluids and how these interactions might alter microbicide efficacy.

Title: **Congenital Transmission of Lineages I and II of Trypanosoma cruzi**
P.I.: **Pierre Buekens**
Institution: **Tulane University of Louisiana**
Grant No.: **AI083563-02**
Award: **$10,000**

T. cruzi has been divided into two main lineages: T. cruzi I (TcI) and T. cruzi II (TcII). TcI is predominant in Mexico and Central America, while TcII is predominant in most of South America, including Argentina. In recent studies from Argentina, the risk of congenital transmission has been estimated to vary between 2.6 percent and 7.9 percent. By contrast, we know very little about the congenital transmission of TcI. It has been suggested that congenital transmission of T. cruzi is strain related, and there is an urgent need to know if TcI transmits differently than TcII. Our primary hypothesis is that congenital transmission rates are different for TcI versus TcII. Our secondary hypothesis is that the characteristics of T. cruzi infected mothers (e.g., age, parity, transmission in previous pregnancies) and their exposure to vectors are different in regions where TcI is predominant versus regions where TcII is predominant. To test these hypotheses, we propose to conduct a prospective study to enroll at delivery 10,000 women in Mexico, 5,000 women in Honduras, and 5,000 women in Argentina. We will measure transmitted maternal T. cruzi antibodies in cord blood, and, if the results are positive, we will identify infants who

are congenitally infected by performing parasitological examinations on cord blood and at 4-8 weeks, and serological follow-up at 10 months. We will also perform standard PCR, real-time quantitative PCR, and T. cruzi genotyping on maternal blood, standard PCR and T. cruzi genotyping on the cord blood of congenitally infected newborns, and serological examinations on siblings. We will estimate the exposure to vectors in the household. In addition, we will measure prenatal outcomes among infected and uninfected infants with seropositive mothers, and the birth weight of their siblings. The specific aims of this study are: 1) To determine the rate of congenital transmission of TcI compared to TcII; 2) To compare the T. cruzi infected mothers' characteristics and exposure to vectors in regions where TcI is predominant and regions where TcII is predominant; and 3) To describe the birth outcomes of infected and uninfected infants born to TcI and TcII seropositive women.

Title: **Designing Optimal Microbicide Delivery Integrating Rheology and Acceptability**
P.I.: **John Edward Hayes**
Institution: **Pennsylvania State University**
Grant No.: **AI094514-01**
Award: **$18,750**

This year perhaps 2.5 million people will be added to the approximately 35 million already infected with HIV/AIDS, 50% of whom are women. Topical microbicides offer these women a means to prevent sexually transmitted infections (STIs), including HIV. However, in addition to concerns about the biological efficacy of current microbicides, user acceptance of and adherence to their use is suboptimal. It has been estimated that a single microbicide with even limited efficacy could prevent millions of new HIV cases annually. The design of vaginal microbicide dosage forms has challenged formulation scientists. Safe and efficacious products are necessary, but not sufficient to assure adherence. User acceptability depends both on the physical properties of the material and behavioral factors. Constraints that drive acceptance must be identified and addressed early in development. The acceptability of the product to women must be evaluated preclinically. We propose the rational preclinical design and development of a dosage form that delivers an immediate efficacious dose of active pharmaceutical ingredient (API) followed by the slow release of API over a period of 1-3 days to maintain efficacy. This dosage form can be thought of as a temporal vaginal ring/diaphragm that releases API(s) as it slowly erodes away. These products will be an adaptation of current softgel capsule technology. However, unlike current gelatin capsules, we will develop a range of non-gelatin capsules varying in shape and firmness (texture). Human perceptual data will be assessed throughout and guide the design process. Carrageenan will be used for the development of heat-stable softgels that, unlike current gelatin capsules, will not melt in tropical environments. The two-phase nature of softgels ('ovules') will permit the inclusion of a second component. Our R21 goals provide for proof-of-concept of this new delivery system, and the R33 goals will optimize both acceptability and biophysical functionality. The R33 will also explore potential higher-order functionality, like mucoadhesion or delivery of probiotics. Here, we propose a new microbicide delivery system, designed to overcome both biological (insufficient HIV neutralization) and behavioral (poor acceptability and adherence) deficiencies of current products. By designing formulations that function for optimal efficacy and optimal use (acceptability / adherence), microbicides produced via these methods are likely to have a greater impact on the HIV/AIDS pandemic than those currently in the development pipeline. Also, by developing a methodology for design of vaginal products where multiple factors (shape, texture, size, and multi-stage delivery) play a central role, we increase the options women have in microbicide use. Critically, our product type is flexible—allowing for multiple textures, sizes, shapes and antiviral strategies—to accommodate a range of user preferences.

Title: **Development of a Novel Nanoparticle Pyrimidinedione Vaginal Polymeric Film as an Anti-HIV Microbicide**
P.I.: **Anthony Sang Won Ham**
Institution: **ImQuest Biosciences**
Grant No.: **AI088586-02**
Award: **$21,429**

Pyrimidinediones (PYD) are highly potent small molecule inhibitors that have a dual anti-HIV mechanism of action: viral entry inhibition and non-nucleoside reverse transcriptase inhibition (NNRTI). The PYD compounds have shown in vitro subnanomolar levels of activity as an NNRTI and nanomolar levels of activity as inhibitors of entry occurring prior to chemokine receptor binding and fusion. However, as microbicides compounds are being developed, delivery issues that are part of the formulation of the compound have lagged behind causing a critical delay in product development. Due to low solubility and poor penetration through the mucosa to the target site of action, Pyrimidinediones face significant obstacles as microbicides. Strategic drug delivery design is essential for Pyrimidinediones to advance as viable microbicide products. We propose a combination of innovative drug delivery strategies to enhance PYD anti-HIV efficacy through polymer biochemistry formulations. Specifically, nanoparticle encapsulation has been used to overcome many of the challenges presented when using hydrophobic drug molecules; however, its use as a vaginal drug delivery system has not been investigated. In the R21 phase of this project, we propose to develop nanoparticle encapsulation of PYD as a novel drug delivery method to improve the potency of HIV inhibition activity by increasing long term drug release, protecting against enzymatic degradation, enhancing submucosal tissue penetration and cell localization. Additionally, we propose to further formulate the nanoparticle PYD formulation into a vaginally delivery polymer film dosage form. Such "quick dissolving" solid dosage forms have recently been proposed as a innovative alternative to address several acceptability and compliance issues observed in more traditional vaginal delivery systems (gels, creams, intra-vaginal rings). Our nanoparticle PYD film delivery approach offers several innovative advantages in microbicide development by suggesting enhanced apparent activity without active pharmaceutical ingredient (API) reformulation, conferring HIV protection over long periods of time through controlled drug release, making such a microbicide coitally-independent, and introducing a novel drug delivery method through vaginal films that addresses many of the acceptability issues with gels and other semi-solid dosage forms. Biological characterization and evaluation will be preformed to confirm the efficacy of PYD nanoparticles in biologically relevant conditions. The encapsulation of PYD into biodegradable nanoparticles will be characterized and evaluated in specifically designed in vitro assays to determine drug targeting and release. Additionally, the anti-HIV efficacy of the nanoparticle PYD will be compared to unformulated PYD in biologically relevant in vitro assays to determine the optimal formulation. Finally, the formulation will be introduced into a solid vaginal film dosage form to evaluate its biological properties in HIV prevention.

Title: **Development of an HIV-1 Entry Inhibitor Pre-drug as a Microbicide**
P.I.: **Min Lu**
Institution: **University of Medicine and Dentristry of New Jersey, Robert Wood Johnson Medical School**
Grant No.: **AI094555-01**
Award: **$18,750**

With no vaccine in sight, there is an urgent public health need to develop an effective topical microbicide that can reduce the number of new HIV-1 infections in women. The potential role of virus-cell fusion inhibitor-based microbicides in preventing mucosal transmission of HIV-1 has been clearly identified. However, none of the reported gp41 fusion inhibitors has made significant progress toward clinical trials. HIV-1 infection requires fusion of the viral and cellular membranes, driven by association of two heptad-repeat regions in the gp41 ectodomain to form

a highly stable six-helix bundle structure. Whereas this postfusion motif comprising native N36 and C34 peptides has no inhibitory activity, the isolated peptides inhibit HIV-1 entry by binding to their cognate sites on gp41. Our goal in this MIP VI application is to develop an inexpensive, potent, structured 'pro-drug' form of the N- and C-peptide fusion inhibitors that exhibits significant microbicidal activity upon use in situ. Our development effort will be based on preliminary data obtained with a truncated six-helix bundle that inhibits in vitro infection by primary HIV-1 isolates with low nanomolar IC50 values. We propose a comprehensive, interdisciplinary approach that combines high-resolution structural determination, recombinant protein production and mutagenic analyses, virology, and animal model efficacy studies. In this project we seek to conduct in vitro and in vivo preclinical and animal model-based research intended to facilitate the development of new HIV-1 gp41 peptide fusion inhibitor as a practical microbicide. The Specific Aims are: 1. To optimize and identify HIV-1 peptide fusion inhibitors for development as a vaginal microbicide. (a) To identify and incorporate specific amino-acid residue substitutions that optimize both potency and solubility of fusion inhibitor peptides. (b) To develop and optimize robust procedures for the large-scale bacterial expression and purification of select fusion inhibitor peptides. (c) Investigate the mechanisms of resistance to peptide inhibitors so as to avoid eliciting resistance. 2. To characterize the specificity, potency and toxicity of optimized peptide fusion inhibitors and their in vitro synergistic interactions with the CCR5 inhibitor CMPD167 and the entry inhibitor BMS-378806. (a) Determine the virucidal activity of optimized fusion inhibitor peptides against a diverse set of primary HIV-1 isolates. (b) Evaluate their toxicity, immunogenicity and drug stability in the rabbit model. (c) Study antiviral synergy in vitro in order to make rational predictions for lead inhibitor combinations for in vivo efficacy testing. 3. To test the effectiveness of the fusion inhibitor peptides to protect against mucosal HIV-1 infection. (a) Characterize the specificity and potency of effective peptide inhibitors in an in vitro model of HIV-1 infection of human cervical and vaginal tissue. (b) Use the NOD/SCID-hu BLT mouse vaginal transmission model to assess the in vivo potency and breadth of activity of highly effective peptide inhibitors alone and in combination with the small-molecule CCR5 inhibitor CMPD167 and the small-molecule entry inhibitor BMS-378806.

Title: **Development of Antimicrobial Peptides as Topical Microbicides**
P.I.: **Robert Walter Buckheit**
Institution: **ImQuest Biosciences**
Grant No.: **AI082689-02**
Award: **$21,428**

We hypothesize that novel anti-HIV and anti-STI topical microbicides based on natural antimicrobial peptides collected in the Antimicrobial Peptide Database developed by the co-PI's laboratory (*http://aps.unmc.due/AP/main.html*) can be discovered and improved through peptide engineering technology. During the R21 phase, we will methodically screen peptides from the database and define specific inhibitors of HIV and HSV-2 as well as broad based inhibitory peptides. These active agents will be further developed in order to understand their range and mechanism of anti-HIV action. Superior peptides identified in SA1 will be characterized in SA2 to provide a rationale for continued development in SA3 using various molecular strategies which will result in the improvement of the therapeutic index of the peptide agents, with and without other small molecule microbicides, in order to begin development of an effective microbicide product. This product will be formulated and evaluated in animal models and safety assessment studies in the R33 portion of the project. Our goal is to produce a female controlled preventative agent which can be utilized to prevent the sexual transmission of viral, bacterial and fungal organisms with a focus on inhibiting the transmission of HIV. The research data will be entered into the existing antimicrobial peptide database to facilitate the use by funding agencies, other researchers, students and the public.

Title: **Engineering Antiviral Innate Immunity for Safe and Effective Microbicides**
P.I.: **Hong Shen**
Institution: **University of Washington**
Grant No.: **AI088597-02**
Award: **$21,429**

HIV infections afflict millions of people and cause tremendous health and economic burdens. One of the major risk factors for HIV-1 transmission is the pre-existing infections caused by sexually transmitted agents such as herpes simplex virus type 2 (HSV-2). Therefore, a rational prevention strategy to halt HIV spread is to target HSV-2 infection and control its spread. In the absence of vaccines against HSV-2, a more practical and effective intervention for HSV-2 is the utilization of microbicides. A promising microbicidal approach is to potentiate antiviral innate immunity effective against a broad range of viruses at the site of viral encounters. The toll-like receptor (TLR)-based innate immunity have been shown to be crucial in initiating a cascade of antiviral activities mediated by type I interferons (IFNs). Both TLR3 and TLR9 agonists, polyinosinic: polycytidylic acid (poly IC) and CpG oligonucleotides (ODNs) are effective in protection against HSV-2 infections. However, undesirable inflammatory responses and autoimmunity accompanying the non-specific stimulation of TLRs are of major concern, which could severely limit the use of TLR agonists as microbicides. Thus, the key to developing TLR agonists as microbicides is to target them to relevant cell types at the potential sites of viral exposure and to elicit IFN responses in a regulated fashion. We propose to develop localized, controlled-release, and cell-targeted delivery systems to regulate the stimulation of TLR-based innate antiviral immunity. In the R21 Phase, three aims will be accomplished: Aim 1: to design and characterize cell-targeted delivery systems based on poly (lactide-co-glycolide) (PLGA) nanoparticles to specifically and locally target pDCs and epithelial cells with TLR agonists; Aim 2: to evaluate the effectiveness against genital HSV-2 infections by locally and selectively targeting CpG ODNs and/or poly ICs to pDCs and epithelial cells with cell-targeted nanoparticles; Aim 3: to evaluate toxicity by locally and selectively targeting CpG ODNs and/or poly ICs to pDCs and epithelial cells with cell-targeted nanoparticles. Built upon the results from the R21 phase, in the R33 phase, we will accomplish: Aim 4: to design and characterize delivery systems for sustained release of TLR agonists; Aim 5: to evaluate the effectiveness against genital HSV-2 infection and toxicity by localized, sustained-release and cell-targeted nanoparticles loaded with CpG ODNs and/or poly IC; Aim 6: to evaluate the adaptive immunity against genital HSV-2 infection mediated by localized, sustained-release and cell targeted nanoparticles loaded with CpG ODNs and/or poly IC. This application will enable the translation of TLR-based antiviral innate immunity to effective and safe microbicides.

Title: **Epithelial Barrier Programs in Asthma and Allergic Disease**
P.I.: **Michael J. Holtzman**
Institution: **Washington University**
Grant No.: **AI070489-06**
Award: **$12,500**

The overall goal of this AADCRC proposal is to define the role of the epithelial cell barrier in the pathogenesis of asthma and allergic disease and to use that information to prevent this type of disease. We combine expertise in airway as well as gut and skin epithelial cell biology, and we use cell and mouse models with high fidelity to directly translate our findings to humans. The AADRC therefore consists of three interrelated Projects that ask, first, how airway epithelial cells mediate effective antiviral defense under one condition but asthma under another (Project 1), second, how airway epithelial cells remodel towards an overabundance of mucous cells in post-viral and allergic asthma (Project 2), and third, how epithelial injury in the skin triggers the march from atopic dermatitis to asthma (Project 3). Each project addresses the respective question with a novel but overlapping molecular approach to mechanism and takes advantage of a breakthrough discovery to set a new scientific paradigm for the system under study.

Thus, Project 1 unravels a new IFN signaling pathway that offers improved protection against viral infection and post-viral asthma and is specific to the airway epithelial cell barrier; Project 2 dissects a new pathway for autophagy proteins to support proper mucous cell function and prevent mucous cell metaplasia in the airway in a manner reminiscent of the intestinal epithelial barrier; and Project 3 defines a new TSLP production and secretion pathway that drives airway inflammation based on its expression in the skin epithelial barrier. Each Project is constructed so that the first aim will establish a basic pathogenic mechanism using cell and mouse models that are shared among projects and supported by the Cores for tissue and cell processing (Core C) and mouse models (Core D). In turn, each Project will conduct a second aim to validate and translate its findings using samples from children and adults with asthma and/or atopic dermatitis supplied by the Core for human subjects and data analysis (Core B). Sharing samples and overlapping scientific goals among projects create a synergistic program that can be coordinated by a common Administrative Core (Core A). Project and Core interactions are based on the overall principle that each Project begins with molecular hypothesis building in cell and mouse models and translates findings from these models to studies of humans with asthma and/or allergy. In each project, we aim to validate a clinically useful biomarker of the disease process and lay the groundwork for the future development of biological and/or small molecular weight compounds that might influence the process as a therapeutic strategy.

Title: **Epithelial Genes in Allergic Inflammation**
P.I.: **Gurjit K. Khurana Hershey**
Institution: **Cincinnati Children's Hospital Medical Center**
Grant No.: **AI070235-06**
Award: **$12,500**

Allergic disorders are a major global health concern affecting 150 million people worldwide. Recently, epithelial cells have emerged as central participants in the pathogenesis of allergic inflammation: (1) they interface with the environment and initiate the response to environmental triggers; (2) the mucosal epithelium in the lung, skin, and gut functions as a physical barrier against pathogens and environmental exposures including allergens; and (3) epithelial cells have been directly implicated in Th2 responses, serving as a critical interface between innate immune responses and Th2 immunity. The overall objective of these studies is to elucidate the mechanisms by which epithelial cells contribute to the pathogenesis of allergic disorders. The overarching hypothesis of this Center proposal is that epithelial cell genes play a central role in the pathogenesis of allergic disorders. This hypothesis will be tested by three integrated projects that use the Center for coordination and synergistic extension of the projects beyond the scopes and capabilities of the individual projects. This Center will provide important insights into the genes and pathways that may be Important in epithelial driven allergic inflammation and provide a basis for the design of novel therapeutic strategies aimed at the epithelial surface, i.e. lung (asthma), skin (atopic dermatitis), or gut (food allergy or eosinophilic esophagitis). Furthermore, integration of data across projects will provide novel insights into a key question in allergy—What are the mechanisms underlying tissue specific disease manifestations of allergic inflammation? Each project in the Center is focused on distinct epithelial cell genes and their roles in allergic disorders. Project 1 will examine the association of epithelial genes with allergic diseases that target distinct mucosal surfaces. Project 2 will dissect the role of epithelial desmoglein-1 in the pathogenesis of the allergic disorder eosinophilic esophagitis. Project 3 will focus on delineating the mechanisms by which epithelial-derived IL-33 is regulated by trefoil factor 2 (TFF2) during the early innate immune events that initiate allergy and asthma; and better define the role of the TFF2/IL-33 pathway in the pathogenesis of allergic disorders.

Title: **Exploring the Role of Vif Antagonists in Preventing Sexual HIV Transmission**
P.I.: **Mario Stevenson**
Institution: **University of Miami School of Medicine**
Grant No.: **AI088595-03**
Award: **$21,429**

Since it has proven difficult to develop a vaccine against HIV-1, the major cause of the AIDS pandemic, the research community has shifted some of its focus to the development of topical microbicides. Since both the vaginal and rectal tract are portals of HIV-1 entry, topical microbicides suitable to protect both sites need to be developed. In this grant, we focus on a novel mechanism that has not previously been explored for HIV prevention. In 2002, it was found that the cellular target of the HIV-1 protein Vif is APOBEC3G (A3G). A3G is an enzyme of the AID/APOBEC family, characterized by the targeted deamination of cytosine to generate uracil within DNA. APOBEC3G plays an important role in retroviral defense by acting on viral reverse transcripts and mediates numerous critical immune responses. We believe that A3G is an important innate retroviral defense mechanism in the vaginal and rectal tract. By using inhibitors of the viral protein Vif, the Vif-APOBEC3G interaction is blocked and APOBEC3G is not degraded by the proteosome. As a consequence, fatal hypermutations are introduced into the viral cDNA transcripts and HIV is rendered incompetent for replication. Our grant has four specific aims: Specific Aim 1: Explore the role of the restriction factor A3G in mucosal tissues of the vaginal and rectal tract Specific Aim 2: Examine whether RN18 and its analogs are active in microbicide cell-based assays and ex vivo explant HIV transmission models Specific Aim 3: Vaginal humanized BLT mouse model testing of promising Vif inhibitor candidates Specific Aim 4: Macaque microbicide model testing of promising Vif inhibitor candidates It is expected that these studies will define the role of A3G in the vaginal and rectal tract and whether inhibitors of the viral Vif protein can prevent sexual transmission of HIV.

Title: **Host and Viral Determinants of Infant and Childhood Allergy and Asthma**
P.I.: **Ray Stokes Peebles**
Institution: **Vanderbilt University Medical Center**
Grant No.: **AI095227-01**
Award: **$12,500**

The long term objective of this application is to define the relationship between infant respiratory syncytial virus (RSV) infection and the host response that enables asthma inception. There is abundant evidence that children who experience severe RSV bronchiolitis during infancy are at greater risk for developing asthma later in childhood; however the host and viral determinants of severity of illness are not fully defined. Also unknown is whether mild RSV-induced illness in infancy may protect against the subsequent development of childhood asthma. In Project 1, we utilize the ReSPIRA (Respiratory Study for Protection of Infants from RSV to Asthma) cohort of 2000 infants to focus on host immune responses to RSV infection and the subsequent risk of recurrent wheezing and childhood asthma. Specifically, in Project 1 we will a) establish the relationship between the host phenotypic response to RSV infection in the first 6 months of life and the risk of recurrent wheeze and asthma, and b) identify the host genetic and immune response determinants of the RSV infection phenotype that affect the development of early childhood wheezing and asthma following RSV infection. In Project 2, we will focus on the contribution of specific RSV strains to early childhood wheezing and asthma development. RSV strains isolated from the ReSPIRA cohort will be genotyped and clinical parameters such as bronchiolitis severity score, as well as mediators of the host immune response measured in respiratory secretions will be studied to determine how RSV genotypes impact the host response. In Project 3, we will utilize a mouse model of RSV infection to examine the role of the prostaglandin 12 (PGI2) on airway dysfunction of an RSV strain (01/2-20) that has been associated with severe infant bronchiolitis and which induces airway pathology in the mouse. We previously reported that PG12 and signaling through its receptor (IP) is a critical determinant of severity of illness in RSV strain

A2 infection. This project will determine the role of host PGI2 in RSV airway pathogenesis and also determine if a PGI2 analog currently used in the treatment of human disease is a target for RSV bronchiolitis. Further, in Project 3, we will use RSV strains isolated from ReSPIRA in Project 2 to determine the generalizability of PGI2 as a therapeutic target.

Title: **Mechanisms of Beta Cell Responses in Autoimmune Disease—ACE**
P.I.: **Eugene William St. Clair**
Institution: **Duke University**
Grant No.: **AI056363-08**
Award: **$30,000**

This application is a competitive renewal of the Autoimmunity Center of Excellence (ACE) at Duke. Its research focus will continue to be modulation of B cell responses in autoimmune disease. The ACE will be under the leadership of Dr. E. William St. Clair, Professor of Medicine and Immunology. For the past 5 years, Duke has been a productive member of the ACE network, contributing new insights into the developmental pathways of B cells and the mechanisms of B cell directed therapy. The proposed ACE builds on these discoveries and will support 2 new basic science projects, 5 ongoing and 2 new clinical trials, and an Administrative Core, and continue to emphasize a strong and fluid integration between the bench and the bedside. Tedder and colleagues have recently found that a phenotypically unqiue subset of B cells secreting IL-10 (called B10 cells) serve as critical negative regulators during adaptive CD4+ T cells responses, and dramatically suppress Th1 immune responses and autoimmune disease in mice. For Basic Research Project 1, they will examine the hypothesis that antigen-specific regulatory B10 cells modulate autoimmune responses in mice and man and that they can be manipulated for therapeutic gain. A picture is gradually emerging about the precursors of self-reactive B cells in autoimmune disease. Kelsoe and coworkers in Basic Research Project 2 will investigate developmentally regulated expression of activated cytidine deaminase (AID) in human fetal and neonatal pre-, pro, and immature/transitional B cells and its relationship to the generation of self-reactive B cells in human autoimmune disease, potentially eludidating another pathway of B cell self-reactivity outside the confines of normal tolerance mechanisms. We propose two new clinical trials to investigate lymphotoxin-beta receptor fusion protein as a treatment for primary Sjögren's syndrome, and rituximab therapy for bullous pemphigoid. A Pilot Research Project is also proposed to engineer tetramers of self-antigen enabling the identification and characterization of self-reactive B cells, which will have implications for the goals of the clinical and other basic research projects. Overall, the Duke ACE will bridge these basic and clinical studies to advance our understanding of autoimmune disease. The B cell is a type of immune cell essential to autoimmunity. The goal of the proposed Autoimmunity Center of Excellence at Duke is to improve our understanding of the roles played by B cells in human autoimmune disease. The projects are designed to be highly integrative between the bench and the bedside, with collaborations between basic and clinical scientists. These studies may lead to better treatments. CLINICAL COMPONENT: Clinical Component (ST CLAIR, W) CLINICAL COMPONENT DESCRIPTION: The Clinical Research Component of the Autoimmunity Center of Excellence shares with the Basic Research omponent an overall goal of advancing our understanding about the role of B cells in the pathogenesis of autoimmune diseases. This component will be directed by Dr. E. William St. Clair. During the past 5 years, the Duke ACE has brought 3 new clinical trial concepts to the ACE Steering Committee, resulting in 1 completed trial, 1 ongoing trial, and 1 protocol in development. We are also participating in 3 other ongoing ACE-sponsored clinical trials. Therefore, substantial clinical research activity will carry over to the next funding cycle. Our center is organized to support clinical trials in rheumatology, dermatology, gastroenterology, hematology, and neurology. We have access to several large patient populations, including patiens with rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome, scleroderma, autoimmune blistering disease, psoriasis, inflammatory bowel disease, autoimmune hepatitis, anti-phospholipid antibody syndrome, and myasthenia gravis. Each of these disease areas has

leadership from one or more physician-investigators with significant clinical trial experience, including an example of a productive inter-institutional collaboration. The physician leadership is supported by an ample infrastructure that provides clinical research space, infusion facilities, experienced clinical coordinators, and an Immune Monitoring Component. The Clinical Research Component aligns with the ACE at a thematic level, with substantial collaborations between basic and clinical scientists. To this end, the proposed clinical trial concepts will focus on B cell directed therapy. In one case, we propose to examine the clinical efficacy of lymphotoxin-beta receptor fusion protein in the treatment of primary Sjögren's syndrome, and have already secured commitment from the industry sponsor to provide study drug for this trial. The other application will investigate rituximab as initial therapy for bullous pemphigoid. The mechanistic studies for these proposed trials as well as current trials are highly integrated with the basic research projects. The Clinical Research Component will make a significant contribution to the ACE enterprise during the upcoming funding cycle. The Clinical Research Component will support clinical trials sponsored by the Autoimmunity Centers of Excellence in several disease areas, including rheumatology, dermatology, gastroenterology, hematology, and neurology. It has been productive during the current funding cycle, and has the capability, as shown in this application, to generate new ideas for clinical trials that can be translated into well-designed studies.

Title: **Mucosal Tissue Explants as Surrogates for In Vivo Efficacy of Microbicides**
P.I.: **Carolina Herrera**
Institution: **University of London, Imperial College of Science, Technology and Medicine**
Grant No.: **AI094515-02**
Award: **$18,750**

The HIV microbicide field is dependent upon testing in non-human primates (NHPs) as the only relevant model to study infection. However, the predictive accuracy of NHP studies of efficacy in humans has not been validated and as such the economic value is unknown. Hence, refinement of this model and development of a novel correlate of efficacy in humans that will reduce the potential use of NHPs is key for the global progress of microbicides and specifically of the Microbicide Innovation Program's mission. This proposal addresses these issues by testing the hypothesis that ex vivo tissue explant cultures can provide a potential surrogate of in vivo efficacy through measurement of intra-tissular drug pharmacology and ex vivo infection/protection. This will be investigated using combined expertise in modeling mucosal tissue infection and measurement of antiretroviral (ARV) drug pharmacokinetics and pharmacodynamics in tissue. The proposal will focus on a reverse transcriptase inhibitor, PMPA (tenofovir), and an entry inhibitor, maraviroc, used alone and in combination as candidate microbicides. In the R21 component of the proposal we will demonstrate the robustness of our ex vivo explant models for analysis of pharmacological parameters and ex vivo infection independently of the origin (human or NHP) and the type of mucosa (cervicovaginal or colorectal). This will be investigated through two Specific Aims: 1) to define ex vivo pharmacological dose-responses (pharmacokinetics and pharmacodynamics) in human and rhesus macaque mucosal tissue explants; 2) to define whether the viral backbone affects pharmacological correlates of activity. The next step of our proposal in the R33 component will involve validation of the model as a surrogate for prediction of in vivo efficacy of ARV drugs as vaginal and colorectal microbicides. Here the two Specific Aims are: 3) to assess whether activity of drugs titrated in vivo can be predicted with ex vivo challenge models: 4) to correlate ex vivo and in vivo protection and drug dosing in NHPs. The iterative design of the overall proposal will allow us to assess correlates between intra-tissular pharmacological dosing and efficacy at all levels: tissue type, origin of tissue, route of dosing and challenge, and nature of experiment (ex vivo, in vivo). These correlates will define "conversion factors" of microbicides efficacy between the NHP model and in humans, which will be key for the rational development of existing and future candidate microbicides. PUBLIC HEALTH RELEVANCE: This project seeks to establish methods to predict in humans the potential of candidate microbicides to prevent sexual HIV infection. Currently microbicides are often tested

in non-human primates (NHPs) to determine if they can prevent vagina or rectal infection with SHIV (a monkey equivalent of HIV). However there is no way to determine whether the dose of drugs shown to be protective in NHPs would be the same as that required to protect humans. The main goal of this project is to test whether biopsies taken from animals or humans treated with microbicides are protected from infection when challenged in the laboratory. The series of experiments proposed in this study will test whether use of human biopsies have potential for predicting the dose of drug required to protect individuals using a microbicide from sexual transmission of HIV.

Title: **Mucus-Penetrating Particles for Rectal Microbicides**
P.I.: **Justin S. Hanes**
Institution: **Johns Hopkins University**
Grant No.: **AI094519-01**
Award: **$18,750**

For reliable protection against STD transmission, rectal microbicides must be formulated in a way that will deliver the active agent to all the surfaces that are susceptible to infection. These include the entire rectum as well as a large fraction of the colon (due to peristaltic stirring of colonic contents). Colorectal surfaces are columnar epithelia that are mechanically and osmotically fragile, and are highly susceptible to STD transmission. Although continuous mucus secretion by these susceptible surfaces helps protect against trauma and pathogens, this continuously secreted mucus also poses a significant barrier against effective delivery of microbicides to the epithelial surface. Recently we developed novel mucus penetrating nanoparticles (MPP) that can overcome this barrier and provide sustained, well-distributed delivery of drugs to mucosal surfaces. Our hypothesis is that MPP will significantly increase the protective efficacy of rectal microbicides by achieving more uniform and complete colorectal distribution, sustained drug activity, and thus longer duration and more complete protection compared to drug delivered in gels ("free drug") or drug delivered in conventional nanoparticles, "CP", that adhere to mucus and fail to penetrate mucus barriers. In the R21 phase, we will determine optimal MPP properties for penetration of mouse colorectal mucus, and we will characterize the uniformity of MPP distribution and retention times in the mouse colorectum compared to CP and free drug. We will then prepare drug-loaded biodegradable and biocompatible MPP that provide sustained release of antiviral drugs (valacyclovir for HSV and UC-781 for HIV). We will deliver these MPP in both a rectal enema format and a rectal lubricant gel format since both formats are frequently used for enhancing rectal intercourse. Moreover, an enema may deliver MPP to large regions of the colon unlikely to be reached by a gel. The key milestone for the R21 phase will be development of valacyclovir-MPP and UC-781–MPP that provide more complete and persistent coverage of the rectal epithelial surface, with minimal toxicity, compared to CP formulations or free drug. In the R33 phase, we will extensively test these MPP formulations for safety and protective efficacy in our mouse/HSV rectal model and in the hu-BLT-SCID mouse/HIV model (via a subcontract with Dr. J. Victor Garcia-Martinez at UNC).

Title: **Nanoparticle Microbicides for Delivery of Combination Antiretroviral Drugs**
P.I.: **Kim A. Woodrow**
Institution: **University of Washington**
Grant No.: **AI094412-01**
Award: **$18,750**

Sexual transmission through the genital tract or rectal mucosa is the most common route for acquiring new HIV infections and accounted for ~70% of the 2.7 million people worldwide who became newly infected in 2007. A cure or effective vaccine that would contain the global spread of this epidemic is not expected in the near term, and new HIV infections continue to outpace advances made in treatment with antiretroviral drugs. There is consequently an urgent need to

develop agents that can be applied topically to mucosal surfaces to prevent the sexual transmission of HIV. However, several large-scale clinical trials testing the efficacy of agents that disrupt the integrity of the viral envelope (detergents) or prevent adsorption or fusion of the virus with its target cells (polyanions) have failed to protect against HIV infection. The success of highly active antiretroviral therapy (HAART) provides a paradigm for developing the next generation of microbicides, raising the possibility that a combination of potent and broadly active inhibitors that exhibit multiple and complementary mechanisms of action may be vastly superior to the delivery of single compounds. To fully realize the potential of these potent antiretroviral (ARV) drugs, the challenges of formulating and delivering compounds with markedly different chemical stability and aqueous solubility in a topical combination product must be overcome. This research plan is designed to evaluate nanoparticle-based vaginal drug delivery systems for HIV prevention. The experimental focus is to achieve protection against vaginal transmission of HIV-1 by topical delivery of a combination of antiretroviral drugs using mucus- and tissue-diffusing nanoparticle microbicides. This research would be the first to control the temporal and spatial co-delivery of a combination of antiretroviral agents that have different mechanisms of action against HIV-1 (Aim 1). If successful, our studies would be the first to determine the size range and penetration depth accessible for nanoparticulate drug delivery systems in the vaginal mucosa (Aim 2). Our proposed research will also provide valuable data on the transport, biodistribution, and pharmacokinetics of encapsulated and released antiretroviral agents that are administered topically to the vaginal mucosa using nanoparticle microbicides (Aim 3). Finally, we will conduct preclinical safety and anti-HIV efficacy studies to rapidly advance our nanoparticle-based microbicides to human safety and efficacy trials (Aim 4). The outcomes from our proposed research may highly impact the field of microbicide research for HIV and other sexually-transmitted infections.

Title: **Oklahoma Autoimmunity Center of Excellence**
P.I.: **Judith A. James**
Institution: **Oklahoma Medical Research Foundation**
Grant No.: **AI082714-03**
Award: **$30,000**

The Oklahoma Medical Research Foundation is home to outstanding clinical and basic science investigators who have research interests in the etiology and pathogenesis of autoimmune diseases and seek to identify novel therapeutics for more effective patient treatments. The scientific expertise, extensive clinical trial experience, access to geographically distinct patient populations, as well as unique patient registries, repositories and core technologies provide a solid foundation for the Oklahoma Autoimmunity Center of Excellence (ACE) application to which we have added a multidisciplinary team of clinical and basic science investigators. The focus of the Oklahoma ACE application is on expediting the translation of scientific discoveries in autoimmunity to clinical application in the diagnosis and treatment of systemic autoimmune diseases. To accomplish this, the Oklahoma ACE comprises two research projects, a proposed pilot research project, a Clinical Center (Joan Merrill, PI) and an administrative core (Judith James, PI). The research projects focus on thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and Sjögren's syndrome, which are also focuses of the Clinical Center. Multiple sclerosis, rheumatoid arthritis, pediatric arthritis, insulin-dependent diabetes, idiopathic thrombocytopenia and pediatric lupus are other key disease emphases of the Clinical Center. Two complimentary, but unique, research projects focus on understanding early events in the development of lupus autoimmunity and in defining targetable genetic associations in Sjögren's syndrome. The pilot project uses complimentary methods to address roles of elevated interferon activity in patients with TTP and a novel animal model of thrombocytopenia. In addition, two clinical trials are proposed; both of which enhance or build upon the basic science projects. The first studies efficacy and mechanistic affects of anti-IFN in select SLE patient subsets by applying a patient centric, dose optimization strategy. The second tests the efficacy and early MRI changes of a novel MEK1/MEK2 inhibitor in RA with

additional mechanistic studies. The Administrative Core will provide leadership and management through acting on behalf of the Oklahoma ACE members within the ACE Network and NIH Program, ensuring fiscal responsibility for the ACE, and providing an educational foundation for a multi-disciplinary approach to autoimmune disease research. Thus, the Oklahoma ACE will unite Oklahoma-based clinical and basic science experts to facilitate access to unique patient populations for participation in clinical trials and to understand basic mechanisms of etiology and pathogenesis. The Oklahoma ACE brings together adult and pediatric rheumatologists, neurologists, endocrinologists, dermatologists, hematologists, dentists, ophthalmologists, geneticists, immunologists, molecular biologists, epidemiologists and biostatisticians to provide a multidisciplinary approach to discovering and applying novel therapeutics in systemic autoimmune diseases. Through strong basic science projects paired with clinical expertise the Oklahoma ACE will provide unique research and clinical opportunities to the ACE Network. CLINICAL COMPONENT: CLINICAL CENTER (Merrill, J) CLINICAL COMPONENT DESCRIPTION: The Oklahoma ACE Clinical Center brings together disease-specific and interdisciplinary clinics in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, thrombotic thrombocytopenic purpura, insulin dependent diabetes mellitus, pediatric SLE and juvenile inflammatory arthritis to forward translational research in autoimmunity. Patients from each of these disease populations are available and committed to participate in potential national ACE investigations. With adult and pediatric rheumatologists, adult and pediatric endocrinologists, neurologists, hematologists, dermatologists, ophthalmologists and dentists, as well as basic scientists from various areas of immunology, molecular biology, genetics, epidemiology and biostatistics, our investigative team is poised to make basic advances regarding disease pathogenesis and to help translate these discoveries to the clinic. The Clinical Pharmacology program at OMRF will serve as the primary home for the SLE, RA, Sjögren's syndrome and TTP clinics. Currently leading or participating in more than 20 active clinical trials, this clinical center is accustomed to participating in clinical trials, managing confidential patient information, and providing multidisciplinary care. In addition, the Clinical Pharmacology space provides investigators access to state-of-the-art research tools directly adjacent to the patient care unit. Pediatric IDDM and rheumatology clinics are housed across the street at OUHSC and a large, community based multiple sclerosis clinic will participate for MS patient investigation. Joan Merrill, MD serves as the leader of our Clinical Center. She is the current medical director of the Lupus Foundation of America and a leader in SLE clinical trial development. She has served as the lead investigator on large, multi-site trials. Combining her extensive knowledge of clinical trial design and the known heterogenic presentation of SLE, she proposes to devise patient-centric clinical trials that use biomarkers of disease to optimize therapeutic doses. Our Clinical Center proposes two potential clinical concepts. Based upon our basic science investigation regarding pivotal roles for increased interferon activity in pre-clinical SLE, Sjögren's syndrome and potentially TTP, our first trial examines the efficacy and biologic impact of anti-INF alpha in SLE patients with arthritis and select dermatologic manifestations. The second trial proposes use of a first-in-class target of MEK1/MEK2 inhibition in RA to assess impact on MRI progression of disease and on select biomarkers. Both of these trials have mechanistic studies proposed to address key scientific questions regarding pathogenesis and response. The Oklahoma Autoimmunity Center of Excellence Clinical Center will provide interdisciplinary investigators with unique populations of well-characterized patients to participate in ACE network autoimmune disease clinical trials. With our rich Native American heritage and large rural populations, the patients provided by the Oklahoma ACE will be previously understudied and provide unique insights for therapeutic trials.

Title: **Pathophysiologic and Therapeutic Mechanisms of Aspirin Exacerbated Respiratory Disorders**
P.I.: **Joshua A. Boyce**
Institution: **Brigham and Women's Hospital**
Grant No.: **AI095219-01**
Award: **$12,500**

This Proposal for support of an Asthma and Allergic Disease Cooperative Research Center (AADCRC) grant is focused on the mechanistic basis of aspirin-exacerbated respiratory disease (AERD), a distinctive clinical syndrome that accounts for a disproportionate percentage of individuals with severe asthma and recurrent nasal polyps. AERD is associated with both characteristic clinical reactions to ingestion of nonselective inhibitors of cyclooxygenase (COX), persistently elevated generation of the cysteinyl leukotrienes (cys-LTs), especially during reactions to aspirin, and selective airway hyperresponsivness to leukotriene E4 (LTE4), the most stable and abundant of the cys-LTs. We have discovered a molecular pathway through which LTE4 induces pulmonary inflammation (requiring P2Y12 receptors and platelets) and vascular leak (requiring a putative novel LTE4 receptor, GPR99). We have also discovered that leukocytes from individuals with AERD display a defect in expression of COX-2 and COX-2-dependent generation of prostaglandin E2 (essential to maintain homeostasis in AERD), and that this reverses with desensitization to aspirin. We have also found that platelets and leukocytes from individuals with AERD lack the EP2 receptor for PGE2. A team of highly accomplished investigators with complementary skills will apply cellular, molecular, and whole animal strategies, combined with a proof-of-concept clinical trial to determine the cellular and molecular basis for these findings, their relevance to disease pathophysiology, and their amenability to therapy. Project 1 (J. Boyce, PI) focuses on the physiologic and functional consequences of EP2 receptor deficiency, and determines its epigenetic basis. Project 2 (Y. Kanaoka, PI) will verify the identity and function of GPR99 and determine its susceptibility to desensitization and its requirement for downstream effectors (platelets, P2Y12, and thromboxane) to elicit physiologic responses. Project 3 (E. Israel, PI) will determine the efficacy of P2Y12 antagonism on the severity of clinical reactions to aspirin, and the mechanism by which aspirin treatment restores COX-2-dependent PGE2 generation. The coordination of the AADCRC is enhanced by an administrative Core.

Title: **Phosphorothioate Oligonucleotides as Microbicides Against HIV Transmission**
P.I.: **Peter D. Katsikis**
Institution: **Drexel University**
Grant No.: **AI082680-02**
Award: **$21,428**

Developing interventions that inhibit the transmission of HIV infection are critical for halting the HIV epidemic. Topical prevention strategies usually termed microbicides have been proposed as one strategy to halt or slow down the HIV epidemic. We have identified novel lead microbicides that potently inhibit HIV and SIV infection/replication in vitro. During our previous submission we reported an oligonucleotide with a phosphorothioate backbone (OPB) that could inhibit HIVBaL or SIVmac251 infection and/or replication in human or simian PBMC, respectively. OPB also inhibited infection/replication in cell-free infections of P4-R5 MAGI cells by HIVBaL and HIVIIIB. OPB exhibited no toxicity against PBMC or P4-R5 MAGI cells after 24h continuous exposure. Preliminary data suggested that OPB may also inhibit other viruses as it was also effective against influenza type A virus. Thus, our first generation OPB may be a potent microbicide against HIV that prevents infection at mucosal sites when topically applied. Our preliminary studies were carried out with a 13mer Poly T or Poly A oligonucleotide of OPB and this suggested that the effect was sequence independent and may even be mediated by the phosphorothioate deoxyribose sugar backbone. Indeed in our current re-submission we present data on our next generation compound, a baseless phosphorothioate 2′ deoxyribose backbone (PDB) that has more potent HIV inhibitory activity than OPB. A 14mer PDB we show here has

no toxicity, is a potent inhibitor of HIV and has the advantage of being a TLR7/9 antagonist that inhibits HIV-induced IFNα production. This later property is important as the establishment of HIV infection may depend on HIV-induced mucosal inflammation triggered by TLR. Importantly, we show that PDB is active when formulated in hydroxyethylcellulose (HEC) gel at pH 4.4, survives pH transition to a neutral pH, and in retains its activity in HEC for long periods. We hypothesize that PDB binds enveloped viruses and inhibits their infectivity by acting as a "chemical lectin". We further hypothesize that PDB can act as a microbicide against HIV and can prevent SIV vaginal infection of rhesus macaques. The studies planned in the R21 phase will further optimize and characterize the safety and effectiveness of PDB in vitro and its safety in the Swiss Webster mouse vaginal/cervical model of irritation. They will determine the optimal size and composition that remains effective against HIV and exhibits no toxicity. Finally, the mechanism of action of PDB will be investigated, the effect of inclusion into hydroxyethylcellulose gel will be tested and PDB's effect on the growth of commensal lactobacilli will be determined. Five specific milestones have been set for the progression from the R21 Phase to the R33 Phase. The R33 phase will test the effectiveness of PDB in preventing vaginal SIV infection, investigate the effect of seminal plasma and pH transition on the efficacy of OPB, determine its safety with human genital epithelial tissue, and investigate its effectiveness against HSV-2. The current application will allow for an extensive evaluation of PDB as possible novel microbicide candidates. The studies proposed here address the important public health problem of developing treatments that inhibit the transmission of HIV infection. The current application investigates a novel chemical that may be used to inhibit infection with HIV.

Title: **Plant-Produced Actinohivin as a Candidate HIV Microbicide**
P.I.: **Nobuyuki Matoba**
Institution: **University of Louisville**
Grant No.: **AI088585-02**
Award: **$21,429**

Safe, effective, and inexpensive topical microbicides are urgently needed to curb the global human immunodeficiency virus type-1 (HIV-1) epidemic. Actinohivin (AH) is an actinomycete-derived lectin. This lectin specifically binds to high-mannose clusters uniquely found on the HIV-1 envelope (Env), thereby eliciting nanomolar antiviral activity against multiple HIV strains. Preliminary analyses revealed that AH has a high safety profile in human peripheral blood mononuclear cells (PBMCs) and in the rabbit vaginal irritation assay. Meanwhile, a translational AH-AH fusion protein (recombinant dimer [rd] AH) was suggested to have stronger and broader anti-HIV-1 activity than the original monomer. Given these high potentials, we hypothesize that rAH and/or rdAH (r/rdAH) are excellent HIV-1 microbicide candidates. This project's goal is to reveal the feasibilities of r/rdAH in terms of manufacture, antiviral efficacy, and safety upon use as a vaginal microbicide. In the R21 phase, we will initially focus on developing a highly efficient, scalable production system for r/rdAH that allows for extensive efficacy and safety studies and possible global use. We will utilize recombinant plant virus-based expression systems and various molecular biological approaches for rapid and high-level expression of high-quality r/rdAH. Upon obtaining bulk r/rdAH active pharmaceutical ingredients with high purity standards, we will analyze HIV-1 neutralization effects against selected R5-type viruses in two in vitro HIV neutralization assays based on Env-pseudotyped virus-reporter gene expression and primary isolate-PBMC infection systems. Next, r/rdAH' cytotoxic, mitogenic, and inflammatory potentials will be tested in PBMCs and/or human cervicovaginal (CV) epithelial cell lines to establish the minimal safety profile. Our success criteria in the R21 phase are: (1) establishing the bulk preparation procedure; (2) demonstrating cross-clade antiviral effects to R5 viruses; and (3) demonstrating no apparent in vitro cytotoxicity, mitogenic activity, or inflammatory potential at >100 times above an average anti-HIV IC50, for plant-made r/rdAH. Upon approval of our transition to the R33 phase, we will comprehensively analyze anti-HIV-1 efficacy of r/rdAH for various modes of HIV-1 infection and transmission, using various in vitro assay systems. In

addition, we will investigate potential overlap, complementation, synergy, and antagonism of anti-HIV activities between r/rdAH and other inhibitors toward potential microbicide combination strategies. Finally, we will perform extensive evaluations of r/rdAH upon vaginal application in rabbit and mouse models. We will thoroughly evaluate r/rdAH' vaginal toxicity, inflammatory potential, and stability. Upon determining the maximal tolerated dose of r/rdAH, we will examine their potential immunogenicity and toxicity after a long-term exposure. Potential toxicity to the symbiotic vaginal commensal bacteria, the Lactobacillus species, will be examined. In summary, the proposed studies should answer the question of whether r/rdAH is justified for advanced next-stage preclinical studies. The proposed studies will analyze the feasibilities of the novel HIV-1-binding lectin Actinohivin and its derivative recombinant dimer, as a candidate vaginal HIV-1 microbicide. The proposed studies should generate a comprehensive data set that will reveal their large-scale producibility, anti-HIV-1 efficacy, and broad toxicity profile upon vaginal application, thereby providing criteria of whether Actinohivin and its derivative are justified for further extensive preclinical and clinical studies.

Title: **Role of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin in Asthma**
P.I.: **Joel Barry Baseman**
Institution: **University of Texas Health Science Center at San Antonio**
Grant No.: **AI070412-06**
Award: **$12,500**

The San Antonio Asthma and Allergic Diseases Cooperative Research Center (SA-AADCRC) represents a tightly focused, integrative and innovative effort to understand the role of Mycoplasma pneumoniae and its unique ADP-ribosylating and vacuolating toxin, designated Community Acquired Respiratory Distress Syndrome ToXin (CARDS TX) as important mediators of acute and chronic airway diseases, including new onset asthma and exacerbations, as well as persistent pulmonary dysfunction in children and adults. The basic science and clinical investigators who comprise the SA-AADCRC team share broad expertise and are highly collaborative. The SA-AADCRC's broad strategy of attack interlinks basic science and clinical research projects and cores. Project 1 uses the murine model and human materials to address fundamental questions on how CARDS TX induces asthma-like disease and exacerbates allergic pulmonary inflammation. Project 2 focuses on identifying CARDS TX ADP-ribosylating airway protein targets, delineating functionally important CARDS TX domains and essential amino acids that mediate CARDS TX binding to human surfactant protein A (SP-A) and airway cells, and generating antibody reagents that block/neutralize CARDS TX. Project 3 applies state-of-the-art biophysical techniques to uncover the structure and action of CARDS TX by using single crystal X-ray diffraction to determine CARDS TX three dimensional structure in the presence and absence of its cofactor NAD; neutralizing monoclonal antibody Fab fragments; and surfactant protein-A (SP-A). Clinical Core will collect human material from subjects with well controlled asthma, poorly controlled asthma and healthy controls and help in evaluation and follow-up of patient-related studies. Diagnostic Core will process clinical and experimental samples for diagnostic analysis by providing highly sensitive and specific diagnostic assays for rapid detection of M. pneumoniae CARDS TX. Pathology Core will provide necessary biopsy and necropsy procedures, lung pathology interpretation, histochemical and immunocytochemical evaluations, and qualitative and semiquantitative histopathologicai analyses. Administrative Core will oversee all SA-AADCRC-related activities and coordinate interactions and collaborations between projects and cores. Therefore, the SA-AADCRC represents a network of collaborators/colleagues who continuously ask fundamental and translational questions about asthma, airway-related pathologies, immunopathogenesis, and M. pneumoniae/CARDS TX biology and virulence mechanisms.

Title: **The Semen Enhancer of HIV Infection as a Novel Microbicide Target**
P.I.: **Stephen Dewhurst**
Institution: **University of Rochester**
Grant No.: **AI094511-01**
Award: **$18,750**

Human semen contains cationic amyloid fibrils, termed the "Semen Enhancer of Virus Infection" (SEVI), which strongly enhance HIV-1 infection and may play an important role in viral transmission. Our preliminary data show that amyloid-binding molecules bind to SEVI, and block semen-mediated enhancement of HIV-1 infection. This suggests that (i) SEVI is responsible for semen-mediated enhancement of HIV infection and (ii) SEVI represents a novel microbicide target. We therefore propose to explore a novel, innovative approach to HIV-1 microbicide development, using agents that selectively target SEVI. This high-risk/high-reward approach is fundamentally different from traditional microbicidal strategies that target the virus itself, and is expected to be highly complementary with direct antiviral approaches. Indeed, our long-term goal is to use SEVI-targeting agents in combination with traditional microbicides, to achieve optimal antiviral effectiveness. In the R21 phase, we will test whether novel amyloid-binding small molecules inhibit semen-mediated enhancement of HIV infection. The feasibility of this approach has been established using two amyloid-binding small molecules which contain "shielding" oligo-ethylene glycol (EG) moieties: BTA-EG4 and -EG6. These agents efficiently inhibit SEVI- and semen-mediated enhancement of HIV infection. In Aim 1, we will generate and test novel derivatives of these and other amyloid-binding molecules, including oligovalent molecules that are expected to possess increased SEVI binding affinity. We will then test their ability to inhibit SEVI- and semen-mediated enhancement of HIV infection using a panel of R5 virus strains (including different clades and transmitted strains). In Aim 2, we will examine the interaction between novel amyloid-binding small molecules and cells from the female reproductive tract. We will evaluate whether our compounds are toxic to human cervicovaginal epithelial cells (HCEC), and we will test whether they inhibit SEVI-enhanced binding of HIV-1 to HCEC and/or SEVI-enhanced trans-infection of PBMC by HCEC exposed to HIV-1 virions. The R33 phase will be undertaken only if well-defined milestones are achieved. In Aim 3, we will use structure-activity relationship (SAR) data to refine our chemical compositions. We will also test whether our lead molecules have efficacy in a cervical explant model for HIV-1 infection, and whether they have a synergistic or additive effect on the ability of other candidate microbicides to inhibit HIV-1 infection in the presence of semen. In the final Aim, we will assess the toxicity and inflammatory effects of the most promising candidate molecules, using beneficial Lactobacillus strains and cervical explants. The R33 phase will culminate with an evaluation of the safety and tolerability of the most promising compound in the rabbit vaginal irritation (RVI) model. The overall goal of these studies is to carefully determine whether small molecules that target SEVI have potential utility as a novel class of microbicides.

Title: **Sex Differences in Protective Immunity Against Influenza A Viruses**
P.I.: **Sabra L. Klein**
Institution: **Johns Hopkins University**
Grant No.: **AI090344-02**
Award: **$243,540**

Sex differences in the incidence and severity of influenza A virus infection have been documented in humans. Although exposure rates are often higher in men, fatality following exposure to pathogenic influenza A viruses is reportedly higher in women. Sex differences also are reported in response to influenza virus vaccines, with women consistently mounting higher antibody responses and developing more frequent and severe side effects following vaccination than men. Small animal models are critical for establishing the mechanisms mediating why males and females respond differently to influenza virus infection and vaccination. Following primary inoculation with the mouse-adapted influenza A viruses A/PR/8/34 (PR8; H1N1) or A/HK/68 (HK68; H3N2), female mice mount

higher inflammatory and humoral immune responses than males. Our preliminary data further reveal that elevated immunity in females against influenza A viruses represents a delicate balance between immune responses conferring protection or causing pathology. The goal of this proposal is to develop a small animal model to test the hypothesis that protective immunity to heterosubtypic influenza A virus challenge differs between the sexes and is modulated by sex steroid hormones. In Specific Aim 1, we will establish whether neutralizing antibody responses, virus-specific T cell responses, and protection against lethal influenza A virus challenge is greater among females than males. Whether males and females differentially rely on subsets of adaptive immune cells for protection against lethal influenza A virus infection has not been documented; thus, we also propose to compare heterosubtypic immune responses between male and female mice devoid of specific adaptive immune cell populations. If protective heterosubtypic immunity is elevated in females compared with males, then estrogens and/or progestins may enhance and androgens may suppress adaptive immunity against heterosubtypic influenza A virus challenge. In Specific Aim 2 we will test this hypothesis by manipulating sex steroid concentrations in vivo and establishing the effects on humoral and cell-mediated immunity as well as protection from lethal influenza A virus challenge. These are a series of high risk-high return experiments because there are no data to date assessing the sex-specific induction of heterosubtypic immunity in response to influenza A virus infection. Demonstrating that females mount a broadly protective immune response, however, will have important implications for dealing with annual epidemics of influenza, as this may explain why the attack rates for influenza are higher in men than in woman and influenced by pregnancy.

Title: **Sexual Dimorphism and Dysregulated Immune Responses in SLE: The Role of Leptin**
P.I.: **Antonio La Cava**
Institution: **University of California, Los Angeles**
Grant No.: **1R21AI095921-01**
Award: **$231,000**

This proposal aims to advance the current understanding of the cellular and molecular immune events that associate with the increased susceptibility to develop systemic lupus erythematosus (SLE) in females. Gender disparities associate with several biological differences that most apparently involve an evident dissimilarity between sexes in the levels of sex hormones and their receptors. However, although very important, the differences in the expression and responsiveness to sex hormones may not be sufficient to fully explain the increased incidence of SLE in females. During the past decade, our group has been interested in investigating the effects of the hormone adipokine leptin on immune responses. We and others have shown that this sexually dimorphic hormone—found at concentrations 5-10 times higher in females than in males with similar body mass index—has proinflammatory activities that greatly favor the development and the progression of several autoimmune diseases including SLE. We have also shown that leptin constraints the ability of regulatory T cells to suppress autoreactive immune responses in vitro and in vivo, and together with others we have shown that regulatory T cells can modulate SLE disease activity. Here we propose to dissect the effects of leptin on regulatory T cells in SLE by testing the hypothesis that elevated levels of leptin in females can modulate key characteristics of the regulatory T cells in SLE. Three integrated aims will study the influence of leptin on the phenotype and function of regulatory T cells in SLE at the cellular, molecular and biochemical levels. By identifying specific events that can be modulated by leptin in SLE, we aim to ultimately identify surrogate markers of therapeutic intervention that could lead to a better management of the disease. PUBLIC HEALTH RELEVANCE: In this application we will explore new mechanisms that may contribute to the increased susceptibility to develop systemic lupus erythematosus (SLE) in females. We will investigate the role of a hormone that is expressed in much higher concentration in females as a possible major contributor to the pathogenesis of SLE. The role of this hormone, leptin, will be investigated in great detail for its capacity to inhibit the activity of cells that suppress autoimmunity in SLE, as preliminary work seems to suggest.

Title: **A Systems Biology Approach for Pediatric and Adult Autoimmune Diseases—ACE**
P.I.: **Maria Virginia Pascual**
Institution: **Baylor Research Institute**
Grant No.: **AI082715-03**
Award: **$30,000**

We propose to create an Autoimmunity Center of Excellence that will incorporate the efforts of clinicians, human immunologists (both basic and translational), physician-scientists with clinical expertise and research experience in autoimmunity, bioinformaticians, and geriomics/systems biologists. Together, the assembled group has an extensive background in clinical trials and a proven track record for merging basic and clinical science. This team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. Within this collaborative setting, a systems biology approach is proposed to focus on both pediatric and adult autoimmune diseases. The goals of the Center are: 1) To assess the efficacy of novel targeted therapies, 2) To develop simple and robust biomarkers using state-of-the-art genomic approaches, 3) To understand the role of recently identified T cell subsets in disease pathogenesis, and 4) To assess antigen-specific responses in pediatric and adult autoimmune diseases. These projects will provide a better understanding of the pathogenesis of specific autoimmune diseases and allow us to develop a strategy to assess disease activity based on novel transcriptional markers as well as to identify autoantigen-specific immune responses. The Center will deliver: 1) Innovative clinical trials targeting specific cytokines in psoriasis & dermatomyositis. 2) Development of biomarkers for dermatomyositis, psoriasis, lupus and multiple sclerosis. 3) Identification of novel therapeutic targets in dermatomyositis. 4) Development of assays to test autoantigen-specific immune responses. 5) Development of a unique microarray database of human autoimmune diseases. CLINICAL COMPONENT (Cush, J) CLINICAL COMPONENT DESCRIPTION (provided by applicant): Baylor Institute for Immunology Research aims to bring together a distinguished team of clinical investigators to conduct cutting-edge clinical trials on specific autoimmune diseases. This unique group of investigators and clinicians has appointments at Baylor University Medical Center, UT Southwestern Medical Center, Texas Scottish Rite Hospital in Dallas and Northwestern University. These talented individuals have been enlisted from diverse programs with subspecialties in dermatology, rheumatology, neurology, pediatrics, and human immunology. They provide a set of inimitable resources for clinical trials and have a proven track record for merging basic and clinical science. Indeed, this team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. With such outstanding collaborative players, a systems biology approach is proposed here which investigates both pediatric and adult autoimmune disease. To this end, two Phase II randomized, double-blind, placebo-phase controlled clinical trials are proposed. The first trial investigates whether blocking IL-1 with Anakinra will result in objective disease improvement for patients with Juvenile Dermatomysitis. The trial design will demonstrate: 1) if the time to improvement for patients receiving Anakinra early in the study will be earlier than those who receive later treatment; and 2) if the proportion of patients improved at week 8 of the blinded phase will be significantly greater in the early treatment group. Mechanistic studies will utilize gene expression profiling assays to find a novel diagnostic test for JDM as well as disease activity measures and biomarkers to follow and predict patients' response to therapy. The second clinical project proposes to use a-IL-17 in patients with plaque psoriasis as well as psoriatic arthritis. Specifically, this study will assess the safety and efficacy of a-IL-17 in these patients and determine both the time to achieve endpoints of a PASI 75 or ACR20 and sustainability of such responses at 24 weeks. Associated studies will establish blood transcriptional markers to predict clinical responses in patients treated with a-IL-17, determine if transcriptional scores can be used to assess disease activity, and analyze the effect(s) of IL-17 blockade on B and T cell subsets. A dynamic team of clinical investigators assembled at BUR to conduct state-of-the-art clinical trials on autoimmune disease would be of great value and accelerate the process of bringing research from the laboratory bench to the bedside. This team proposes two important trials that will assess a-IL-1 treatment in Juvenile Dermatomyositis and IL-17 blockade in psoriatic diseases.

Title: **T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy**
P.I.: **Andrew D. Luster**
Institution: **Massachusetts General Hospital**
Grant No.: **AI095261-01**
Award: **$12,500**

The Massachusetts General Hospital/Harvard Medical School AADCRC entitled "T cell effector and regulatory mechanisms in asthma and food allergy" seeks to gain a better understanding of the role of allergen-specific effector and regulatory T cells in determining the physiological response to an allergen at mucosal surfaces. It is becoming increasingly clear that the net outcome of an inflammatory response is the balance of allergen-specific effector T cell activity and opposing regulatory T cell activity. Antigen-specific effector and regulatory T cell numbers and activity are in large measure determined by the outcome of allergen-loaded dendritic cell (DC) interactions with antigen-specific T cells. The MGH/Harvard AADCRC will explore the balance of effector and regulatory activity in asthma and food allergy and the ability of tolerogenic DCs to affect this balance. The Center will focus on two allergic conditions relevant to the mission of the NIAID, namely allergic asthma and food allergy, and utilize two clinical models [endobronchial segmental allergen challenge (SAC) and oral immunotherapy (OIT)] as a foundation for its studies. Project 1 focuses on the role of antigen-specific effector and regulatory T cells in determining airways inflammation and airways hyper-reactivity by correlating the numbers, phenotype and function of these cells in allergic asthmatics (AA) and allergic nonasthmatics (ANA) using innovative imaging techniques; Project 2 focuses on correlating the numbers, phenotype and function of these same T cell subsets with clinical outcomes of milk allergic patients undergoing milk OIT; and Project 3 focuses on the ability of tolerogenic DC therapy to manipulate the balance between these two opposing T cell populations in favor of regulatory T cells and tolerance in both asthma and food allergy. The three interrelated projects will be supported by Cores that will recruit, enroll and characterize allergic subjects for SAC and OIT, provide MHC class II tetramers to specifically identify and study allergen-specific T cells, and perform sophisticated transcriptome phenotypic analysis on T cell and DC subsets. The goal of this Center is to understand the balance of effector and regulatory allergen-specific T cell activity that determines clinical disease in asthma and food allergy and to establish the utility of using tolerogenic DCs to manipulate this balance to induce allergen-specific tolerance. This would pave the way for new therapeutic approaches to treat these and other allergic diseases.

Title: **Targeted siRNA Delivery as an Anti-HIV Microbicide**
P.I.: **Derek Michael Dykxhoorn**
Institution: **University of Miami School of Medicine**
Grant No.: **AI088601-02**
Award: **$21,428**

Human immunodeficiency virus (HIV) is a highly lethal lentivirus which over a protracted course destroys the host's adaptive immune system leaving them vulnerable to numerous opportunistic infections. Unlike most viruses whose genome replicates independently of the host cell's genome, the HIV-1 genome integrates into and is replicated with the host genetic material. Therefore, even if therapeutic approaches can inhibit new virus production, the viral genome remains intact and competent. Therefore, strategies that can prevent the uptake and integration of the virus would be of tremendous clinical value. The vast majority of HIV infections occur as a consequence of viral transmission through mucosal surfaces, such as the vaginal mucosa. The delivery of siRNAs that specifically silence host factors required for early events in the HIV life cycle to lymphocytes in the vaginal mucosa could prove to be an effective means of protecting individuals from HIV infection and serve as a potential microbicide. One of the main challenges facing the clinical application of siRNAs as a genetic therapy is the ability to delivery siRNAs to the cytoplasm of the appropriate target cell types. We have recently developed a novel lipid nanoparticle that is coated with an antibody recognizing the integrin molecule LFA-1 which is

broadly expressed on lymphocytes. These immuno-nanoparticles will be used to deliver siRNAs to lymphocytes present in the vaginal mucosa of humanized mouse models of HIV. Given the high level of sequence heterogeneity, the propensity of HIV-1 to mutate and the inability of anti-HIV siRNAs to target the incoming viral RNA genome and prevent integration, alternative therapeutic targets are required to prevent the transmission of HIV. Host factors that are necessary for early events in the HIV lifecycle but are dispensable for cellular functioning could prove to be an effective therapeutic alternative. Using a high-throughput RNA interference-based screening platform, we have identified a large number of potential therapeutic targets that could serve to inhibit HIV integration when silenced. However, these factors require extensive analysis and characterization to ensure their safety and efficacy. We will be combining the LFA-1-mediated cell-type specific vehicle to introduce siRNAs targeting therapeutically relevant host factors as a potential means to inhibit viral infection in humanized mouse models of HIV. These experiments will provide the preclinical groundwork necessary for the development of an effective RNAi-based anti-HIV microbicide. Heterosexual transmission is the leading cause of new HIV infections in the world. A microbicide providing true intracellular immunity would make a significant contribution to controlling the spread of this deadly virus.

Title: **Thermostable Vaginal Probiotic Microbicide**
P.I.: **Victor Bronshtein**
Institution: **Universal Stabilization Technologies, Inc.**
Grant No.: **AI094508-01**
Award: **$18,750**

Recently revised statistics show the number of individuals living with HIV at over 33 million worldwide, with 68% being in sub-Saharan Africa. Current HIV prevention methods, such as condom use, monogamy and abstinence, are not always feasible. The need for improved HIV preventative technologies remains urgent. The development of topical microbicides represents a new and exciting field in the prevention of sexually transmitted diseases. Of these, application of live probiotic bacterial microbicides (PBM) represents a promising preventative method. Our ultimate goal is to develop potent optimized multistrain thermostable and easily deliverable probiotic vaginal topical microbicides. To achieve this goal we will stabilize vaginal probiotics for long-term storage at high ambient temperatures and short term survival at temperatures required for quick dissolve film manufacturing (60°C and above). The cornerstones of this proposal are: 1) Preservation by Vaporization (PBV)—an innovative, patent pending method of dry-stabilizing probiotics bacteria and other fragile biologicals at high ambient temperatures, and 2) Quick-dissolve thin film technology that is being optimized to deliver conventional vaginal microbicides. The strategy can be described briefly as, to occupy the vaginal epithelium and provide a long lasting protective environment against HIV, BV, and STI acquisition small (10-50 μm) glassy sugar particles containing PBV vaginal probiotic bacteria will be formulated into thin films which utilize a water soluble polymer base. Thin films offer a unique delivery platform which has a number of advantages over other dosage forms. In a recent study comparing women's preference between films, tablets and ovules, the film dosage form was shown to have greatest acceptability among women studied. We believe that women will prefer using a vaginal film over other potential methods of probiotic microbicide delivery especially if a long-acting effect of the bacteria colonizing vaginal epithelium allows for less frequent use. Biologic properties of PBM after long-term storage at ambient temperatures will be characterized using cell culture models of vaginal and cervical epithelium.

Title: **Vitamin D and the Prevalence, Incidence, and Persistence of Bacterial Vaginosis**
P.I.: **Abigail Norris Turner**
Institution: **Ohio State University**
Grant No.: **1R21AI095987-01**
Award: **$291,875**

Bacterial vaginosis (BV) is a vaginal condition that develops when the concentration of healthy Lactobacillus species in the vagina declines and is replaced by other (largely anaerobic) bacterial species. BV is the most common vaginal infection worldwide in women of reproductive age. Pregnant women with BV have increased risks of spontaneous abortion, preterm labor, preterm birth, chorioamnionitis and other detrimental obstetric and gynecologic outcomes. According to a recent meta-analysis of more than 30,000 women, prevalent BV was associated with a 60% increased risk of acquisition of human immunodeficiency virus (HIV). However, the etiology of this complex condition is not clear. We hypothesize that low vitamin D levels contribute to BV pathogenesis. Vitamin D is essential to immune function, serving both to stimulate mechanisms associated with pathogen elimination and to regulate immune response. In the United States (US), the strongest risk factor for BV is non-white race, and non-white women are also much more likely to have insufficient or deficient vitamin D levels. Indeed, two recent cross-sectional analyses report that vitamin D insufficiency is associated with prevalent BV in pregnant African-American women; a third publication found the same association between vitamin D and BV in a nationally-representative population of pregnant women including all racial/ethnic categorizations. These data suggest that the consistent association between race and BV (despite adjustment for other BV risk factors) may be mediated by vitamin D. Little data exist on vitamin D levels in resource-limited settings, including sub-Saharan Africa where BV prevalence is high and BV-associated morbidities are substantial. Using stored serum samples from nearly 600 Zimbabwean women who previously participated in the prospective, observational "Hormonal Contraception and Risk of HIV Acquisition" (HC-HIV) study, we propose to measure the association between serum vitamin D levels and a) BV prevalence; b) BV incidence; and c) BV persistence. In an exploratory analysis using stored cervical and serum samples from a subgroup of 50 BV-positive and 50 BV-negative women, we will also evaluate correlations between BV-associated cervical immunoinflammatory mediators and vitamin D-associated serum immunoinflammatory mediators to elucidate the possible immunological mechanisms through which vitamin D may affect BV. Vitamin D is safe, inexpensive and has many health benefits. If vitamin D is also associated with BV, supplementation with this essential vitamin may have substantial impact on women's reproductive health worldwide. PUBLIC HEALTH RELEVANCE: Bacterial vaginosis is the most common vaginal infection in women of reproductive age worldwide. We hypothesize that low vitamin D levels contribute to increased risk of bacterial vaginosis. This study will test stored, prospectively-collected biological samples and use existing demographic, behavioral and clinical information from almost 600 Zimbabwean women to assess the influence of vitamin D on the prevalence, incidence and persistence of bacterial vaginosis.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Title: **Delayed Pubertal Development on the Mechanism of Bone Loss at Maturity**
P.I.: **Vanessa R. Yingling**
Institution: **Temple University**
Grant No.: **5R03AR057518-02**
Award: **$73,440**

Osteoporosis is "a pediatric disease with geriatric consequences". Simply stated, suboptimal skeletal development in childhood and adolescence may result in decreased bone strength and an increase in lifetime fracture incidence. A delay in the onset of puberty (primary amenorrhea) correlates with both low bone mass; and an increased incidence of stress fracture. Suboptimal

bone accrual may have long term consequences. Even with current treatment options as studies that treated amenorrheic dancers for 2 years with hormone replacement therapy found no difference in bone mineral density between treated and placebo groups. The most significant factors during development may be nutritional and lifestyle factors. Therefore, our overall goal is to ascertain the affect of delayed pubertal development on the mechanism of bone loss at maturity. Density measures alone, although widely used clinically, cannot identify osteoporotic subjects who will sustain fractures, due to the large overlap in bone mass measures in individuals with fractures and those without fractures. Other factors including bone size, architecture and material properties must be considered. We have recently developed a texture analysis approach using Gabor filters, which is capable of providing insight into bone structure from localized texture information on a pixel level. The texture approach is therefore a potentially powerful tool in analyzing trabecular bone texture where orientation, shape and architecture as well as density are the fundamental components. Our previous work was analyzing 2D images but we propose to transfers this approach to 3D images. This novel approach will indicate not only bone mass changes but changes in orientation which may be very significant later in life. In Aim #1, we will test the hypothesis that the mechanism and magnitude of bone loss in a mature animal is dependent on bone development. Specifically, delayed pubertal onset will alter the architecture of bone that will affect the mechanism of bone loss at maturity. Pubertal delay will be completed by gonadotropin releasing hormone antagonist (GnRH-antagonist) injections. At 50 days of age changes in bone morphology will be evaluated using a novel 3D texture analysis. The following biomarkers will be measured to assess the response of pubertal delay on systemic changes in bone metabolism osteocalcin (a marker of bone formation) and N-telopeptide of collagen type I (NTx) (a marker of bone resorption). Serum estradiol and IGF-1 will also be assayed to confirm the hormonal response to the protocol. Fluorescent histomorphometry will assess bone formation rates on trabecular bone. At maturity (150 days of age) the experimental rats will undergo ovariectomy surgery to model post-menopausal bone loss. Changes in bone morphology will be evaluated using static and dynamic histomorphometry, micro-CT and texture analysis. By using a systems approach relating environmentally induced delayed puberty to bone growth, we propose to gain a new understanding of the important relationship between growth and its variability and the bone structure we become heir to during the aging process PUBLIC HEALTH RELEVANCE: Fracture risk in the elderly has its origins during growth and development. A delay in the onset of puberty results in both low bone mass and an increased incidence of stress fracture in young women. Therefore, the failure to accrue peak bone mass during the adolescent years represents a missed opportunity to optimize bone mass during one's life.

Title: **Epidemiology of Patellofemoral Pain Syndrome: Identifying Gender-Specific Risk Factors**
P.I.: **Michelle Clara Boling**
Institution: **University of North Florida**
Grant No.: **5R03AR057489-02**
Award: **$69,952**

Patellofemoral pain syndrome (PFP) is one of the most common causes of knee pain, affecting approximately 25% of the physically active population, with females being 2-3 times more likely to develop PFP compared to their male counterparts. The overall objective of this proposal is to determine the mechanical (structural and biomechanical) and non-mechanical (demographic and psychosocial) risk factors that are associated with PFP and identify the risk factors specific to females and males. The approach will be to use a prospective cohort design to identify risk factors that are associated with incident PFP. The central hypothesis is that individuals who develop PFP will have altered movement patterns, abnormal lower extremity anatomical alignments, decreased lower extremity strength, previous history of knee injury, previous participation in a low number of athletic activities, decreased levels of hardiness, and increased number of healthcare visits. A secondary hypothesis is that females and males will have different

risk factor profiles. We will utilize baseline risk factor data that has been collected on 5690 freshman (males=3482, females= 2208) during the summers of 2005-2008 at the following military academies: United States Naval Academy, United States Military Academy, United States Air Force Academy. Baseline risk factor data was collected through a current NIH funded project (R01-AR054061001), entitled JUMP-ACL. Each participant will contribute follow up time for incident PFP until they graduate from their respective academy. Medical record reviews will be performed to identify those participants who developed PFP during their respective follow-up time. Based on the two years for the proposed investigation, follow up time will be 4 years for all participants enrolled in the JUMP-ACL investigation from 2005-2008. Poisson regression analyses will be performed to determine the risk factors for PFP. Additionally, males and females will be analyzed separately to determine gender specific risk factor profiles. The proposed project is making an efficient use of already collected risk factor data by adding analysis of a new outcome (PFP) that would not otherwise be investigated by the JUMP-ACL project. Additionally, the proposed investigation is cost effective due to no funds being required for baseline data collection. Our rationale for the proposed investigation is that there is a crucial need for prospective studies that identify the risk factors for PFP so that more focused prevention strategies can be developed that are appropriately gender specific. PUBLIC HEALTH RELEVANCE: Patellofemoral pain syndrome (PFP) is one of the most common chronic knee conditions affecting young adults, with an increased occurrence in females. Individuals suffering from this condition may experience symptoms lasting multiple decades, limiting their participation in physical activity, and predisposing them to chronic diseases associated with inactivity such as obesity, arthritis, coronary artery disease, diabetes, and cancer. The results from this investigation may be used to identify those at greatest risk to PFP and develop appropriate prevention programs to decrease the occurrence of this condition, particularly in females.

Title: **FAK/Pyk2 Signaling Pathway and Bone Formation**
P.I.: **Teresita M. Bellido**
Institution: **Indiana University–Purdue University at Indianapolis**
Grant No.: **AR059357-01A1**
Award: **$200,000**

Mechanical forces enhance bone mass and strength, whereas glucocorticoid excess (GC) decreases bone formation and increases bone fragility. Mechanical stimuli increase proliferation of pre-osteoblasts, accelerate osteoblast differentiation, and inhibit osteoblast and osteocyte apoptosis; and directly activates Wnt-dependent transcription and downregulates the Wnt antagonists sclerostin and Dkk1. In contrast, GC inhibit osteoblast differentiation and induce osteoblast and osteocyte apoptosis; and inhibit Wnt-dependent transcription and increase Dkk1 expression. Work leading to this application indicates that these converse effects might stem from opposing actions on the focal adhesion kinases FAK and Pyk2, which regulate interactions between cellular integrins and the extracellular matrix. Thus, mechanical stimuli prevent osteoblast/osteoblast apoptosis by outside-in signaling mediated by integrins resulting in activation of FAK and ERKs; and GC oppose these survival signals by activating Pyk2 and its target JNK, leading to inside-out signaling and cell detachment–induced apoptosis. Remarkably, FAK/ERK activation and anti-apoptosis induced by mechanical stimulation is abolished by Dkk1 or β−catenin degradation. Conversely, Pyk2-dependent apoptosis by GC is inhibited by Wnts; and Pyk2 activates GSK3β, the enzyme responsible for degrading β−catenin. Based on these lines of evidence, it is hypothesized that there is an antagonistic interplay between mechanical forces and GC governed by FAK/Pyk2 signaling, which regulates the Wnt/β-catenin pathway, bone formation, and osteoblast/osteocyte survival. This hypothesis will be tested by a combination of in vitro studies using established cell lines and primary osteoblasts and osteocytes, and in vivo approaches using transgenic and knockout mice. Aim 1 will determine the role of FAK-mediated outside-in signaling and Wnt activation in mechanotransduction. It will be investigated whether loading-induced anabolism is impaired in mice lacking FAK in osteoblasts

and/or osteocytes, and whether this response is rescued by β−catenin stabilization; and whether there is a cell autonomous requirement of FAK for mechano-responsiveness using osteocytes and osteoblasts in which FAK was knocked-down or knocked-out. Aim 2 will determine the role of Pyk2-mediated inside-out signaling and Wnt inhibition in GC effects. It will be investigated whether inhibition of Pyk2 or downstream targets JNK and RhoA/Rock prevents osteoblast/osteocyte apoptosis, the decrease in bone formation, and the loss of strength induced by GC, by using Pyk2 and FAK null mice and mice treated with Pyk2, JNK, or Rock inhibitors; whether β−catenin stabilization or enhanced Wnt signaling prevents GC deleterious effects, using mice treated with GSK3β inhibitors or Sost null mice; and whether activation of Pyk2 is responsible for Wnt inhibition by GC in vitro, using cells in which Pyk2 is knocked-out or knocked-down, or cells treated with Pyk2 inhibitors. Aim 3 will investigate whether mechanical forces and GC antagonize in vivo and the role of FAK in the protective action of loading when applied simultaneously, before, or after initiation of GC treatment.

Title: **Fatigue and Lifestyle Physical Activity in SLE**
P.I.: **Rosalind Ramsey-Goldman**
Institution: **Northwestern University, Feinberg School of Medicine**
Grant No.: **AR059989-01A1**
Award: **$100,000**

Systemic lupus erythematosus (SLE) affects up to 1.5 million persons in the US. Although excess mortality has decreased in SLE patients since the 1970's, substantial morbidity persists. Fatigue is the most disabling and enduring complaint in patients affected with this chronic incurable inflammatory autoimmune disease. The ramifications of fatigue are significant and include decreased quality of life, an increased risk of work disability, and an associated increase in health care costs. The overarching goal of this R21 application is to explore ways to improve the measurement of two constructs, physical activity and fatigue, as a necessary first step in a broader effort to use a behavior management intervention to lower fatigue scores by increasing lifestyle physical activity in persons with SLE. We propose a novel application of a relatively new technology to objectively measure physical activity (triaxial accelerometry, which provides a validated measurement of daily physical activity in the community dwelling setting). In addition, we propose to measure covariates of fatigue using computerized adaptive tests (CATs) patient-reported outcomes (PROs) that have been developed using state-of-the-art cognitive, qualitative, quantitative and health survey methodologies as part of the NIH-funded Patient-Reported Outcomes Measurement Information System (PROMIS). PROMIS tools were developed to standardize measurement of self-reported health domains affected by many chronic illnesses and these tools offer the advantages of minimizing patient burden and maximizing precision. Using a cross-sectional study design, the following specific aims will be tested in this R21 application: Aim 1. Evaluate the frequency, intensity, and duration of physical activity as measured by accelerometry to obtain patient-specific average daily activity counts, average daily moderate-to-vigorous minutes of activity (MVPA) (defined as e 2020 activity counts/min), average daily minutes of light physical activity (< 2020 activity counts/min), and average daily minutes of any activity (i.e., minutes of non-zero activity counts) in patients with SLE. Aim 2. Characterize the cross-sectional relationships between objectively measured physical activity and fatigue (primary outcome, Fatigue Severity Score, (FSS) in patients with SLE. We will do this with and without adjustment for the major factors that influence fatigue including sleep and wake disturbance, depression, anxiety, and pain interference using PROMIS tools, and SLE disease activity and severity. The adverse clinical, social, and economic implications of fatigue support the critical need for an improved understanding of factors contributing to fatigue in SLE, a research priority identified in the NIH/NIAMS monograph entitled, "The Future Directions of Lupus Research".

Title: **Health of Children Born by Mothers with Rheumatoid Arthritis**
P.I.: **Jorn Olsen**
Institution: **University of California, Los Angeles**
Grant No.: **AR059931-01A1**
Award: **$193,877**

Many women with rheumatoid arthritis (RA) will have one or more pregnancies while having RA. Little is known about long term pregnancy outcomes for children born by women with RA but studies show more perinatal complications and fetal growth restriction which may activate fetal programming. Fetal programming in this group of children has not been investigated due to lack of large datasets that allow long-term follow up of children born to mothers with RA. Medications used to treat RA may also be harmful to the fetus, since medications are often required to manage disease activity during pre-conception and early stages of pregnancy. Our long-term aim is to investigate health conditions as measured by mortality and hospital discharge diagnoses in children born by mothers who had RA taking into consideration birth weight, gestational age and perinatal complications. Specific aims: To set up a cohort of children born by women who had been hospitalized for RA and a cohort of children born by mothers without this history. To record congenital malformation, gestational age, birth weight and other reproductive failures in these cohorts. To further characterize exposed pregnancies according to treatment for RA in the pregnancies that occurred after 1995. These cohorts can be followed for up to 30 years at present but follow may be continued if needed. Design and Methods: A National cohort study using national registries in Denmark, with complete information on all Danish citizens (5.5 million and about 65,000 births per year) as well as long-term follow up of their children. Prescription data will be obtained from the National Registry of Medicinal Product Statistics and diagnoses will be obtained from the National Patient Registry of Hospital Discharges. Data on social and occupational factors will be available from the other national registers. All data in all registers are personally identifiable by means of the civil registration number (CPR) that has been given to all citizens from 1968 and forward in time. The CPR allows for linkage between registers and for linkage of biological and adopted children to the parents. Outcomes: Miscarriages, birth defects, adverse pregnancy outcomes, disease pattern in childhood and early adulthood. Exposures: RA, medical treatments for RA during pregnancy, RA in mother, mothers with RA who were medically treated during pregnancy. Statistical analyses: Data will be analyzed using Cox models. Several potential confounders will be taken into consideration such as age, parity, cohabitation, social conditions and place of living. All analyses will be performed using Stata/SAS Statistical software packages. Implications: The findings will add evidence on adverse birth outcomes and long term disease patterns in children born by mothers with RA. Knowledge will be generated about the potential differential impact of different RA treatments on the unintended outcomes. The results will indicate if more active monitoring and early intervention are needed to reduce the potentially increased risk for the unborn child. The study may also provide additional information on the potential fetotoxic effects of drugs used in treating RA.

Title: **HERV-K18 as a Risk Factor for CFIDS**
P.I.: **Brigitte T. Huber**
Institution: **Tufts University School of Medicine**
Grant No.: **AR053821-05**
Award: **$164,058**

The etiology of Chronic Fatigue Syndrome (CFS) is far from understood and is likely due to multiple genetic components. Infection with EBV and treatment with IFN-a have been implicated in the pathogenesis. Our laboratory has shown that EBV-infection, and exogenous IFN-alpha, activate transcription of the env gene of a Human Endogenous Retrovirus, HERV-K18. This provirus is normally silent, but when induced it encodes a superantigen (SAg), which is a class of proteins that is capable of deregulating the immune system. Three alleles of

HERV-K18 env have been documented, K18.1, K18.2, K18.3, whose gene products have SAg activity, but are predicted to differ biochemically and functionally. Our working hypothesis is that HERV-K18 is a risk factor for CFS. In a pilot study, the allele and genotype distributions of the HERV-K18 env gene were compared between various groups of CFS patients and healthy controls. Although only a limited number of samples were available in the various cohorts, the odds ratios that were obtained were statistically significant. The most intriguing interpretation of these data are that they provide genetic evidence for the unique etiology of at least one group of CFS patients. Thus, it may be possible to delineate different subtypes of CFS, depending on the clinical history of the patients. It is now proposed to substantiate these pilot results, using a much larger cohort of 400 CFS patients associated with EBV that has been assembled by the co-investigator, Dr. Renee Taylor. Dr. Ben Katz, board certified in both Pediatrics and Pediatric Infectious Diseases, will clinically evaluate the patient cohort, and Dr. Inga Peter, a genetic epidemiologist and biostatistician, will oversee the statistical analyses. In addition, the expression pattern of the HERV-K18 SAg during active disease versus intermission will be measured. Furthermore, T cell stimulatory activity of this SAg, expressed on peripheral blood lymphocytes of patients during the course of the disease, will be tested ex vivo, using a T cell hybridoma reporter assay that has been developed in our lab. Since SAg-activated T cells produce massive quantities of chemokines, lymphokines and neurokines, the expression of the HERV-K18 SAg could influence not only the immune system, but other organs as well. A positive association between CFS and either HERV-K18 alleles or expression patterns would open new avenues for the development of clinical treatments of this chronic disease. CFS is a disease that affects a significant number of people worldwide, yet the underlying mechanism(s) of pathogenesis remains unclear. The herpesvirus EBV and IFN-a have been suggested to be associated with CFS, although these concepts are far from accepted. We propose a novel genetic aspect in the EBV/ CFS association, namely the presence of certain HERV-K18 alleles that differ in their superantigen activity.

Title: **A Link Between Parity, Trunk Muscle Function, and Degenerative Spondylolisthesis**
P.I.: **Jacek Cholewicki (contact); Lawrence W. Mysliwiec**
Institution: **Michigan State University**
Grant No.: **5R21AR056404-02**
Award: **$159,833**

This study will examine relationships between pregnancy, cesarean section (CS) and other abdominal surgery, trunk and abdominal muscle deficiency, and degenerative spondylolisthesis (DS) in older females. The key question is whether pregnancy and/or CS mediated trunk muscle deficiency could be a precipitating factor in the development of DS later in life. Three specific aims are to determine whether: (1) parity/CS/other abdominal surgeries are associated with DS, (2) trunk muscle deficiency is associated with DS, and (3) parity/CS/other abdominal surgeries are associated with trunk muscle deficiency. The costs associated with the treatment of degenerative low back disease make it one of the top 5 most expensive conditions in the American healthcare economy. DS is considered one of the major causes of low back pain among the older population. Women suffer from DS at a 3-9 times higher rate than men, as yet, without a clear explanation. Previous studies documented relationships between pregnancy and low back pain, and suggested abdominal muscle deficiency as an underlying cause. Of special concern is the effect of CS. The rates of CS rose three-fold over the last 3 decades and may cause significant public health problems regarding DS in coming years. We propose to conduct a case-control study of 200 DS patients and 200 age-matched (in 5 year age groups) controls, including a more detailed assessment of trunk muscle function in 80 DS and 80 matched control subjects. Group designation will be based on a DS diagnosis from a sagittal view x-ray. The 400 subjects will be administered a detailed questionnaire regarding their parity, CS, previous surgeries, and other potential covariates. A subset of 80 subjects from each group will in addition undergo a physical examination of their abdominal and trunk muscle function and quantitative assessment of motor control. Physical exam will include

abdominal muscle and hip extension tests. These tests examine the ability of the abdominal and paraspinal muscles to stabilize pelvis and the lumbar spine during simple hip flexion and extension maneuvers. Motor control tests will quantify muscle reflex latencies in response to sudden trunk perturbations, and postural control while balancing on an unstable seat. Both delayed muscle reflex responses and poor postural control are associated with low back pain and constitute predisposing risk factors to future low back problems. Poor motor control could lead to spine instability, chronic problems and degenerative changes in the spine over time. All measures will be quantified (continuous or categorized) and used in the regression and chi-square analyses to test the hypotheses. Innovative aspects of this proposal comprise of quantifying muscle function objectively and documenting variables related to parity in women with and without DS, which gives a better chance of finding any relationships that might exist. PUBLIC HEALTH RELEVANCE: The costs associated with the treatment of degenerative low back disease make it one of the top 5 most expensive conditions in the American healthcare economy. Women suffer from DS at a 3-9 times higher rate than men, as yet, without a clear explanation. If the number of childbirths and cesarean sections predisposes women to this condition later in life, proactive planning of effective intervention strategies and educational campaigns would be prudent.

Title: **A New Hip Fracture Risk Prediction Tool Based on Common Predictors and Hip Geometry**
P.I.: **Zhao Chen**
Institution: **University of Arizona**
Grant No.: **AR060811-01**
Award: **$165,622**

Osteoporosis is a major public health problem. Women are at a particularly high risk for osteoporosis and 50% of women age 50 or older may suffer from a fragility fracture in their remaining lifetime. Hip fractures are the most detrimental type of fractures. Research has been conducted to assess hip fracture risk so prevention methods could be used to reduce this risk in the growing number of older women. However, previous risk assessment approaches are limited to a few variables and linear combinations of these factors. Also, there is an increasing number of available measures, such as bone structures and skeletal muscle mass, that can be extracted, for instance, from dual-energy X-ray absorptiometry (DXA), and no reliable risk prediction model exist based on this wealth of information. The overall goal of this study is to develop a comprehensive and flexible model to assess the risk of hip fracture for a specific woman. This will be achieved by constructing a novel predictor that classifies data that include hip structural geometry, sarcopenia measurements as well as risk factors identified in previous studies. The construction of the predictive model will be partly based on a study conducted among a large (n = 11,432) multi-ethnic bone cohort from the nationwide Women's Health Initiative (WHI). In addition, to enhance the quality of the risk prediction, computational data from finite element simulations will be used. There are three specific aims. The first aim is to generate a risk model, based on clinical data that accounts for the coupling effects of the factors involved in hip fracture. This research introduces a new approach in the field of hip fracture, Support Vector Machines (SVM), which explicitly identifies the configurations of factors that are likely to lead to hip fracture. The second aim is to refine the prediction/decision model from the first aim using both the SVM classifier and finite element modeling. A scheme has been developed to select, in a high dimensional space, data points that would improve the accuracy of the SVM-based risk prediction model. These data points would be evaluated (fracture or not) using a finite element model. The novelty of the proposed finite element model stems from its full parameterization so that the variability of the bone response can be studied with respect to variations (even small) of structural geometry and material parameters. The third aim is to validate and compare the SVM-based risk with and without the use of finite element analysis and develop a hip fracture risk calculator for the web. A cross validation will be performed using data sets from the WHI as well as other cohorts. The flexibility of the SVM classification approach makes it easily deployable on

the Internet. This study will be carried out using existing cohorts by an interdisciplinary team with experience in epidemiology of osteoporosis research, DXA measurements including hip structures and sarcopenia, fracture assessments, biostatistics approaches for large datasets, high dimensional analysis and finite element modeling, thus making this study highly feasible. The study results will have an extremely significant public health impact by providing an innovative tool for hip fracture risk assessments.

Title: **North American Rheumatoid Arthritis Consortium: The Genetics of Rheumatoid Arthritis**
P.I.: **Peter K. Gregersen**
Institution: **Feinstein Institute for Medical Research**
Grant No.: **AR044422-13**
Award: **$175,363**

This renewal application has the overall goal of identifying all of the major common genetic variants that underlie susceptibility to rheumatoid arthritis, and to begin to identify rare susceptibility alleles, if they exist. In preliminary data we have identified a number of candidate genes and regions on the basis of linkage analysis in multiplex RA families, as well as by whole genome association studies using approximately 550,000 SNPs on a panel of over 900 RA patients and matched controls. We now wish to identify the specific causal variants and understand their mode of action. In specific aim 1 we will identify the causal genetic variants within the common genes that confer risk for rheumatoid arthritis. We have already identified several genes and regions of interest, including STAT4 on chromosome 2q. In specific aim 1a we will replicate these initial associations in case-control datasets totaling up to 5,000 patients. Various methods of genomic control for population stratification will be utilized for these replication studies. In specific aim 1b we will carry out fine mapping of candidate regions. This will generally involve haplotypic analysis using custom sets of SNP markers. In specific aim 1c we will utilize various approaches to identify the likely causative genetic variants in the gene under study. Examples of the approaches to be used in specific aim 1c are given for STAT4. In specific aim 2, we will apply a staged approach to identify gene-gene and gene-environment interactions that contribute to RA susceptibility. The top performing markers in the univariate analyses of specific aim 1a and 1b will be examined for interactions using Classification and Regression Tree (CRT) as well as traditional logistic regression methods. Top performing models will be tested in replication datasets of cases and controls. In specific aim 3, we will identify rare genetic variants that contributes to RA susceptibility. This specific aim is based on preliminary analysis indicating that "slightly deleterious" SNPs (sdSNPs) are a significant component of the genetic burden underlying complex disease. These sdSNPs are enriched in the low frequency (MAF < 5%) component of the SNP population. We will initially investigate a limited number of candidate genes with high-throughput sequencing on the Solexa platform, along with follow up analysis in large case control datasets. Larger scale and more comprehensive approaches to this issue may be employed in the later years, depending on technical advances in the field.

Title: **Osteoarthritis Initiative**
P.I.: **Michael Nevitt (UCSF)**
Institution: **University of California, San Francisco (coordinating center); Memorial Hospital of Rhode Island; Ohio State University; University of Maryland; University of Pittsburgh**
Grant No.: **AR022258, 26820120031C*1**
Award: **$650,000**

Knee osteoarthritis (OA) is the most common cause of disability in adults. The "Osteoarthritis Initiative (OAI): A Knee Health Study" is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis

symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a four-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual follow-up visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee pain and physical disability will be assessed at study start and at each of the follow-up visits by questionnaire and examination.

Title: **Predictors of Pregnancy Outcome in SLE and APS**
P.I.: **Jane E. Salmon**
Institution: **Hospital for Special Surgery**
Grant No.: **AR049772-09**
Award: **$192,240**

Pregnancy complications in women with the antiphospholipid syndrome (APS) and/or SLE include recurrent miscarriage, preeclampsia, placental insufficiency, and intrauterine growth restriction (IUGR). The mechanisms leading to placental and fetal injury in vivo are incompletely understood and treatment remains sub-optimal. We have identified complement as an early effector in pregnancy loss and/or IUGR associated with placental inflammation in a mouse model of APS and shown that complement activation causes the release of anti-angiogenic factors and abnormal placental development. The PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) is a first-time effort to translate our novel findings in mice to humans and determine if elevations of complement split products predict pregnancy complications in patients with antiphospholipid (aPL) antibodies and/or SLE. In the first 4 years of this prospective, observational study of pregnant patients grouped and analyzed according to the presence or absence of aPL antibodies and preexisting SLE, we have enrolled 342 pregnant patients in 7 centers, obtained detailed medical and obstetrical information monthly, and serially collected plasma, serum, DNA, RNA, and urine. Preliminary data suggest that elevated levels of complement activation products antecede and predict poor fetal outcome, consistent with our hypothesis that complement is a proximal mediator of fetal loss and IUGR. We propose to increase our target sample size from 400 to 700 pregnant patients to maintain study power given lower than expected outcome rates, and to leverage the infrastructure and rich collection of patient data and samples by expanding the array of biomarkers and scope of adverse pregnancy outcomes. Specifically, in Aim 1 we will determine whether elevations of split products generated by activation of complement pathways predict poor fetal and/or maternal outcome in patients with aPL antibodies and/or SLE and, in Aim 2, whether the balance of circulating angiogenic and anti-angiogenic factors predicts preeclampsia or delivery of IUGR infants. In Aim 3, a new direction, we will use the PROMISSE cohort to affirm in humans our recent findings in mice, that certain anti-DNA antibodies cross-react with N-methyl-D-aspartate receptors (NMDAR) and cause neuronal death with ensuing cognitive and behavioral impairment. We propose to quantitate anti-NMDAR antibody levels throughout pregnancy in PROMISSE SLE patients and test the hypothesis that in utero exposure to maternal anti-NMDAR antibodies alters behavior and cognitive development in offspring by evaluating cortical function tasks in 12 month and 3.5 year old children. This competitive renewal and extension of the PROMISSE Study provides an outstanding opportunity to translate knowledge from mouse models to patients, define pathogenic

mechanisms, identify predictors of poor pregnancy outcome in APL and/or SLE, and define novel therapeutic targets to prevent such outcomes.Patients with systemic lupus erythematosus (SLE) and/or antiphospholipid (aPL) antibodies are at increased risk for miscarriage, preeclampsia and fetal growth restriction—major causes of maternal, fetal, and neonatal morbidity and mortality in the US and worldwide—whose etiology and mechanism remain unknown and for which therapy is limited. In addition to causing placental dysfunction, maternal autoantibodies may also directly impair fetal brain development. Identification of biomarkers that predict poor pregnancy outcome in these patients will elucidate mechanisms of disease, define targets for treating patients, and generate clinically applicable indicators to permit initiation of interventional trials in patients at greatest risk for pregnancy complications.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Title: **Achieving a Critical Mass of Women Biomedical Faculty: Impact of Three U.S. Programs**
P.I.: **Deborah Lynne Helitzer**
Institution: **University of New Mexico**
Grant No.: **HD064655-03**
Award: **$175,144**

Although there are numerous career development programs for women faculty, women continue to leave academic medicine at alarmingly high rates. This study will examine the impact on retention and career success of individual women faculty who participated in three long-standing national programs, each of which targeted a separate career stage, as compared to women and men, at the same career stages, who did not participate in these programs. This research also aims to elucidate the patterns and processes that contribute to the experience of individuals and their institutions as a means to identify the barriers and facilitators—historic and new, individual and institutional—that face women faculty in attaining positions of leadership at academic health centers (AHCs) and transforming institutional culture. Informed by the guidance of an Advisory Board composed of highly respected female and male senior leaders in academic medicine, the goal of the research is to assess the impact of participation in intensive career development training programs on individual women faculty at early and mid-career stages and their institutions, in terms of retention and promotion, while verifying and illuminating the ways in which participation in these programs affect career trajectories. We will attempt to discover how the findings on retention, academic promotion and administrative advancement are influenced by (i) individual dynamics and personal/professional development factors addressed in leadership development programs; (ii) organizational factors in institutions that send their women faculty to such programs; (iii) how these factors may have led to enhancement of leadership development and gender experience for women participating in these programs; and (iv) how the interaction of these factors has or can lead to a change in organizational culture to ensure the ability of institutions to capitalize on the intellectual capital of women science faculty members. Along with this retrospective analysis, we will prospectively identify new emerging challenges that affect women Assistant and Associate Professors attending intensive career development programs, and create an infrastructure for future research on retention and promotion. Additionally, this study will provide a comprehensive set of findings which can serve as the basis for a future design of an innovative women-focused leadership program as well as providing helpful information on the culture change needed to improve recruitment and retention of America's leading scientific minds.

Title: **Bench to Bedside: Adrenal Hyperplasia Among Adolescent Patients Polycystic Ovarian Syndrome**
P.I.: **Constantine A. Stratakis**
Institution: **NIH/NICHD and SUNY Downstate Medical Center**
Grant No.: **Y2-OD-1200-01**
Award: **$135,000**

Polycystic ovarian syndrome (PCOS) is a heterogeneous group of disorders presenting with hyperandrogenism in adolescents and young women. The etiology of this condition remains unknown, despite its many identified links to insulin resistance, hypertension and metabolic syndrome, as well as its potential connection to adrenogenital disorders, such as the various forms of congenital adrenal hyperplasia (CAH). We propose that there is a subgroup of patients with PCOS who actually have non-CAH primary forms of bilateral adrenocortical hyperplasia (BAH). To investigate this possibility, we propose to study the hypothalamic-pituitary-adrenal axis (HPAA) over the next 2 years in 100 young girls and women (ages 16 to 25 years) that we will compare to 30 age- and race-matched normal females. Patients will be recruited primarily (although not exclusively) from a busy New York City clinic run by the Pediatric Endocrine Division at the Infants and Children's Hospital of Brooklyn at Maimonides and SUNY Downstate. All patients will undergo standard testing of the HPAA including oral low- and high-dose dexamethasone (DEX)-suppression testing (Liddle's test). "Paradoxical" rise of cortisol and/or other steroid metabolites in response to DEX is considered a sensitive test for the diagnosis of BAH. Patients with such responses will be molecularly investigated for the known causes of BAH (GNAS, PRKAR1A, PDE11A, and PDE8B mutations). The transcriptome will be studied in patients who had paradoxical responses to DEX but are mutation-negative (to these genes). The goal of this study is to identify any possible contributions of the BAH phenotypes and genotypes to the pathophysiology of PCOS, a yet unknown factor in the etiology of this multifaceted disorder. This proposal addresses the possibility that PCOS may be linked to a form of primary adrenal hyperplasia. The clinical protocol resulting from this project will provide new knowledge about the diagnosis, natural history, and potential treatment of PCOS. Our laboratory has committed resources to the investigation of adrenal disorders and cAMP signaling. From the available evidence, we certainly expect that this pathway is involved in steroidogenesis. Our findings will lead to improved guidelines for treatment, and ultimately, new, therapies for PCOS. This work represents a new initiative; it is not covered by existing protocols; it represents an intramural/extramural collaboration and was stimulated by the availability of this special funding mechanism, as existing laboratory and clinical budgets of the participating investigators could not possibly cover this endeavor.

Title: **Brown/WIH Pelvic Floor Disorders Network Site**
P.I.: **Deborah Lee Myers**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **HD069013-01**
Award: **$25,000**

The mission of the PFDN is to identify optimal diagnosis and management strategies for women with pelvic floor disorders (PFDs) and this is directly in line with Women and Infants Hospital (WIH)/Brown's mission and commitment. WIH is a women's hospital, focused solely on advancing women's health and research and our extremely high volume, stable patient base, expertise of our multi-disciplinary collaborative and established research infrastructure provide the ideal environment to conduct large-scale, clinical research at the highest level. The aim of this application is for WIH/Brown to become the first PFDN site in New England by demonstrating: 1)our academic productivity and experience in multi-site, collaborative surgical, pharmaceutical and non-surgical clinical trials; 2)highly committed investigators with expertise in research methods and a specialized research team qualified to conduct multiple protocols, manage high quality data, and maintain high recruitment and retention; 3)a long-standing,

formal relationship with multi-disciplinary collaborators committed to advancing the care of women with PFDs led by Urogynecology (including Urology, Colorectal surgery, Women's Gastroenterology, Women's Physical Therapy, and Women's Radiology); and 4)our high clinical volume (In 2009, the Division of Urogynecology evaluated 1211 new patients and performed 583 PFD surgical procedures; vaginal, abdominal, laparoscopic and robotic approaches are all represented). We present a concept proposal describing a 3-stage, randomized trial of a combined non-surgical and surgical approach to treatment of mixed urinary incontinence (MUl) in women who have failed conservative therapy and/or elect surgical treatment. Women suffering from MUl are at high risk for failure of segregated treatments and are often excluded from clinical trials focused on either stress or urge urinary incontinence alone. Clinical management of MUl remains a challenge and trials targeting this population are urgently needed. WIH has a long-standing history of supporting network collaboratives and our goal is to participate and become a leader in the PFDN in terms of protocol development and completion, data interpretation and quality, recruitment and retention and high quality dissemination of findings. RELEVANCE: Female pelvic floor disorders including urinary incontinence, pelvic organ prolapse and fecal incontinence are common, disabling conditions and are a significant public health issue. Although a variety of treatment options exist, high quality evidence to guide clinical management and to improve treatment specificity is still needed. Through the PFDN, WIH/Brown is committed to advancing high quality scientific evidence to help improve the care of women and reduce the burden of these disorders.

Title: **Cleveland Clinic Clinical Site**
P.I.: **Matthew Barber**
Institution: **Cleveland Clinic Lerner College of Medicine**
Grant No.: **HD054215-06**
Award: **$25,000**

The goal of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with pelvic floor disorders (PFD) using the highest quality research methods available. The Cleveland Clinic offers a stable academic and research-oriented environment for the conduct of PFDN studies including experienced investigators with complementary clinical and research backgrounds that have a particular interest and a successful history of conducting clinical trials evaluating both surgical and nonsurgical therapies for women with PFD. The specific aims of this application are: 1) to demonstrate that the Cleveland Clinic (CC) Clinical Site has contributed substantially to the academic, administrative, and clinical aspects of the PFDN since joining in its 2nd 5-year cycle; that it possesses the personnel, patient, clinical and administrative resources needed for successful participation; and that continued participation would be advantageous to the successful attainment of the Network's scientific goals and 2) to present a concept proposal for potential conduct by the PFDN. We propose evaluating the comparative effectiveness of sacrospinous hysteropexy (SSH), the most well-studied uterine-sparing pelvic organ prolapse (POP) surgery, relative to total vaginal hysterectomy with sacrospinous ligament fixation (TVH/SSLF), a commonly used hysterectomy-based vaginal uterovaginal prolapse procedure. The specific aims of the concept proposal are: 1) compare the anatomic, functional, sexual and health-related quality of life outcomes of SSH to TVH/SSLF in women undergoing surgery for Stage 2-4 POP uterovaginal prolapse 2 years after surgery; 2) compare surgical recovery and short- and long-term morbidity of SSH and TVH/SSLF in these same women and 3) determine the incremental cost-effectiveness of SSH compared to TVH/SSLF for the treatment of Stage 2-4 POP. Enrolled subjects will be randomized in the operating room on the day of surgery to receive either SSH or TVH/SSLF (1:1) using a random permutated block design. Randomization will be stratified by surgeon to account for the varying experience and expertise. Subjects and study coordinators will be blinded to treatment assignment until completion of the study. RELEVANCE: Nearly one quarter of all women report symptoms of at least one PFD, including prolapse. POP is the most common indication for hysterectomy in

postmenopausal women and it is unknown whether the addition of hysterectomy to POP surgery is integral to successful surgical outcome. The results of our concept proposal could justify or eliminate the need for as many as 70,000 hysterectomies in the US each year.

Title: **Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team**
P.I.: **Pamela A. Moalli**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **HD061811-03**
Award: **$66,666**

Each year roughly 200,000 U.S. women undergo a surgery to repair pelvic organ prolapse (6, 7). Biologic and synthetic meshes are widely used in prolapse repairs to improve anatomical outcomes over native tissue repairs which currently have a failure rate of over 30%. To date, however, there is little scientific data to guide surgeons in the selection of a particular product. As a result, meshes are used based on the recommendations of a local vendor and consequently, are placed in women on a trial and error basis. There is growing evidence, however, that the complications associated with prolapse meshes cause unacceptably high rates of morbidity including infection, mesh shrinkage, mesh erosion, mesh exposure, pelvic, rectal and bladder pain and dyspareunia. Such complications have become significant enough for the FDA to recently release a warning about mesh use, especially when it is placed transvaginally. In this proposal, we therefore, aim to establish an interdisciplinary team of scientists dedicated to the comprehensive testing of previously or newly marketed prolapse meshes and for the development of the next generation of graft materials based on specific scientific criteria. In the first phase of the study, we determine how biochemical and structural changes in the prolapsed vagina impact passive and active mechanical behavior so as to develop a mesh in which these deficiencies are repaired or compensated for, allowing us to restore the prolapsed vagina to the nonprolapsed condition. In the second phase, we hypothesize that the shortcoming of current prolapse meshes is that they are too stiff. While this results in a repair with increased tensile strength, it occurs at the expense of tissue function with accelerated tissue contraction, decreased elasticity and compliance, and deterioration of smooth muscle function. To test our hypothesis, we implant commonly used synthetic prolapse meshes into the vagina of nonhuman primates with prolapse using the gold standard surgical procedure (the abdominal sacrocolpopexy) and then define the cellular, biochemical and biomechanical impact on the vagina at 6 months post implantation. Eventually, we will implant meshes transvaginally to characterize the distinct host response to this surgical approach. In the third phase, we explore the development of future grafts for prolapse surgery. We hypothesize that because of its bioinductive effects, a combined biologic/synthetic mesh will be superior to a synthetic mesh alone in restoring vaginal structure and function. We propose that a key yet poorly developed component of prolapse repairs is the re-establishment of smooth muscle reactivity and therefore, test the use of a temporary biologically active scaffold in achieving this process. In this way, this grant proposal provides a mechanism to establish the first team of scientists dedicated to the comprehensive unbiased evaluation of prolapse meshes as a means of educating both current and future prolapse surgeons, and the public regarding potential problems associated with certain materials. Indeed, the development of such a group is imperative for protecting the health of women.

Title: **A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response**
P.I.: **Candace S. Brown**
Institution: **University of Tennessee Health Science Center**
Grant No.: **HD065740-01A1**
Award: **$200,000**

Approximately 14 million U.S. women have provoked vestibulodynia (PVD), a type of localized vulvar pain which causes major disruption in the everyday lives of up to 60% of affected women and negatively impacts sexual function in 45%. The financial burden imposed on the health care system is also significant, as these women visit multiple clinicians and specialists, and try numerous, unproven treatments. To date, few randomized controlled trials (RCTs) have been conducted to establish evidence based protocols for PVD management. The first immediate goal is to conduct a multicenter RCT of gabapentin treatment for PVD. Gabapentin was selected because of its efficacy in treating other neuropathic pain conditions and the promising, preliminary data on its use in PVD. This is a significant research project because PVD is a highly prevalent, chronic pain condition that is costly to the health care system and that currently has limited management options available to affected women. The second immediate goal is to define psychophysiologic measures of gabapentin response and to define mechanistically-based PVD subtypes, which may be related to abnormalities in central sensitization, muscle hypertonicity, and autonomic dysregulation. Identifying predictors of treatment response in PVD would have clinical applicability to other chronic pain syndromes, and is consistent with NIH's mission to investigate coexisting pain conditions in order to identify common etiological pathways and develop therapeutic targets. The specific aims are (1): to test the prediction that pain from tampon insertion (primary outcome measure) is lower in PVD patients when treated with gabapentin compared to when treated with placebo. Additional outcome measures include reported intercourse pain and 24-hour pain, and (2) to test the prediction that gabapentin treatment will reduce mechanical allodynia, reduce area and duration of hypersensitivity induced by intradermal capsaicin, reduce vaginal muscle pain to palpation, decrease the number and intensity of somatic tender points, and increase cardiac beat-to-beat variability. This 16-week, randomized, double-blind, placebo-controlled, crossover study will enroll 120 women between 18-50 years of age who report tenderness localized to the vulvar vestibule, pain with tampon insertion, and, when sexually active, insertional dyspareunia. Electronically entered daily diaries will be used to determine if pain is lower in PVD subjects when treated with gabapentin (up to 3600 mg/d) compared to when treated with placebo. The approach is innovative because it focuses on an understudied condition, in a multicenter setting, using a novel outcome measure (the tampon test), and a newly developed web-based recruitment and patient-reporting tool. Data management will include a mechanism-based analysis of drug effectiveness. These study outcomes will ultimately lead to our long-range goal of identifying underlying pathophysiologic mechanisms of PVD in order to create evidence-based differential diagnoses of subtypes of PVD for more effective and cost-effective management options.

Title: **Empowering Daughters and Mother-in-Laws to Mitigate Gender-Based Violence and Promote Women's Health in India**
P.I.: **Suneeta Krishnan**
Institution: **Research Triangle Institute**
Grant No.: **HD062821-02S1**
Award: **$50,438**

The prevalence of physical, psychological, and sexual gender-based violence (GBV) is staggeringly high among young, married women in India. However, few GBV prevention interventions have been implemented, and none of these interventions has been rigorously evaluated. We aim to fill this gap by conducting exploratory research on an innovative women's empowerment-based GBV prevention intervention. The proposed study builds on our previous research

in urban poor communities in Bangalore, India, which revealed that efforts to enhance young, married women's power and to mitigate GBV will be limited if the broader context of their lives, which is shaped mainly by the marital family, is unaddressed. Previous research suggests that mothers-in-law (MILs) are a strategic familial entry point and that it may be possible to redirect the power they wield in the family toward reducing GBV against daughters-in-law (DILs). Based on this evidence and women's empowerment approaches that have successfully reduced GBV elsewhere, we developed the intervention Dil Mil (meaning "Hearts Together" in India's national language, Hindi). Guided by the Social Cognitive Theory and Heise's social-ecological framework of GBV, Dil Mil aims to empower DIL-MIL dyads with knowledge, skills, and social support critical to the mitigation of GBV and related adverse health outcomes among DILs. We chose antenatal care as the context for implementing this intervention because of women's nearly universal use of antenatal care in urban India. A phase 1 pilot study demonstrated that our approach is acceptable and likely to be safe. The aim of this R21 is to conduct a phase 2 trial to examine the feasibility, safety, and potential effectiveness of Dil Mil in order to determine if a phase 3 effectiveness trial is merited. The proposed study is a randomized controlled trial with 140 dyads comprising pregnant DILs (aged 18 to 30 years, in their first or second trimester of pregnancy, with a history of GBV) and their MILs. Recruitment will take place at four primary health centers serving poor communities in Bangalore. Dyads will be offered standard care or standard care plus the Dil Mil intervention, and evaluations will be conducted at 3 months and 6 months postpartum. We will characterize the study population using descriptive statistics and assess feasibility and safety of the intervention using qualitative and quantitative data (Aim 1). Data on the effect of the intervention on intermediary outcomes-the empowerment of DILs and MILs (Aim 2)-and on the incidence of GBV among DILs during the first 6 months postpartum, DILs' perceived quality of life and psychosocial status, and maternal and infant health outcomes (Aim 3) will be analyzed using the intention-to-treat principle. Based on this evidence, we will determine if a phase 3 trial is merited. In conclusion, this study will generate important insights on a novel, urgently needed response to GBV in a high prevalence setting and is highly likely to have a significant public health impact.

Title: **Gender Equity-Focused, Male-Centered Family Planning for Rural India**
P.I.: **Anita Raj**
Institution: **University of California, San Diego**
Grant No.: **HD061115-04**
Award: **$60,559**

The major barrier to India meeting its national goal of replacement fertility is the huge discrepancy between urban and rural family planning, with rural young women at highest risk for unplanned and unspaced pregnancies. These concerns are considered to drive the persistent and unacceptably high rates of maternal and infant mortality in India. Major impediments to these young wives' acquisition of family planning services include high male partner control over reproductive decision-making, low mobility, and very low access to family planning services in villages. Such findings document the need for male-centered family planning efforts available at the village level, to better meet the needs of rural young wives. These male-centered efforts must address male gender role and gender inequity ideologies and norms (e.g., son preference, wife abuse) and marital communication, as these factors are associated with lower likelihood of contraceptive use in rural young Indian couples. Hence, the proposed study involves development and testing of the Children's Health and Responsible Mothering (CHARM) Program, a gender equity (GE)-focused, male-centered family planning (FP) program delivered by private village health providers (VHPs), via a public-private partnership with primary health centers (PHCs) serving rural India. In Phase 1 we will conduct formative research including health care resource mapping of Vasai within the Thane district of Maharashtra to identify villages and VHPs for inclusion in subsequent research and intervention. We will also conduct in-depth interviews with rural young husbands (n=30), rural young wives (n=20), and health care providers (n=12),

as well as focus groups with mothers' of rural young husbands (n=40). These data will be used to develop the CHARM program and efficacy trial. Phase 2 will involve development and pilot testing of CHARM protocols and training of VHPs for their role in the intervention trial (Phase 3). The CHARM intervention will involve VHP-delivered GE and FP counseling and services, delivered over 3 intervention sessions + 2 booster sessions. Phase 3 will involve evaluation of CHARM, using a two-armed randomized controlled trial design. Villages (N=50) will be randomized to receive either CHARM or the control program (standard FP referral to government public health centers [PHCs] located outside of villages), to assess treatment impact on spacing contraceptive use, pregnancy, and unmet family planning need. Intervention effects will be assessed via behavioral surveys collected on hand-held computers (PDAs) with rural young husbands (18-30 years) and their wives (N=1500 couples, 30 couples per village) at baseline and 6,12, and 18 month follow-up, as well as pregnancy tests from wives, conducted at baseline and 18 month follow-up. A process evaluation will be undertaken via interviews with study participants and VHPs, as well as through VHP observations and clinical record review, to assess program adherence, participation rates, response to program, and ease of delivery. In-depth interviews will also be conducted with key informants from the village and public and rural health systems to assess sustainability and institutionalization of the model.

Title: **Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women**
P.I.: **Brahim Aissani**
Institution: **University of Alabama at Birmingham**
Grant No.: **HD064398-02**
Award: **$83,333**

Uterine leiomyomas (ULs) are the most common pelvic tumors in women of reproductive age, accounting for over 600,000 hysterectomies annually in the United States. Several lines of evidence support a genetic liability in the pathogenesis of ULs, yet no susceptibility gene is known. Advances in research on the genetics of ULs (fibroids) have so far been limited by the paucity of genetic epidemiologic studies and infrastructure to conduct them. The goal of this epidemiologic study is to evaluate the contribution of a region of Chr.1q43 that predisposes to uterine fibroids but remains inadequately investigated. Genetic predisposition to ULs has been studied primarily in the context of two rare inherited autosomal-dominant conditions, the hereditary leiomyomatosis and renal cell cancer (HLRCC) and the multiple cutaneous and uterine leiomyomatosis (MCUL1) syndromes, where germline mutations were found in the gene on Chr. 1q43 encoding the tricaboxylic acid cycle (Krebs cycle) fumarate hydratase (FH) enzyme. However, a direct role of this important metabolic housekeeping gene in tumorigenesis remains to be proven. Inactivating FH mutations have rarely (< 1-2% of the tumors analyzed) been observed in nonsyndromic (common) ULs; however, loss of FH appears to be a significant event in the pathogenesis of a subset of these tumors. Furthermore, several observations support the existence of an alternative or additional candidate gene on Chr.1q43 acting alone or interacting with FH to increase the risk of ULs in susceptible individuals: 1) the absence of FH genotype-phenotype correlations, 2) the marked genetic heterogeneity in ULs, and 3) the failure to observe ULs or multiple leiomyomatosis in siblings or parents of cases with fumarase deficiency, a severe recessive disorder. Taken together, these observations underscore the importance of exploring an extended FH region in a population-based study of ULs. To this end, we will generate a high-density single nucleotide polymorphism genotyping data across a 2-Mb region spanning FH in subsets of African American (n=582) and Caucasian (n=455) women enrolled in the NIEHS-Uterine Fibroids Study. This is a well designed cross-sectional study of ULs that includes data on most potential confounders. Our study is not intended to shift any paradigm about the origins of ULs; rather it will extensively investigate the role of FH in nonsyndromic ULs, dissect the intricate genetic correlates of Chr.1q43 markers in the expression of the disease phenotype and evaluate their effects in two populations with a marked difference in disease risk. Recent

updates in the genome databases have revealed new potential candidate genes for tumor growth and important structural variations including a large (~308 Kb) copy number variation in the vicinity of FH; these new findings further justify a study with the proposed depth and extent of genetic coverage. This study will likely open new avenues for research and may ultimately redirect current preventive and therapeutic approaches or enhance their efficacy.

Title: **Genetic Studies of Uterine Leiomyomata**
P.I.: **Cynthia Casson Morton**
Institution: **Brigham and Women's Hospital**
Grant No.: **HD060530-02**
Award: **$83,334**

Uterine leiomyomata, or fibroids, are the most common pelvic tumors in females and occur in a minimum of 20-25% of women of reproductive age. Although benign neoplasms, they constitute a major public health problem as 25-50% of affected women experience debilitating symptoms including excessive menstrual bleeding and pelvic discomfort as well as reproductive failure. Fibroids are the major indication for hysterectomy accounting for over 200,000 procedures annually in the United States. It is highly likely that there is a genetic liability to develop fibroids; they are at least three times more frequent in African American than Caucasian women (representing a serious health disparity) and twin-pair correlations for hysterectomy in monozygotic twins are about twice that observed in dizygous twins. Despite these findings and enhanced research in this area in recent years, much remains to be known about this racial predisposition and specific genes involved in the pathogenesis of fibroids. Also of particular interest and of unknown molecular mechanism, fibroids rarely proceed to their malignant counterpart, uterine leiomyosarcoma. Thus, it follows that uterine leiomyomata may serve as an important model system to study the genetic events that distinguish benign and malignant neoplasms. Consistent chromosome aberrations have been observed in fibroids indicating the location of genes involved in these tumors. A number of cytogenetic subgroups have been identified and we have been successful in using positional candidate gene approaches in determining that two high mobility protein genes, HMGA2 and HMGA1, located on chromosomes 12 and 6, respectively, participate in the pathobiology of uterine leiomyomata, in addition to MYST4, located on chromosome 10. The major goal of this proposed application is to further our understanding of the biology of uterine leiomyomata. Experiments are focused on continuing to develop and use a uterine leiomyomata tissue bank and database for gene discovery, gene expression studies, and genotype-phenotype correlations. A variety of molecular and cytogenetic approaches will be used in the identification, isolation and characterization of genes involved in the pathogenesis and pathobiology of uterine leiomyomata. Chromosomal rearrangements in tumor cells will provide biological landmarks for positional cloning experiments. Transcriptional profiling offers a powerful approach to discriminate genes that differentiate fibroids of different cytogenetic subgroups as well as fibroids of variant histologies from their normal smooth muscle counterpart, the myometrium, or their malignant counterpart, uterine leiomyosarcoma. Lastly, the potential role of sequence variants in HMGA2 will be explored by a variety of mechanistic experiments to assess their role in uterine leiomyomata.

Title: **Identification of Genes Predisposing to Pelvic Floor Disorders**
P.I.: **Lisa Cannon Albright**
Institution: **University of Utah**
Grant No.: **HD061821-03**
Award: **$66,667**

The investigators propose a unique and powerful collaboration between basic and clinical scientists in Utah to identify genes affecting predisposition to pelvic organ prolapse (POP). The co-PIs both have significant experience, Dr. Norton in Pelvic Floor Disorder (PFD) genetics and

Dr. Cannon-Albright in predisposition gene identification. The investigators will access the Utah Population Database, a computerized genealogy of Utah combined with decades of medical data from the two largest healthcare systems in Utah (serving 90% of the state), to identify and recruit surgically treated cases of POP (1,250 cases in 5 years). All POP cases sampled will be genotyped with the Illumina 610Q SNP marker set. The PIs will apply multiple different genetic analyses to this resource of genotyped POP cases to aid in the identification of predisposition genes. The record linkage of medical procedure codes (identifying surgeries performed on each patient) to individual genealogy data allows us to identify all genetic relationships among the POP cases. We will perform genome-wide association analysis, using software we have developed which allows inclusion of both independent and related cases. We will identify all genetic relationships between the sampled POP cases and perform linkage analysis in informative, high-risk POP pedigrees. We will identify chromosomal regions shared Identical by Descent (IBD) in very distantly related cases in these pedigrees, and we will identify IBD sharing within the small subset of POP cases (2%) who are inbred. Initial collaborative analysis of data obtained by Dr. Norton's NIH funded study of affected PFD sib-ships has already provided significant evidence for a predisposition gene localization on chromosome arm 9q, and suggestive evidence for at least one other locus on chromosome 1. In summary, we will create a population-based resource of surgically treated POP cases, we will pursue established and new methods to identify and localize predisposition genes affecting POP, and we will begin a detailed search for the chromosome 9 gene we have localized.

Title: **India Human Development Survey**
P.I.: **Sonalde B. Desai**
Institution: **University of Maryland, College Park**
Grant No.: **HD041455-06S1**
Award: **$42,600**

Researchers from the University of Maryland, the National Council of Applied Economic Research, and AMS Consulting, together with an interdisciplinary team of collaborators, propose to field the second round of the India Human Development Survey (IHDS-II), a nationally representative survey of 41,554 households who were surveyed in 2004-2005 under NIH grants R01HD041455 and R01HD046166. This survey is designed to be a premiere public resource for researchers interested in studying different dimensions of human development in India. The proposed project has two specific aims: A. Resurvey the households initially surveyed in 2004-5 once again in 2011-12. Given the vast changes in India since 2005, IHDS-II will provide a multitopic, multi-purpose source of data for international and Indian research on health, education, income, employment, gender and social inequality. Panel data will allow an exploration of lagged effects as well as better estimation of causal relationships. IHDS-II will permit the analysis of two major government programs initiated since 2005—the National Rural Employment Guarantee Scheme and the National Rural (and now Urban) Health Mission. These programs introduce exogenous changes in the male/female wage gap and provide cash incentives for hospital deliveries. Panel analyses of these changes create new opportunities to investigate the determinants of gender gaps in employment, education, and health. B. Expand the range of data collected. Data collection will be expanded in two principal ways: 7 Some questions from IHDS-I will be revised and extended based on our field experience, analysis results, and user feedback. 7 New modules will be added to study the mechanisms through which spatial disparities in health and education emerge. Research conducted under the parent grant has highlighted the importance of spatial disparities in health, education, income, and employment as well as caste and gender differences in these outcomes. Analyses of IHDS-I have showed us that these large regional differences persist in spite of a wide range of controls for individual level factors. In this renewal, we seek to measure a broader range of mechanisms through which these spatial disparities emerge. New efforts focus on supplementing the household surveys with expanded geographic data and institutional surveys.

Title: **Interdisciplinary Research Training: NCD Epidemiology and Prevention in India**
P.I.: **Nikhil Tandon**
Institution: **Centre for Chronic Disease Control**
Grant No.: **HD065249-03S1**
Award: **$50,240**

There is an acute shortage of post-doctoral and junior faculty research capacity in India, with no postdoctoral programs in epidemiology and prevention of non-communicable diseases (NCDs). The proposed interdisciplinary training program will focus on the epidemiology and prevention of NCD across the life-course, in cross-connecting subject areas (child health; nutrition and lifestyle, environmental health, obesity and diabetes, stroke and other vascular diseases) and population science disciplines (epidemiology and biostatistics; clinical trials; translation research, social sciences, and economics). This effort will leverage an established network of research collaborations involving partners in India and the US (Ovations Center for Excellence in Chronic Diseases, New Delhi). The program will have two components: (1) Short-term training in year 1: Eight junior faculty researchers will receive four months of training at Emory to acquire specific and focused mentoring and research skills. (2) Long-term training in years 2-5: A total of ten post-doctoral fellows (one batch of five in years 2-3 and one batch in years 4-5) will receive 24 months of training (four months at Emory in the first year, six weeks at Emory in the second year, and the remaining 18.5 months in India). Training components include mentored research, coursework, professional development (ethics, grants-writing, communication skills), and an emphasis on context-specific innovation in health programs and research. Collaboration with Emory will compliment India-based mentoring and training, and permit transfer of skills and expertise in specific areas. The program will build a critical mass of NCD researchers and incorporate them within integrated NCD research programs in India. An important innovation of our program is the emphasis on retaining talented young scientists in India, enabling them to develop world-class research skills in an Indian-based training program, facilitating international collaborations, and providing end-of-training grants to promote in-country research projects. We expect the program to have a cascade effect, as each of the 18 trainees will serve as a resource upon completion of the program, disseminating knowledge and skills to other researchers at in-country institutions.

Title: **A Longitudinal Study of Loss of Imprinting in First Trimester CVS Samples Compared to Placental Samples at Birth**
P.I.: **Men-Jean Lee**
Institution: **Indiana University–Purdue University at Indianapolis**
Grant No.: **HD068873-01A1**
Award: **$273,068**

For most human genes, maternal and paternal alleles are bi-allelically expressed. However, a specific subset of genes are imprinted and mono-allelically expressed. The current dogma is that this embryonic imprint is stable across the lifespan of the organism. Loss of imprinting (LOI) leads to bi-allelic expression of the imprinted gene, potentially causing a doubling of gene dosage or gene dysregulation, resulting in disease. Because the methylation marks of imprinted genes are considered permanent after fertilization, any acquired changes in the intrauterine environment may lead to stable transgenerational effects. The regulatory complexity of these imprinted gene domains may render them particularly sensitive to environmental changes such as diet and nutrition. Emerging evidence implicates aberrant imprinting in the pathophysiology of many common human diseases, including complications of pregnancy such as intrauterine growth restriction (IUGR) and preeclampsia (PE); and even postnatal disorders such as obesity, cardiovascular disease, and type 2 diabetes. We have developed a highly sensitive and quantitative allele-specific PCR analysis to measure LOI in a panel of imprinted genes in the human genome. Using this methodology, we have already determined that pregnancies complicated by PE and IUGR are associated with dysregulation of a set of imprinted genes in the placenta. Both of these

obstetrical disorders have their origins in an early intrauterine environment associated with aberrant placentation and trophoblast invasion. We also have novel evidence to suggest that genomic imprinting patterns are not permanently fixed in placental development. Contrary to the prevailing theory, we hypothesize that patterns of LOI are not static in the human placenta and are subject to developmental and environmental influences over the course of pregnancy that predispose to adverse pregnancy outcome. We now propose a longitudinal trial as a secondary study to the NuMOM2B Trial to monitor LOI in placenta samples from first trimester CVS to birth and determine which LOI patterns in the first trimester lead to normal pregnancy outcomes and which patterns are predictive of pregnancy complications.

Title: **Molecular Basis of Treating Endometriosis by Prostaglandin E2 Receptor Inhibitors**
P.I.: **Joe A. Arosh**
Institution: **Texas A&M University**
Grant No.: **HD065138-01A1**
Award: **$200,000**

Endometriosis is an estrogen dependent disease. Current medical therapies to inhibit estrogen biosynthesis and actions fail to prevent reoccurrence of the disease and compromise success of pregnancy in child-bearing age women. This suggests a crucial need to identify potential cell signaling pathways for nonestrogen therapeutic targets for endometriosis. Prostaglandin E2 (PGE2) promotes survival of endometriosis, however; the underlined molecular mechanisms are largely unknown. Our long-term goal is to understand molecular and cellular aspects of PGE2 biosynthesis and signaling cross-talk in the pathogenesis of endometriosis in order to identify new targeted therapies. The objective of this application is to understand PGE2 signaling pathways in survival and growth of endometriosis. Our central hypothesis is that loss-of-function of PGE2 receptors EP2 and EP4 inhibits survival and growth of endometriosis. Specific Aim-1 will determine the mechanisms through which loss-of-function of EP2 and EP4 induces apoptosis of endometriosis. Specific Aim-2 will determine the mechanisms through which EP2 and EP4-mediated PGE2 signaling immunomodulate and enhance the phagocytic ability of macrophages in endometriosis. Specific Aim-3 will determine the mechanisms through which loss-of-function of EP2 and EP4 decrease estrogen production in endometriosis. Our experimental approaches include: (i) genomic and pharmacological inhibition of EP2 and EP4; (ii) stable fluorescence-labeled human endometriotic epithelial cells, stromal cells, macrophages, and eutopic and ectopic endometria from endometriosis patients, (iii) nude and Rag2g(c) mice xenograft models, (v) molecular, cellular, biochemical, and microscopy-based assays; and (vi) whole animal bioimaging method. The rationale is that successful completion of the proposed research will contribute a missing and fundamental element to our base of knowledge without which the mechanism through which selective inhibition of EP2 and EP4 induces apoptosis of human endometriotic cells cannot be understood. In addition, the expected results will advance the current knowledge of the pathogenesis of endometriosis and increase the understanding of PGE2 signaling in survival of endometriosis. The acquisition of such knowledge is critical and could be translated to treat women suffering from endometriosis. It is our expectation that selective inhibition of EP2 and EP4 will induce apoptosis of endometriotic cells, increase phagocytic ability of infiltrated macrophages in endometriosis per se, and decrease estrogen production by the endometriotic cells through multiple mechanisms. Our findings would have clinical impact because it would allow for the first time to develop new and much needed therapeutic strategies to inhibit EP2 and EP4 signaling as novel nonestrogen targets for the treatment of endometriosis in child-bearing age women. This is a R21 application addresses the mission of NIH/NICHD on women's reproductive health.

Title: **Molecular Mechanism of LPA3-Mediated Uterine Receptivity**
P.I.: **Xiaoqin Ye**
Institution: **University of Georgia**
Grant No.: **HD065939-01A1**
Award: **$200,000**

Defective uterine receptivity, including delayed uterine receptivity and non-receptive endometrium, is the key maternal factor for infertility and early pregnancy loss. The molecular mechanism of how a uterus transforms into a receptive state for embryo implantation is not well understood. It is well recognized that progesterone receptor (PR)-mediated hormonal signaling is essential for the establishment of uterine receptivity in all mammals studied. PR has dynamic spatiotemporal expression patterns in the peri-implantation uterus. The disappearance of PR from uterine luminal (LE) and glandular epithelium is associated with the establishment of uterine receptivity. Failure of such down regulation of PR in uterine epithelium during the expected "implantation window" is associated with defective uterine receptivity. LPA3 (LPAR3/EDG7) is the third receptor for lysophosphatidic acid. Down regulation of uterine LPA3 is implicated in defective uterine receptivity in endometriosis patients and deletion of Lpar3 in mice leads to delayed uterine receptivity. Sustained PR expression in LE is detected in the non-receptive day 4.5 Lpar3(-/-) mouse uterus (normal implantation: ~day 4.0 in mouse). How the sustained PR expression in LE during the expected "implantation window" blocks uterine receptivity and how PR-mediated hormonal signaling interacts with local targets to control uterine receptivity remain as significant knowledge gaps. The long-term goal is to understand the molecular mechanism of uterine receptivity thus help overcome infertility and early pregnancy loss associated with defective uterine receptivity. The overall objective of this application is to fill the mentioned knowledge gaps, specifically the significance of sustained PR expression in LE and the interplay between PR and LPA3 in LE. The central hypothesis, formulated based on supportive preliminary data, is that PR interplays with LPA3 to coordinately regulate uterine receptivity. The rationale is that understanding the significance of PR in LE and its interplay with LPA3 will provide more insight into the molecular mechanism of uterine receptivity. To achieve the goal of this application, three specific aims will be pursed. Aim 1. Determine molecular pathways dysregulated in LE with sustained PR expression, based on the working hypothesis that sustained PR expression in LE dysregulates genes/molecular pathways leading to a non-receptive uterus. Aim 2. Determine interplay between PR and LPA3 in LE, based on the working hypothesis that PR and LPA3 mutually regulate each other in LE for the establishment of uterine receptivity. Aim 3. Determine role of LPA3 in regulating molecular pathways in preimplantation day 3. 5 endometrium, based on the working hypothesis that LPA3 regulates its uterine target genes to influence uterine receptivity directly and/or via PR in LE. Laser microdissection, gene profiling, immunoblotting, ChIP assay, and immonoprecipitation are among the approaches that will be employed. The proposed work is significant because understanding the molecular mechanism of uterine receptivity is critical for developing diagnostic and therapeutic approaches to detect and treat infertility and early pregnancy loss associated with defective uterine receptivity.

Title: **Novel Approaches for Disrupting Gene Expression in Mammalian Oocytes**
P.I.: **Janice P. Evans**
Institution: **Johns Hopkins University**
Grant No.: **HD069165-01A1**
Award: **$200,000**

This R21 project seeks to develop new approaches for the genetic manipulation of mammalian oocytes, which we envision will accelerate advancing our knowledge of oocyte function and reproductive health. Genetic manipulation of mammalian oocytes has primarily used two methods: RNA interference and knockout mice. While RNAi has been a highly successful method of RNA ablation and subsequent protein knockdown in oocytes, RNAi approaches are not without limitations, as knockdown can be inefficient. Furthermore, double-stranded RNA and siRNAs have

to be introduced into oocytes by microinjection, which is labor- and time-intensive and makes it impractical do use a large-scale RNAi approach (e.g., siRNA library-based screens). Knockout mice certainly have provided significant insights into mammalian oocyte biology as well, but knockout approaches also are not without pitfalls, including the time and expense involved in obtaining a knockout. This project seeks to develop alternatives to these methods, utilizing different established nucleic acid-based methods in novel combinations and with specialized modifications for the applications proposed here. In Aim 1, we will augment the use of siRNAs for post-transcriptional gene silencing with another reagent, a short single-stranded nucleic acid called a triplex-forming oligonucleotide (TFO) for pre-transcriptional silencing. TFOs bind to homopurine tracts in double-stranded DNA, and have been used to regulate gene expression in cultured cells and in vivo. The hypothesis for Aim 1 is that TFOs will inhibit transcription of a targeted gene, while siRNAs will mediate degradation of any residual mRNAs that were transcribed. This will be tested in vitro with isolated oocytes as well as with follicle-enclosed oocytes for longer-term culture. In Aim 2, we will develop methods for delivery of agents into oocytes. We will identify a novel agent for oocyte-specific delivery, using a screen of an aptamer library (with 1.2 X 1018 oligo-2'-deoxyribonucleotide sequence isomers) to isolate an aptamer that will interact with the oocyte's zona pellucida (ZP). Aptamers are nucleic acid-based molecules that bind with high affinity to target molecules. Aptamers can be used for delivery of agents such as siRNAs into cells; this delivery works in vivo, and aptamers currently are being developed as therapeutics to target drugs and other agents to specific cell types for treatment of a variety of diseases (13 aptamers are in clinical trials). Additionally, as an alternative tool, we will also test a cell-penetrating peptide for intra-oocyte delivery. We will couple siRNAs or TFOs to ZP-binding aptamers and/or a cell-penetrating peptide, and test these for their actions in oocytes. The future direction of this work will be to test the ZP-targeting aptamer for systemic delivery of siRNAs and TFOs, as a means of in vivo oocyte-specific knockdown as an alternative to knockout/transgenic methodologies, as well as potentially the foundation of a novel female contraceptive.

Title: **ORWH/NICHD Leiomyoma Tissue Bank**
P.I.: **James Segars**
Institution: *Eunice Kennedy Shriver* **National Institute of Child Health and Human Development Intramural Program**
Grant No.: **Z01-HD008737-11**
Award: **$50,000**

The health of 30-50% of women in the U.S. is adversely affected by uterine leiomyoma (fibroids). Uterine fibroids are a health disparity issue that disproportionately affects African American women. Research into causes and treatment has lagged behind other disciplines, in part due to lack of available tissues, since surgical samples are often not made available to scientists. To address the problem of tissue availability, and promote research on this condition, this project proposes to establish a fibroid tissue bank as an initiative in the intramural program of NICHD. This tissue bank will provide samples to NIH-funded investigators and DoD-funded investigators to support work on this condition. The Leiomyoma Tissue Bank (LTB) will be physically located in space assigned to Dr. Segars of NICHD. The LTB will be structured after RStaR-banks for endometrium and ovary established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

Title: **Pelvic Floor Disorders Network Clinical Sites**
P.I.: **Lily A. Arya**
Institution: **University of Pennsylvania**
Grant No.: **HD069010-01**
Award: **$25,000**

The goal of this application is to competitively identify clinical sites to conduct clinical trials for female pelvic floor disorders. This application from the University of Pennsylvania with Lily Arya MD, MS (Epidemiology) as Principal Investigator demonstrates our research plan for a new treatment for urge urinary incontinence, myofascial physical therapy. This potentially effective and safe method will greatly enhance treatment choice and improve the quality of life of women with urge urinary incontinence. This application outlines our extensive experience with similar large multi-center clinical trials. We highlight our ability to recruit and maintain subjects in female pelvic floor disorder clinical trials, noting we have been one of the leading recruitment centers in the nation for similar trials. We have often been able to recruit a greater number of subjects than our original estimates. The facilities at the University of Pennsylvania are supportive and outstanding. Our existing research unit and personnel has continuously demonstrated highly successful management of large clinical trials with outstanding organization, attention to detail and compliance with Good Clinical Practice, federal regulations and local Institutional Review Boards. Dr. Arya is an active researcher in the field of health measurement for pelvic floor disorders and she has successfully conducted a number of clinical trials in women's health. Specifically, she and her team of co-investigators and staff have been actively involved in surgical and non-surgical trials for urinary incontinence. She will bring significant expertise regarding study design and health measurement research to the Pelvic Floor Disorders Network. She leads a team of co-investigators who have a track record of collaborative clinical and translational research. We feel that the combination of a high quality personnel, experience in the research area, ability to recruit, and outstanding management and organization will contribute to a high likelihood of successful completion of this and future trials of treatment methods of pelvic floor disorders. RELEVANCE: The University of Pennsylvania has the expertise, infrastructure and experience to be a significant contributor to the Pelvic Floor Disorders Network. The proposed study, to investigate the efficacy of a new treatment for urge urinary incontinance, will improve quality of life of women with urge incontinence and result in considerable savings of health care resources.

Title: **Pelvic Floor Disorders Network: Duke University Medical Center**
P.I.: **Anthony G. Visco**
Institution: **Duke University**
Grant No.: **HD041267-12**
Award: **$25,000**

Pelvic floor disorders research at Duke University Medical Center (DUMC) is sophisticated and comprehensive with committed investigators addressing issues of great importance to women. DUMC has a tradition of excellence in clinical care, training and research in pelvic floor disorders and includes one of the nation's first accredited fellowship programs in the field. DUMC offers detailed evaluation and treatment in a high-volume, multidisciplinary setting that serves as a tertiary referral center for women across the southeast US. Each of the five Duke urogynecology investigators is fellowship-trained with expertise in both surgical and non-surgical management of urinary incontinence (Ul), pelvic organ prolapse (POP), fecal incontinence, and defecatory dysfunction. Last year, our Division cared for more than 1550 new patients and performed more than 400 surgical procedures for Ul and 270 for POP. Our patient population is 80% Caucasian, 15% African American, 2% Asian and 2% Hispanic, from both suburban and rural communities with stable care and follow-up patterns. DUMC is the hub of a multidisciplinary team of outstanding collaborative investigators in urogynecology, urology, colorectal surgery, gastroenterology, maternal-fetal medicine, physical therapy and epidemiology. DUMC offers a wide range of diagnostic resources: multi-channel urodynamic testing, video urodynamics, cystoscopy, defecography, pelvic

MRI, endoanal ultrasound, and needle electromyography. During the current PFDN cycle, DUMC-initiated three active RCTs: 1. Anticholinergic vs Botox RCT (ABC, Dr. Visco, currently enrolling), Interstim vs Botox RCT (ROSETTA, Dr. Amundsen, full protocol), and a RCT evaluating transvaginal mesh for prolapse repair (Dr. Weidner, mini-protocol planned for fall of 2010. DUMC has consistently been a high recruitment site across a wide range of non-surgical and surgical studies with unparalleled retention rates. We have proven our ability to support and successfully complete large-scale, multi-centered investigations through our robust clinical practice and exceptional research infrastructure. Accordingly, Duke University Medical Center is well equipped and uniquely qualified to continue as a valuable and productive member of the Pelvic Floor Disorders Network. RELEVANCE: Female pelvic floor disorders represent a major public health burden given their high prevalence, impairment of quality of life, and substantial economic costs. As part of the Pelvic Floor Disorders Network, Duke University Medical Center is committed to actively participating in innovative clinical trials aimed at improving the evaluation and treatment of pelvic floor disorders through high-quality, high-impact clinical research.

Title: **Pelvic Floor Disorders Network: University of California, San Diego**
P.I.: **Charles William Nager**
Institution: **University of California, San Diego**
Grant No.: **HD054214-06**
Award: **$25,000**

The objectives and aims of this application are for the San Diego site to continue its work In the Pelvic Floor Disorders Network (PFDN). The unique strength of our application is our proven two site model, which combines the strengths of 7 academic investigators at both a tertiary medical center and a large volume HMO. We would like to provide leadership, continuity, innovation, academic expertise, a captured diverse patient population, and a proven research infrastructure to the network. We have a track-record of being the top 2 recruitment in surgical trials for pelvic floor disorders and we want to continue that into the third cycle of the PFDN. As noted in the RFA, "In many cases, clinicians caring for women with pelvic floor disorders have adopted principles of care and surgical techniques before rigorous, objective, controlled evaluation has taken place. New devices and techniques have had a dramatic influence on surgical practice …". Our study addresses this concern. Vaginal mesh is probably the most controversial topic in pelvic floor disorders and a strong argument can be made that the PFDN is the best group to study it. A growing-trend of women is seeking uterine sparing surgery for prolapse and a growing trend of gynecologists and urologists are managing uterine prolapse with vaginal mesh kit procedures. Our proposed randomized trial of uterine sparing, grafted vaginal apical suspension vs. traditional hysterectomy with native tissue suspension addresses the very important question of whether it is necessary to remove the uterus to treat uterine prolapse. This proposed study recognizes the role of new devices and techniques that are changing our care of women with pelvic floor disorders. Our comprehensive outcome measures should allow us to answer whether these new uterine-sparing, apical vaginal procedures are reasonable alternatives to conventional vaginal hysterectomy and native tissue suspension. RELEVANCE: Our site's participation in the next cycle of the PFDN should allow successful network recruitment for surgical trials. Uterine prolapse is a very common pelvic floor disorder and we should determine the best vaginal surgical treatment for this condition. This proposed research study will answer whether uterine-sparing procedures are reasonable alternatives to hysterectomy for this condition.

Title: **Perioperative Pelvic Floor Rehab: A Randomized Trial**
P.I.: **Holly E. Richter**
Institution: **University of Alabama at Birmingham**
Grant No.: **HD041261-11**
Award: **$25,000**

The University of Alabama at Birmingham (UAB) is seeking to successfully compete in the third cycle of the NICHD sponsored Pelvic Floor Disorders Network. As a part of this important research infrastructure we have demonstrated our credible, productive, multidisciplinary clinical approach to the evaluation and treatment of women with pelvic floor disorders including urinary and fecal incontinence as well as pelvic organ prolapse. We have substantially contributed to the Network activities by participating at all levels of clinical trial design, implementation, recruitment, intervention implementation, retention and scientific reporting. We have reported outcomes and implication for care of these research initiatives at national and international scientific meetings and we are committed to continuing these activities. Through this application with its concept proposal, we wish to highlight our ability and commitment to continue these meaningful research activities. Current common treatment options for fecal incontinence (Fl) include behavioral therapy consisting of pelvic muscle exercises, diet and defecatory strategies and surgical approaches including anal sphincter repair, artificial bowel sphincter and as a last resort, colostomy. A significant proportion of women with Fl, however, do not gain benefit from behavioral therapy or sphincter repair yet do not wish to undergo colostomy. As the population of post-reproductive women continues to increase, it is imperative to study other treatment options that improve quality of life for this condition. An existing modality called sacral neuromodulation (SNM, Interstim®) has been FDA approved and utilized for the treatment of refractory urge incontinence. Two small randomized trials and several cohort studies have shown efficacy of sacral neuromodulation for the treatment of refractory Fl (although it is not yet FDA approved for this indication). We propose a randomized trial to credibly characterize the effect of SNM on Fl episodes, symptom specific quality of life, effect on other pelvic floor symptoms, sexual function, predictors of response, adverse events, cost effectiveness and the role of biomarkers in optimal and suboptimal responses to this treatment. This information will allow us to more effectively individualize treatment for women with this condition. RELEVANCE: In order to improve on the care and individualized treatment for women with pelvic floor disorders, it is important that a credible research program exists that helps guide provider care. The Pelvic Floor Disorders Network (NICHD) performs such research and we are competing to continue to participate in this important initiative. As a part of this application, we propose a concept describing a randomized trial of sacral neuromodulation for the treatment of women with fecal incontinence refractory to current standard of care treatments. This exciting new treatment modality may help a cohort of women with diminished quality of life.

Title: **Phospholipid-Reactive T Cells in Pregnancy Loss**
P.I.: **Ramesh Chandra Halder**
Institution: **University of California, Los Angeles**
Grant No.: **HD067413-01**
Award: **$77,000**

Recurrent pregnancy loss is associated with the presence of autoantibodies against phospholipid (PL) antigens in some patients. Mechanisms underlying the development of such autoimmune pregnancy loss are not well understood. Recent reports have suggested existence of T cells that recognize PL antigens bound to an antigen presenting molecule, CD1d. My hypothesis is that such CD1d-restricted PL-reactive T cells induce the production of anti-PL autoantibodies and pregnancy loss associated with these antibodies. In support of this hypothesis, we have found that CD1d-knockout autoimmune-prone (NZB X NZW) F1 mice have significantly reduced serum levels of anti-PL antibodies as compared to their wild-type littermates, suggesting a possible role of CD1d in the development of anti-PL antibodies. Building on my expertise in the

biology of CD1d-restricted glycolipid-reactive T cells and based on the above observations, I will test this hypothesis in three Specific Aims. In Aim 1, I'll test the hypotheses that mice with spontaneous or induced anti-PL antibodies have increased numbers and/or activation of PL-reactive T cells in lymphoid organs; such T cells will infiltrate the pregnant uterine mucosa, called decidua, in increased numbers. Then, I'll determine the effect of CD1d-restricted PL-reactive T cells on the production of anti-PL antibodies by B cells in vitro in Aim 2. In Aim 3, I'll determine the effect of CD1d-restricted PL-reactive T cells on pregnancy outcome. We will further investigate whether PL-reactive T cells directly induce pregnancy loss or whether pregnancy loss is mediated via anti-PL antibodies induced by PL-reactive T cells. It is hoped that this study will elucidate a novel pathogenetic mechanism of recurrent pregnancy loss in autoimmune diseases. The data obtained will also form the basis for my first R01 or another extramural proposal.

Title: **Pittsburgh Pelvic Floor Research Program**
P.I.: **Halina M. Zyczynski**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **HD069006-01**
Award: **$25,000**

The purpose of this proposal is to demonstrate the capabilities of the University of Pittsburgh to participate as a clinical site in the NICHD-sponsored Pelvic Floor Disorders Network (PFDN). Our site has a longstanding track record of successful contribution to multicenter studies of urinary and fecal incontinence, and pelvic organ prolapse. We are particularly well suited to be a clinical site in the PFDN because of our volume, research infrastructure and track record, basic and translational experience and expertise. Access to large numbers of nulliparous women enables us to contribute uniquely to studies of the role of pregnancy and parturition in the etiology and prevention of pelvic floor disorders (PFDs). Magee-Womens Hospital (MWH) is the central resource for gynecologic specialty care for the 19 hospital University of Pittsburgh Health System serving a very large aging population. Our site brings expertise in urogynecology, physical therapy, geriatrics, urology, gastroenterology and mental health. We offer unique technical expertise in genomics, proteomics, tissue regenerative techniques, biochemical and biomechanical impact of meshes on the vagina and central neuronal control of bladder function. We propose to establish a comprehensive, scientifically rigorous clinical and translational research program within the PFDN for prospective comparative studies of mesh materials used in prolapse and incontinence procedures. The program will generate data of immediate clinical relevance as it will present scientifically sound, vendor independent evidence to guide surgeons' selection of specific graft materials and evidence-based practice guidelines for management of mesh complications. The 3 major components of the proposal are: 1) mesh specific infrastructure for implementation in PFDN clinical trials employing mesh inclusive of the development of a Mesh Morbidity Index and establishment of a Biospecimen Repository 2) the first RCT of meshes selected through rigorous analyses of biomechanical and biochemical properties and 3) translational studies on the cellular response to mesh materials and pathophysiology of mesh complications. The RCT will serve to pilot the database, compare clinical outcomes of meshes whilst providing specimens for translational studies.

Title: **Prostaglandin E2 Signaling in Growth and Pains of Endometriosis**
P.I.: **Joe Arosh**
Institution: **Texas A&M University**
Grant No.: **1R21HD066248-01A1**
Award: **$219,750**

Endometriosis is an inflammatory disease characterized by the presence of functional endometrium outside the uterine cavity. The major two symptoms are intolerable pelvic pain and infertility. Prostaglandin E2 (PGE2) plays important roles in the pathogenesis of endometriosis.

PGE2 is the principal mediator in inflammation and pain hypersensitivity. Inhibition of PGE2 biosynthesis using NSAIDs and COX-2 inhibitors has emerged as the main class analgesics. However, clinical use of NSAIDs produces unwanted side effects such as gastric erosion, ulceration, and hemorrhage, and prolonged use of COX-2-selective inhibitors confers a risk for myocardial infarction and stroke. PGE2 produced at the site of inflammation acts on the nociceptors of peripheral terminals through EP1, EP2, EP3, and EP4 receptors by integrating multiple cell signaling pathways. Selective inhibition of PGE2 signaling as therapeutic targets down-stream of COX-2 may provide an opportunity to inhibit pro-nociceptive actions of PGE2 in the pathogenesis of endometriosis. Our long-term goal is to understand molecular and cellular aspects of PGE2 in the pathogenesis and pain of endometriosis with the aim of identifying PGE2receptors as non-steroidal targets for the treatment of endometriosis. The objective of this application is to understand PGE2 signaling in growth and pain of endometriosis. The central hypothesis is that selective inhibition of prostaglandin E2 signaling decreases pain of endometriosis through inhibition of growth of endometriotic cells and development of nociceptive mechanisms. Specific Aim 1 will determine the effects of systemic blockade of EP2 and EP4 receptors on growth, innervations, and pain of endometriosis. Specific Aim-2 will determine molecular mechanisms of through which cell specific knock-down of EP2 and EP4 in endometriotic epithelial and stromal cells inhibits development of innervations and nociceptive mechanisms of endometriosis. Effects of selective inhibition of EP2 and EP4 on growth, innervations, and pain of endometriosis will be determined using genomic, pharmacological, molecular, cellular, biochemical, microscopy, and bioimaging approaches, and xenograft Rag23(c) mice and pain behavior animal models. The proposed work is innovative: (i) because it capitalizes on a new means of identifying PGE2 signaling in the pathogenesis of endometriosis and induction of endometriosis pain, and (ii) expected to decrease pain of endometriosis through inhibition of growth of endometriotic cells, innervations of endometriosis, and development of peripheral and central nociceptive mechanisms. This highly significant advancement in our understanding of endometriosis will provide the knowledge needed to translate selective inhibition of EP2 and EP4 into clinical application as a potential novel non-steroidal therapy for endometriosis in women. In addition, the expected results will fill the substantial gap in the current knowledge of the pathogenesis of endometriosis and perception of endometriosis pain. This is a R21 application addresses the mission of NIH/NICHD on women's reproduction health. PUBLIC HEALTH RELEVANCE: The objectives of the proposed research are to determine molecular and cellular mechanisms through which selective inhibition of prostaglandin E2 (PGE2) receptors EP2 and EP4 inhibits growth of endometriosis and endometriosis-induced pain and to develop EP2 and EP4 inhibitors as new non-steroidal targets for the treatment of endometriosis in women. The expected outcomes of this project are that selective inhibition of EP2 and EP4-mediated PGE2 signaling will decrease growth and pain of endometriosis and fill the substantial gap in the current knowledge of the pathogenesis of endometriosis and perception of endometriosis pain. This highly significant advancement in our understanding of endometriosis will provide the knowledge needed to translate selective inhibition of EP2 and EP4 into clinical application as a potential novel non-steroidal therapy for endometriosis in women.

Title: **RCT of Hypnotherapy vs. Tpolterodine for OAB: Voiding and Brain Activation Changes**
P.I.: **Rebecca Glenn Rogers**
Institution: **University of New Mexico Health Sciences Center**
Grant No.: **HD069025-01**
Award: **$25,000**

The University of New Mexico (UNM) proposes to join the Pelvic Floor Disorders Network (PFDN) to achieve the Network's primary goal of conducting rigorous, multi-center clinical trials to investigate the clinical and health aspects of pelvic floor disorders in women. Our site, in collaboration with other Network sites, aims to reduce the burden of pelvic floor disorders on women and their families. Through the design of innovative trials and participation in

ongoing studies, the UNM PFDN site will make significant contributions to the Network. Dr. Rogers, Principal Investigator, and Dr. Komesu, Alternate Principal Investigator, have extensive experience in the design and conduct of multi-center randomized trials and proven leadership and productivity. The UNM PFDN site brings to the Network a busy clinical service with large numbers of under-represented Hispanic and Native American populations, as well as broad institutional support from the Department of Obstetrics and Gynecology and a recently funded Clinical and Translational Research Center. The concept proposal, based on preliminary data generated by our site and the work of others, is an innovative investigation comparing hypnotherapy to long-acting anticholinergic medicine for the treatment of overactive bladder (OAB). In addition to the hypnotherapy comparative-effectiveness trial, the concept proposal focuses investigation into the underlying mechanisms of OAB on the brain, using functional magnetic resonance imaging (fMRI). This translational, comparative effectiveness clinical trial is an excellent example of cutting edge research that the UNM PFDN site will bring to the Network. Skilled investigators, a busy clinical practice, unique patient populations and broad institutional support make UNM a worthy new clinical site for the PFDN. RELEVANCE: Pelvic floor disorders are common and costly. Performance of rigorously designed, target randomized clinical trials that inform evidence-base health care practices for women with pelvic floor disorders is best done through collaboration with other clinical sites. The University of New Mexico is a highly productive clinical and research site and proposes to join the Pelvic Floor Disorders Network in order to meet the Network's goal of investigating innovative solutions to these common problems.

Title: **Tailored Outcomes for Female Urinary Incontinence**
P.I.: **Vivian W. Sung**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **$217,790**
Award: **1R21HD069962-01**

Urinary incontinence (UI) disproportionately affects women over men and is associated with embarrassment, social and functional decline. Treatments are primarily aimed at improving aspects of a woman's quality of life and function; therefore, high quality patient-reported outcomes (PRO) that cover multiple dimensions are paramount to inform treatment progress. Limitations of existing UI PRO measures include their inflexibility, significant respondent burden, and inability to be personalized. The overarching goal of this proposal is to make a major advance in UI PRO measures by developing an innovative measurement system that is multi-dimensional, flexible, and efficient, can be tailored to individuals, yet also decreases respondent burden. Such a system is likely to be accepted by patients, clinicians, researchers, and industry for evaluating treatment outcomes from the patient perspective and can streamline research findings and patient care. Using item response theory and computerized adaptive testing, The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) has developed core PRO item banks relevant to a wide range of chronic diseases. As comprehensive as PROMIS is, it does not fully address the needs of women with UI. To fill this need, we will build on our previous work to continue validation and calibration of UI-specific item banks based on an expanded PROMIS conceptual framework that is sensitive to the outcomes valued by women with UI. Specifically, our aims are to: 1) confirm face and content validity of our UI item banks and conceptual framework through cognitive-based interviews and expert review; 2) calibrate and field-test the item banks using item response theory in 700 women with UI recruited across two hospital settings; and 3) develop and pilot-test a web-based UI-computerized adaptive test prototype (UI-CAT). We will evaluate item/model/person fit, compare item discrimination power, and assess differential item functioning across demographic variables, UI severity and type, and co-existing pelvic floor disorders. We have convened an interdisciplinary team of experts in female UI, PRO development, PROMIS methodology, item response theory, computerized adaptive testing, and informatics. The application of modern psychometrics and computerized adaptive technology can dramatically improve our PRO measurement capabilities

in female UI and women's health. The UI-CAT can be used to help tailor our treatments to the needs and values of women with UI, improve the specificity of our treatments, and improve the delivery of personalized care to women. PUBLIC HEALTH RELEVANCE: With the aging population, the number of women seeking care for urinary incontinence (UI) will increase. High-quality, patient-important outcomes that can be tailored, are efficient and monitor treatment outcomes from the patient perspective are critical to improving scientific knowledge and the care of women who suffer from UI.

Title: **Uterine Leiomyoma Research Center Program**
P.I.: **Serdar E. Bulun**
Institution: **Northwestern University, Feinberg School of Medicine**
Grant No.: **HD057877-03**
Award: **$250,000**

Uterine leiomyomata (fibroids) represent the most prevalent benign gynecologic disorder in the US. The cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Our multidisciplinary team has designed 3 well-integrated projects focusing on Interactions between biologically critical hormonal pathways in uterine leiomyoma involving the transcription factors progesterone receptor (PR) and FOXO, the signaling pathway PI3K/AKT and the pro-fibrotic factor TGF-beta. Project I (Bulun) will be pursued to understand the mechanisms as to how antl-progestins such as RU486 reduce tumor size. We hypothesize that progesterone regulates a number of critical genes, that favors increased proliferation and decreased apoptosis of leiomyoma smooth muscle cells, whereas anti-progestins reverse this effect by enhancing apoptosis and decreasing proliferation. Project II (Kim/Chakravarti) will determine the role of the PI3K/AKT/F0X0 signaling pathway regulating leiomyoma cell growth and survival in response to progesterone. We hypothesize that progesterone Induces proliferation of leiomyoma cells through activation of the PI3K/AKT/F0X0 signaling pathway and that Inhibitors of the AKT pathway should override the proliferative effects of progesterone and promote apoptosis. Project III (Nowak) will define the mechanisms as to how antifibrotic drugs regulate leiomyoma growth. We hypothesize that the increased proliferation exhibited by leiomyoma smooth muscle cells Is due to a major shift in the extracellular matrix environment caused by increased synthesis of new, monomeric collagen type I by these cells. We will determine whether antifibrotic drugs may be an effective new treatment for leiomyomas. These projects are supported by an Administrative Core (Bulun) and Tissue Procurement and Cell Culture Core (Kurita). Overall, as part of our long range goal, all projects investigate local hormonal signaling regulating apoptosis and proliferation as biologic endpoints and test existing and upcoming pharmaceutical compounds that target these pathways in uterine leiomyomata. RELEVANCE (See instructions): Symptomatic uterine leiomyomata affect millions of US women and cause irregular uterine bleeding, anemia, recurrent pregnancy loss leading to more than 200,000 hysterectomies per year. Available treatments are limited due in large part to the fact that the mechanisms regulating the development and growth of these tumors are unclear. We propose integrated molecular, cellular and translational studies that should lead to a better understanding and future development of novel therapeutics for uterine leiomyomata.

Title: **Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and Its Association with Incidence, Progression, and Recurrence of Pelvic Floor Disorders**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah**
Grant No.: **HD061787-03**
Award: **$66,667**

Pelvic floor disorders affect one in four American women. Few modifiable risk factors have been identified that might reduce the incidence or progression of pelvic floor disorders. Popular wisdom and scant clinical data suggest that strenuous activity causes or promotes pelvic floor disorders. Given the health benefits of activity, women should be encouraged to be maximally active unless there is scientific evidence to the contrary. Existing physical activity instruments are largely designed to assess cardiovascular exertion and are validated using activity diaries, accelerometers, and step counters. Such measures may not accurately measure activities that increase loading on the pelvic floor (such as lifting). After researching available technologies, we concluded that a tool to understand how physical activities impact abdominal pressure in the real world does not exist. Over the past 18 months, our interdisciplinary team of bioengineers, urogynecologists, electrical engineers, and exercise scientists developed and validated the performance of a prototype for an intravaginal abdominal pressure sensor that accurately measures pressure in the upper vagina, an easily accessible space that records pressures similar to the true intraabdominal pressure. In this proposal, we plan first to further develop an integrated system (the "WRAPS", Wireless Remote Abdominal Pressure System) to monitor intraabdominal pressure outside of the clinical setting. This system will consist of three key elements: an intravaginal pressure sensor with wireless data transmission capability, a small portable data monitoring and storage unit, and computer based data translation software for downloading and managing the pressure data. In a controlled exercise laboratory setting, we will then use intraabdominal pressure data generated by the WRAPS to determine the reproducibility of intraabdominal pressures measured during specific types of physical activity and will finalize development of a valid questionnaire that categorizes the magnitude of intraabdominal pressures during activities. Finally, in a real-world setting in which participants wear the intravaginal sensor during waking hours for four 1-week periods over the course of a year, we will characterize intraabdominal pressures experienced by women of varying degrees of habitual physical activity and, using WRAPS data as the gold standard, determine whether activity can be appropriately categorized in terms of pelvic loading by means of self-administered questionnaires, the current standard. Obtaining future evidence about the impact of physical stressors on pelvic floor disorders relies on our ability to measure the risk factor in question. This innovative translational collaboration will remove a critical barrier to progress in understanding the etiology of pelvic floor disorders in women.

Title: **Workshop on the Health Impacts of Indoor Air Pollution in Developing Countries**
P.I.: **William Martin**
Institution: *Eunice Kennedy Shriver* **National Institute of Child Health and Human Development**
Grant No.: **OD-11-289**
Award: **$7,854**

An international workshop was convened May 9-11, 2011 in Arlington, VA to discuss current evidence on adverse health effects of indoor air pollution and to exchange views on improving human health. Every day, millions of women in developing countries spend several hours crouched over small fires cooking. Often their homes have no chimneys and poor ventilation. This daily proximity destroys lungs and small children staying close to their mothers are equally vulnerable. Exposure to smoke from traditional stoves and open fires—the primary means of cooking and heating for 3 billion people in developing countries—causes almost 2 million deaths annually, with women and young children affected most. The World Health Organization

states that indoor air pollution in developing countries is the fourth leading cause of morbidity and mortality, and the second leading environmental contributor to ill health affecting primarily women and children. New designs in cooking stoves are not always comfortable for the women cooking on them, and require changes in cooking methods, some of which made the food taste different. In the kind of patriarchal societies that keep women tied to stoves and kitchen responsibilities, women don't have a lot of autonomy for decision-making, especially not about major household issues like a new stove. At this workshop, more than 150 scientists and policy makers from multiple countries focused on research gaps, exposure assessment, and the burgeoning global initiative that aims to deliver clean, affordable cook stoves to the developing world. The workshop presented a first-ever opportunity to hear the state-of-the-science on the health impacts of indoor air pollution and to identify critical research needs. The need for such a meeting is considerable since the poorer half of the world's population uses biomass—wood, crop residue, or dung—or coal as fuel to cook and heat, contributing to a variety of health conditions including pneumonia, lung cancer, cardiovascular disease, low birth weight, and cognitive impairment. Speakers described the importance of biomarkers and the development of inexpensive, portable electronic monitors as a means to gather exposure assessment data.

Title: **Xenograft Study on Growth-Control of Human Uterine Leiomyomata**
P.I.: **Takeshi Kurita**
Institution: **Northwestern University, Feinberg School of Medicine**
Grant No.: **HD064402-02**
Award: **$83,333**

The ultimate goal of this study is to elucidate the molecular mechanisms of uterine leiomyoma (UL) formation and growth, and identify potential targets for novel therapeutic and preventive treatments of this disease. UL is a benign tumor of the myometrium that affects millions of reproductive-age women. Surgical removal of the entire uterus (hysterectomy) is the primary treatment option, and management of UL puts an enormous burden on the healthcare system. Therefore, finding a new therapeutic treatment replacing surgery is of great interest to the public. Due to the absence of a proper research model system reflecting characteristics of the original tumors, the biological nature and the causes of UL are poorly understood. Although growth dependency of UL on ovarian steroids (172-estradiol and progesterone) is well established, the relative importance and function of 172-estradiol and progesterone are yet to be clarified. In spite of accumulating evidence for the essential role of progesterone in UL growth, no research model has clearly demonstrated a growth-promoting effect of progesterone on UL. To elucidate the function of ovarian steroids in UL, we have established a novel xenograft model in which tissue fragments of human leiomyoma were grafted beneath the renal capsule of immunodeficient mice. The size of the leiomyoma xenografts increased in response to 172-estradiol and progesterone as demonstrated by cell proliferation and accumulation of extra-cellular matrix. In contrast, xenograft growth induced by 172-estradiol and progesterone was blocked by the anti-progestin RU486, indicating the essential role of progesterone and progesterone receptor (PR) in leiomyoma tumor growth. Previously, 172-estradiol has been thought to be the primary stimulus for UL growth. Surprisingly, 172-estradiol by itself neither increased nor maintained tumor size. Likewise, progesterone alone did not affect UL growth in this model. Although not mitogenic, 172-estradiol was required for expression of PR, and was essential for progesterone to act on UL xenografts. Our study clearly demonstrates the pivotal role of progesterone in growth and maintenance of UL. The results of our xenograft model agree with clinical observations, yet radically change the paradigm of steroid hormone-regulated human UL growth by emphasizing the importance of progesterone instead of 172-estradiol. Using the novel xenograft model, we will elucidate the cellular and molecular mechanisms of human UL tumor growth controlled by 172-estradiol and progesterone.

National Institute on Drug Abuse

Title: **Genes, Gendered Contexts, and Substance Use Outcomes**
P.I.: **Edelyn Verona**
Institution: **University of Illinois at Urbana-Champaign**
Grant No.: **DA027140-01A2**
Award: **$184,065**

It is becoming increasingly clear that risk factors for use and trajectories toward desistance may differ significantly for men and women (e.g., Westermeyer & Boedicker, 2000). For example, recent work has uncovered different effects of monoamine genotypes (e.g., serotonin transporter, MAO-A) on male and female psychopathology and behavior (Sjoberg et al., 2007a; Verona, Joiner, Johnson & Bender, 2006). In addition, there is evidence that pubertal onset, childhood sexual abuse, and intimate partner violence (IPV) constitute unique risk factors for antisocial behavior and drug use among women compared to men (Dick, Rose, Kaprio, & Viken, 2000) and can predict drug relapse in women many years later in adulthood (Hyman, Garcia, & Sinha, 2006). Thus, a primary goal of the present application is to identify gender differences in biological and environmental risk factors for substance use outcomes as a way of advancing nuanced conceptualizations of female drug problems. The current project intends to (1) explore various gene by environment (GxE) effects on drug use outcomes, by examining different monoamine genes (5HTT, DRD4, MAO-A) and incorporating gendered environmental risk factors that are not commonly included in studies of drug use (e.g., intimate partner violence), (2) examine the extent to which GxE effects or individual risk factors are specific to substance use outcomes in women relative to men, and (3) identify multivariate models involving GxE effects and mediators of these effects to predict substance use pathways in men and women. The goal is to examine not only GxE effects (e.g., gene-by-abuse, gene-by-IPV) that directly influence substance use outcomes, but identify potential mediators (pubertal development, internalizing symptoms) in an effort to understand nuanced pathways for female substance use. The ultimate goal is to help in the development of tailored interventions to address gender-specific manifestations and etiologies.

Title: **NIH Pain Consortium Centers of Excellence in Pain Education (CoEPEs)**
P.I.: **National Institute on Drug Abuse (coordinating center)**
Institution: **National Institutes of Health Pain Consortium, funding 12 centers**
Award: **$50,000**

The NIH Pain Consortium has established 12 Centers of Excellence in Pain Education (CoEPEs), led by the National Institute on Drug Abuse, to develop and disseminate curriculum resources to improve medical, dental, nursing, and pharmacy education in the assessment, diagnosis, and treatment of pain, while minimizing the abuse of opioid medications, an area that current training under-emphasizes. A wide variety of women's health issues will be addressed, including: Migraine and giant cell arteritis-related headaches; Hormonally-related headaches associated with menstruation, pregnancy, and menopause; Fibromyalgia and/or temporomandibular joint disorders; Stage IV endometriosis experiencing pelvic pain and dysmenhorrhea; Post-operative pain in an infant who underwent a laparotomy to remove an ovarian cyst; Female breast cancer patients and survivors experiencing pain related to or separate from cancer; Pelvic pain of unknown etiology; Musculoskeletal pain in a female who may be a victim of domestic abuse; End-of-life pain management scenario for a female patient with a 30 year history of systemic lupus erythematosus; Irritable bowel syndrome; Neuropathic dental pain, atypical odontalgia (phantom tooth pain), and burning mouth syndrome; and Vulvodynia and chronic fatigue syndrome.

National Institute of Dental and Craniofacial Research

Title: **Comorbid Chronic Pain Conditions—Mechanisms, Diagnosis, and Treatments**
P.I.: **Allen W. Cowley**
Institution: **TMJ Association**
Grant No.: **DE022238-01**
Award: **$28,740**

The Sixth Scientific Meeting of The TMJ Association, "Comorbid Chronic Pain Conditions—Mechanisms, Diagnosis and Treatments", is scheduled to be held on June 5-7, 2010 at the Federation of American Societies for Experimental Biology Conference Center in Bethesda, Maryland. The need for this meeting and that of previous meetings has been based on two important factors. First, the number of people affected in the U.S. by temporomandibular disorders (TMD) is estimated to be approximately 36 million. The majority are women in their childbearing years. The physical, psychological and financial burden on these patients is compelling. Second, there continues to be a dearth of scientific understanding of the etiology of these conditions upon which to base diagnostics and develop safe and effective treatments. To stimulate research in this field, The TMJ Association has organized five scientific meetings beginning in the year 2000. These meetings have convened scientists in the temporomandibular disorders field and other disciplines to characterize and address the multiple symptoms and frequently found comorbid conditions in TMD patients. The theme of the sixth scientific meeting builds upon evidence from the five previous meetings demonstrating that TMD are a complex family of conditions influenced by genetics, gender, environmental and behavioral triggers mediating the vulnerability of patients to TMD and typically manifesting as more than jaw and muscle pain and jaw dysfunction. The sixth meeting will focus on the pathophysiological processes underlying the chronic pain conditions which co-exist with TMD and constitute comorbid chronic pain conditions (CCPC). They include: chronic fatigue syndrome, chronic headache, endometriosis, fibromyalgia, irritable bowel syndrome, interstitial cystitis, and vulvodynia. The meeting will engage key leaders and representatives from funding and patient advocacy organizations who will develop recommendations to advance research in this field. The specific aims of the meeting are to determine: 1. What is currently known about underlying mechanisms of CCPC; 2. What we need to know about CCPC (e.g., case definition, diagnostics); 3. What research areas are most promising to pursue (best approaches, resources); 4. How best to foster the development of treatment modalities for CCPC; 5. What approaches are necessary to encourage, train, and sustain a CCPC research community; and 6. What high-risk research areas have the potential to substantially advance our understanding of CCPC.

Title: **International Research Registry for Sjögren's Syndrome**
P.I.: **Caroline Shiboski**
Institution: **University of California, San Francisco**
Grant No.: **DE32636-23-0-1**
Award: **$150,000**

The purpose of this contract is to develop an International Research Registry Network for Sjögren's Syndrome. Specific aims are: 1. To develop standardized diagnostic criteria for Sjögren's Syndrome (SS) through a prospective cohort study design and based on analysis of existing criteria and their current usage; adoption of a new objective "working standard" (in lieu of a "gold standard"); and measurements of the sensitivity, specificity and accuracy of many combinations of diagnostic tests based on that standard. 2. To collect, process and store clinical data and biospecimens from patients diagnosed using these new criteria and controls. 3. To develop a data and biospecimen bank.

National Institute of Diabetes and Digestive and Kidney Diseases

Title: **Bench to Bedside: Role of Androgen and Estrogen Receptor Signaling in Pulmonary Arterial Hypertension**
P.I.: **Robert Danner**
Institutions: **National Institutes of Health Clinical Center, National Institute of Diabetes and Digestive and Kidney Diseases, and University of Pennsylvania**
Grant No.: **Y2-OD-1456-01**
Award: **$110,000**

Idiopathic pulmonary arterial hypertension (IPAH), a subtype of plexogenic pulmonary arteriopathy (PAH), is a rare disorder associated with poor survival. Despite consistent epidemiological evidence demonstrating a 2 to 4 fold female predominance in IPAH, the underlying mechanisms for this imbalance are unclear. Endothelial dysfunction resulting from 1) genetic susceptibility, and 2) a triggering stimulus that initiates pulmonary vascular injury, the so-called two-hit hypothesis, appears to play a central role both in the pathogenesis and progression of PAH. Inflammation may drive this dysfunctional endothelial phenotype, propagating cycles of injury and repair in genetically susceptible patients with IPAH and patients with disease associated PAH (e.g. scleroderma, HIV, and sickle cell disease). Histologic specimens from patients with IPAH reveal the presence of inflammatory cells, including macrophages and T- and B-lymphocytes, within classic plexiform lesions that are the hallmark of PAH. Pulmonary artery endothelial cells (PAECs) in PAH orchestrate the recruitment of inflammatory cells as well as secreting pro-inflammatory and pro-coagulant cytokines into the circulation. Patients with IPAH have higher levels of circulating IL-1β, IL-6, P-selectin and E- selectin in comparison to healthy controls. Therefore, targeting PAEC inflammation may interrupt the cycles of injury/inflammation and repair that contribute to progressive increases in pulmonary vascular resistance in patients with PAH, and thereby delay or prevent right ventricular failure and death. Both estrogen and testosterone promote vasodilatation and affect vascular inflammation through binding to estrogen (ER) and androgen receptors (AR), respectively, members of the nuclear receptor (NR) family of transcription factors. However, the interaction between sex hormone signaling and IPAH-associated vascular injury/inflammation is not understood. Many NRs inhibit inflammation through a trans-repression mechanism that recruits co-repressor proteins to promoter NFκB and AP-1 binding sites in a tissue and target gene specific manner. Using an in silico bioinformatics approach, we found that the androgen receptor (AR) is relatively over-expressed in primary human endothelial cells compared to phagocytic leukocytes. Initial work in our laboratory using EA.hy926 cells, a human endothelial line, demonstrates that dihydrotestosterone (DHT) can suppress TNFα-induced VCAM1 mRNA expression, while spironolactone, a mixed mineralocorticoid receptor and AR antagonist currently used in PAH for advanced right heart failure, was found to inhibit NFκB signaling. We hypothesize that AR and ER differentially modulate endothelial inflammation in IPAH and this may in part explain the female predominance of this disease. Here, the effects of AR and ER signaling on endothelial dysfunction and inflammation will be investigated in cell culture models. Patients with PAH will be recruited to the NIH to investigate novel MRI-based methods to improve clinical phenotyping and as part of a pilot feasibility study on the effects of early spironolactone on endothelial inflammation in vivo.

Title: **Diabetes Prevention Program Outcomes Study**
P.I.: **Sarah E. Fowler**
Institution: **George Washington University**
Grant No.: **DK048489-18**
Award: **$900,000**

The George Washington University Biostatistics Center proposes to continue as the Coordinating Center for the Diabetes Prevention Program Outcomes Study (DPPOS). This application is companion to the Clinical Centers' application. The Diabetes Prevention Program (DPP), a multi-center controlled clinical trial in a multiracial population of overweight persons with impaired glucose tolerance, established the efficacy of a life-style intervention aimed at a modest degree of weight loss and increased moderate-intensity activity, and of metformin in decreasing the development of diabetes by 58 and 31%, respectively. The DPPOS, a 10-year follow-up, was funded in 2002 for a five-year period with the understanding that it would require refunding via competitive renewal. The overarching goal of DPPOS was to study whether the relatively shortterm benefits of delaying diabetes demonstrated in the DPP would translate into a more long-lasting impact that would reduce the public health burden of the diabetes epidemic. Specifically, DPPOS had the following major goals: 1) to determine the effects of DPP interventions on the long-term microvascular and cardiovascular disease (CVD) complications, atherosclerosis and CVD risk factors; 2) to examine the long-term effects and durability of prior DPP interventions on further diabetes development; and 3) to describe the incidence of long-term complications and their risk factors in new onset type 2 diabetes and IGT. To date, after 10 years of DPP/DPPOS, 93% of the DPPOS cohort attends annual follow-up visits. A durable effect of diabetes prevention associated with the life-style and metformin interventions has been demonstrated with 36 and 19% reductions in diabetes incidence, respectively, compared with the placebo group. Interim analyses also reveal significant reductions in CVD risk factors in the intervention groups, with decreased utilization of medications. The development of diabetes is associated with an increased frequency of retinopathy and microalbuminuria. The development of diabetes is associated with an increased frequency of retinopathy and microalbuminuria. This application is designed to support completing the second five-years of DPPOS focusing on complications that require more time to develop. RELEVANCE: The Diabetes Prevention Program (DPP) and first 5 years of the DPP Outcome Study (DPPOS) have demonstrated that a lifestyle intervention program aimed at weight loss, and metformin, prevent diabetes development over a 10 year period. Completion of DPPOS will examine the impact of diabetes prevention on long-term complications affecting the eye, kidney, nerves and heart, and remains critical to public health.

Title: **Intestinal Satiation in Roux-en-Y Gastric Bypass Rats: Brain Mechanisms and Sex Differences**
P.I.: **Loredana Asarian**
Institution: **University of Zurich**
Grant No.: **DK092608-01**
Award: **$200,000**

Bariatric surgery, in particular Roux-en-Y gastric bypass (RYGB) surgery, is currently the only effective therapy for morbid obesity, which is a grave and growing national health problem. The mechanisms through which RYGB increases satiation and reduces eating and body adiposity are poorly understood. It is thought that the major cause of early satiation at meals and reduced overall intake is increased intestinal satiation caused by the entry of ingesta more distally into the small intestine, i.e., into the jejunum, thus leading to increased release of the gut hormones glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY). This proposal adapts classical rat models to test RYGB's effects on intestinal satiation, at the levels of both of gut-brain signaling and of brain neural processing. RYGB will be done by one of the co-PIs who performs the technique both experimentally and clinically, assuring a close match between the experimental model and the clinical standard. The experiments include tests of nutrient-specific controls of

ingestion that are hypothesized to be affected by RYGB. In addition, both the release patterns and the satiating potency of endogenous GLP-1 and PYY are tested. The brain work builds on progress in the past decade concerning the neural processing of intestinal negative-feedback controls of eating in the caudal brainstem and in the hypothalamus. Finally, because about twice as many women than men suffer from morbid obesity in the USA and because about 85% of patients electing RYGB are women, all the proposed experiments include tests of physiological sex differences, both male-female difference and estrogen-regulated effects in females, the latter especially relevant to understanding and treating the increase in adiposity associated with menopause. Three Specific Aims are proposed: (1) Determine whether the satiating actions of intra-jejunal infusions of Ensure, Intralipid and glucose are increased by RYGB surgery, including the impacts of adipose-tissue loss and of sex differences, i.e., male vs. female and estradiol-treated vs. untreated ovariectomized rats; (2) Determine the effects of RYGB surgery on brain c-Fos expression in response to intra-jejunal infusions of Ensure, glucose and Intralipid, and determine the neurochemical phenotypes of neurons expressing c-Fos, including the impact of sex differences, i.e., male vs. female and estradiol-treated vs. untreated ovariectomized rats and (3) Determine the effects of RYGB on neural signaling mechanisms underlying the satiating actions of intra-jejunal infusions of Ensure, Intralipid and glucose in male vs. female and in estradiol-treated vs. untreated ovariectomized rats. State-of-the-art behavioral, physiological and molecular techniques are used. Thus, the work (1) should help inform behavioral and nutritional counseling for RYGB patients, (2) may suggest strategies for improvement in the RYGB technique, and (3) should provide rational bases for the development pharmaceutical tools to augment or replace RYGB, which is especially desirable for patients who do not desire bariatric surgery or for whom it is not recommended.

Title: **Lifestyle Interventions in Overweight and Obese Pregnant Women**
P.I.: **Xavier Pi-Sunyer**
Institution: **St. Luke's Roosevelt Institute for Health Sciences**
Grant No.: **DK094463-01**
Award: **$100,000**

A randomized controlled trial is proposed to study the effect, in a cohort of racially and ethnically diverse group of overweight and obese pregnant women, of an Intensive Lifestyle Intervention (ILI) compared to Usual Care (UC) on gestational weight gain (GWG), infant fatness, and mothers' post-delivery weight retention. Women in the ILI arm will receive intensive counseling during pregnancy and group counseling after delivery regarding behavior, nutrition, and physical activity change. Visits to counselors will be weekly and additional telephone and internet contacts will occur. The mothers' will be assessed at 14 and 36 weeks of pregnancy and at 12 weeks and 52 weeks post-delivery. The measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (BodPod). The infants' measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (PeaPod) for fatness 12 weeks and 52 weeks. Mothers and children will have cardio-metabolic risk factors measured in plasma. Data will be collected regarding mothers' dietary intake and physical activity (questionnaires and accelerometry) to assist in counseling. Other data to be collected include questionnaires on quality of life, socio-economic status. Careful record will be kept of expenses in providing the ILI, so that cost analysis of the intervention can be calculated. The study is powered on the primary outcome, fatness of the infants at birth. We require 180 participants to attain appropriate power. We will enroll 210 so as to allow for some dropouts along the way. Each mother will be followed during pregnancy and for a year post delivery. Each infant will be followed for a year after birth. We have the ability o continue to follow these participants if further funding is forthcoming, as they are all local to or hospital's catchment area and our own physicians. If aims are achieved, namely that both children and mothers profit from the intervention, there should be a paradigm shift in how overweight pregnant women are treated. At present, there is a dearth of behavioral advice and intervention relating to GWG and physical activity provided to these women. Positive results from our study would provide evidence for ILI preventative intervention.

Title: **The Look AHEAD Continuation: Action for Health in Diabetes**
P.I.: **Rena R. Wing**
Institution: **Miriam Hospital**
Grant No.: **DK056992-13**
Award: **$100,000**

Look AHEAD is randomized clinical trial examining the long-term health effects of an intensive weight loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity, or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and non-fatal Ml and stroke and cardiovascular deaths) over a planed follow-up of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well—the sample of 5,145 was recruited on time; retention has been excellent and the intervention has been effective in producing initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific Aims are to retain the cohort over time, continue to complete annual in-person visits and semi-annual telephone interviews for outcome assessments and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular-related factors and complications, and cost-effectiveness of the intervention.

Title: **Microbiomes of Interstitial Cystitis**
P.I.: **David J. Klumpp**
Institution: **Northwestern University, Feinberg School of Medicine**
Grant No.: **DK094575-01**
Award: **$50,000**

Interstitial cystitis/painful bladder syndrome (IC) is a devastating condition characterized by severe pelvic pain and voiding dysfunction. Despite years of investigation, no etiology or widely effective therapies exist for IC, indicating the needto consider new ideas and approaches. Based on several lines of evidence, the "microbiome" is an emerging field of study that has the potential to play a significant role in our understanding of I. First, many IC patients exhibit Gl or reproductive tract co-morbidities. Second, it is established that crosstalk exists among the bladder, Gl tract, and reproductive tract. Third, we find that bacteria can mediate a range of pelvic pain responses, from pain suppression to causing chronic pain. Fourth, microbial flora densely populate certain body sites, indeed outnumbering human cells, and new findings demonstrate that altered microbiomes can drive complex diseases. We therefore will develop an interdisciplinary team to address this novel question: is an altered gastrointestinal and/or reproductive tract microbiome associated with IC? Our team will bring together clinical expertise in IC, methodologic and biologic expertise in defining microbiomes of the Gl and reproductive tracts, and expertise in the microbial basis of pelvic pain. Our team will exploit the synergies from these key fields to develop specific hypotheses and strategies for defining associations between microbiomes and IC. Moreover, clinically relevant murine models will be developed to establish a causal link between altered microbiomes and modulation of pelvic pain. Defining IC microbiomes has potentially major significance for understanding IC etiology, mechanisms, and treatments. IC patients often have a history of antibiotic treatments for urinary tract infection, yet antibiotics can shift microbial diversity and thereby cause disease. Altered IC microbiomes could result in dysfunctional modulation of pelvic pain via organ crosstalk or expanded reservoirs of uropathogens. Finally, manipulation of microbiomes is proving efficacious in other clinical specialties, suggesting the possibility of possibility of convenient probiotic therapies for IC.

Title: **Ovarian Hormone Suppression and Regulation of Adipogenesis in Women**
P.I.: **Wendy M. Kohrt**
Institution: **University of Colorado Denver**
Grant No.: **DK092718-01**
Award: **$229,500**

Estradiol (E2) deficiency triggers weight gain, and specifically abdominal fat gain, in women. The shift toward central adiposity after menopause likely contributes to increased risk for the metabolic syndrome and associated chronic diseases (i.e., type 2 diabetes, coronary artery disease, hypertension). The long-term aim is to understand the mechanisms by which E2 deficiency mediates increases in abdominal adiposity. The primary aim (PA1) of the R21 is to determine whether ovarian hormone suppression in premenopausal women, which is known to cause fat gain, triggers an increase in adipogenesis (i.e., increase in cell number) in abdominal adipose tissue. This will be assessed by measuring the changes in cell size distribution and the incorporation of deuterium (2H) into DNA of cells in the non-stromal (i.e., mature adipocyte) fraction. Secondary aims are to determine: SA2) effects of ovarian hormone suppression on mRNA expression of factors involved in adipogenesis (C/EBP1, PPAR3) and markers of macrophage infiltration (CD68, Emr-1) and inflammation (IL-6, TNF-1); and SA3) whether new adipocytes arise from non-resident bone marrow progenitor (BMP) cells using cell surface markers (Notch 4, Platelet-derived Growth Factor Receptor (PDGFR) 2, Integrin 15, CD36) that enable detection by flow cytometry. To achieve these aims, 24 premenopausal women will be studied before and after 30 and 60 days of ovarian hormone suppression via gonadotropin releasing hormone agonist therapy with add-back of placebo (GnRHAG+PL) or estradiol (GnRHAG+E2). Hypotheses are: H1a) GnRHAG+PL for 60 days will result in a larger increase in small adipocytes (<40 5m) when compared with GnRHAG+E2. Because fat mass increases during GnRHAG+PL, an increase in the number of small adipocytes will be interpreted as an increase in adipogenesis and not as evidence of adipocyte atrophy; H1b) The incorporation of 2H in the non-stromal cell fraction DNA will be increased in response to GnRHAG+PL, as compared with GnRHAG+E2. Because the non-stromal fraction contains mature adipocytes, an increase in 2H-enriched DNA should reflect adipogenesis; H2) Ovarian hormone suppression will increase mRNA expression of factors associated with adipogenesis, macrophage infiltration, and inflammation (C/EBP1, PPAR3, CD68, Emr-1, IL-6, TNF-1) when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-back (GnRHAG+PL vs GnRHAG+E2); and H3) Ovarian hormone suppression will increase BMP-derived adipocytes when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-back (GnRHAG+PL vs GnRHAG+E2). To the best of our knowledge, this will be the first in vivo study of the role of E2 as a regulator of adipogenesis in humans. Because it is believed that adipocytes are programmed to achieve a certain volume of fat, an increase in adipocyte number would lead to a gain in fat mass that would be very difficult to reverse. Thus, identifying strategies that effectively prevent an increase in adipogenesis during ovarian hormone withdrawal would be of high clinical importance.

Title: **Sensory Sensitivity and Urinary Symptoms in the Female Population**
P.I.: **J. Quentin Clemens**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **DK094583-01**
Award: **$50,000**

Bladder pain and discomfort, as well as urinary urgency and frequency, are common and bothersome symptoms seen in the general population. Clinical diagnostic terms used to describe these symptoms include interstitial cystitis (IC), painful bladder syndrome (PBS), chronic prostatitis, and overactive bladder (OAB), but there is tremendous overlap between these entities, and the distinction between them is based more on imminence than evidence. Pain and/or sensory sensitivity have been suspected to play a role in the pathogenesis of both bladder pain and urinary urgency/frequency. However, there has never been a study to determine whether entities such as

IC/PBS and OAB might merely represent different points in a continuum of bladder sensory sensitivity. Moreover, we know of no studies that have directly compared whether sensory sensitivity in the bladder is related to global (i.e. CNS-mediated) sensory sensitivity. In the proposed study, a team of investigators with complementary expertise will perform a population-based study assessing bladder and overall sensory sensitivity, in a cohort of women chosen to be representative of the general population with respect to the entire continuum of bladder pain (from none to severe), and symptoms of urgency/frequency. These individuals will undergo urodynamics to measure sensory sensitivity in the bladder, as well as pressure pain and auditory loudness thresholds. Our Specific Aims are to demonstrate that in the population, 1) sensory sensitivity in the bladder is related to sensory sensitivity elsewhere in the body, suggesting that this is a CNS-driven mechanism, and 2) those individuals in the population that have more pronounced global sensory sensitivity will display: a) more bladder pain, b) more urgency/frequency, and c) more other symptoms of centrally-mediated pain states, such as pain elsewhere, fatigue, and insomnia. We feel that these studies are crucial to better understand the relationship between sensory sensitivity and urinary symptoms, and to add to the evidence necessary to appropriately diagnose and treat these symptoms and individuals.

Title: **Urinary Incontinence Treatment Network: DCC**
P.I.: **Sharon L. Tennstedt**
Institution: **New England Research Institutes, Inc.**
Grant No.: **DK058229-11**
Award: **$100,000**

This proposal is submitted in response to RFA-DK-06-501 for continuation of the Urinary Incontinence Treatment Network (UITN) Data Coordinating Center (DCC) at New England Research Institutes, Inc. The DCC is responsible for the scientific management of the studies, including directing, training, and monitoring the performance of Clinical Centers in enrollment, data collection, and data management as well as for all data analysis, and reports to the DSMB. In Phase I and continuing to Phase II, NERI has provided several unique and innovative tools and capabilities, including a proprietary Web-based data management system, an automated patient randomization system, and an electronic repository for UDS tracings. The DCC is also responsible for network communications and meeting support and provides a secure study website and a public website. DCC scientists play a leadership role in all network activities, including protocol development, standing committees and work groups, manuscript development and presentations. Phase II will focus on conduct of the TOMUS trial as well as continuation of the observational follow-up studies for the SISTEr and BE-DRI studies (i.e., E-SISTEr and E-BE-DRI) of Phase I. Primary Aims of TOMUS are to compare objective and subjective cure rates for stress incontinence at 12 and 24 months between the retropubic and transobturator midurethral sling procedures. Performance of these procedures is increasing rapidly with limited data available on safety and efficacy. Therefore, this study will compare the efficacy and safety of the retropubic and transobturator (inside-out and outside-in) procedures in a 2-arm RCT; 588 women with stress Ul will be enrolled. Primary Aim of E-SISTEr is to compare long-term (60 mos.) effectiveness and durability of the Burch colposuspension and autologous fascial sling for treatment of stress Ul in a randomized cohort of 655 women. Primary Aim of E-BE-DRI is to examine long-term (26 mos.) durability of the addition of behavioral treatment to drug therapy for treatment of urge Ul in a randomized cohort of 307 women. The UITN is a multi-disciplinary, multi-center group of Investigators dedicated to high impact clinical research regarding the prevention, evaluation and management of Ul to improve the quality of life for adults. The UITN is conducting 3 studies of treatments for both stress and urge urinary incontinence.

Title: **Weight Management in Obese Pregnant Underserved African-American Women**
P.I.: **Samuel Klein**
Institution: **Washington University**
Grant No.: **DK094416-01**
Award: **$100,000**

Maternal obesity and inappropriate gestational weight gain (GWG) increase both maternal and neonatal morbidity and mortality. In addition, offspring of obese women are at increased risk for neurodevelopment delay, becoming obese, and developing metabolic diseases. Women who are socio-economically disadvantaged (SED), especially from African American (AA) populations, are particularly susceptible to adverse pregnancy-related outcomes because of their high prevalence rates of obesity. Therefore, successful weight management during pregnancy in SED, AA women has considerable public health implications. We have experience in testing lifestyle interventions among SED non-pregnant women that have been implemented and sustained within community organizations such as Parents As Teachers (PAT), a national home visiting program that provides parent-child education and services free-of-charge to high needs women, prenatally and post-partum, through up to 25 home visits per year until kindergarten. We propose to conduct a 24-month (6-month prenatal and 18-month post-partum) randomized, controlled trial in obese SED AA women to evaluate the ability of an innovative lifestyle intervention program (PAT-i-), delivered by PAT parent educators during prenatal and post-partum home visits, to improve maternal and neonatal/infant weight, metabolic and health outcomes. An extensive programmatic evaluation will determine the applicability of the PAT+ intervention in real world settings by measuring programmatic reach, implementation, acceptability, and sustainability. If effective, PAT+ can be disseminated through this national organization, which currently reaches over 249,000 mothers and 319,000 children participating in 2,173 PAT programs across all 50 states.

National Institute of General Medical Sciences

Title: **Pharmacogenetics of Phase II Drug Metabolizing Enzymes**
P.I.: **Richard M. Weinshilboum**
Institution: **Mayo Clinic**
Grant No.: **GM061388-12**
Award: **$240,292**

This proposal represents a request for continued funding of the Mayo Clinic Pharmacogenomics Research Network (PGRN) grant "Pharmacogenetics of Phase II Drug Metabolizing Enzymes". The Mayo PGRN is an integrated, multidisciplinary, pharmacogenomic research effort based on a decades-long focus at Mayo on the pharmacogenetics of phase II (conjugating) drug metabolizing enzymes. The Mayo PGRN began by applying a "genotype-to-phenotype" research strategy that included, sequentially, gene resequencing, functional genomic, mechanistic and translational studies. During the present funding cycle, the Mayo PGRN has also incorporated the use of genome-wide techniques and pharmacogenomic model systems, with a special emphasis on functional mechanisms responsible for genetic effects on drug response. We have used that approach to study the pharmacogenomics ofthe endocrine therapy of breast cancer and selective serotonin reuptake inhibitor (SSRI) therapy of depression—research that grew out of the contribution of phase II enzymes to the biotransformation of the estrogens that play such an important role in breast cancer and biotransformation ofthe neurotransmitters that are central to the pathophysiology and treatment of depression. Recently, we have performed pharmacogenomic genome-wide association (GWA) studies of breast cancer, and we will soon perform similar studies of the SSRI therapy of depression. We propose to continue this genome-wide focus during the next funding cycle, with both clinical and model system GWA studies of the drug therapy of breast cancer and depression, always including replication as well as functional

and mechanistic studies. We also propose two "Network Resources", one designed to provide access to "Next Generation" DNA sequencing for all PGRN Centers and the other focused on pharmacogenomic ontology. In summary, the studies in this application build on Mayo PGRN strengths in DNA sequencing and functional genomics—while incorporating genome-wide techniques—to provide insight into the role of inheritance in variation in the efficacy and side effects of drugs used to treat breast cancer and depression. RELEVANCE: Breast cancer is the most frequent cancer of women and depression is the most common major psychiatric illness. Drugs are available to treat both of these serious illnesses, but many patients fail to respond and some suffer serious adverse drug reactions. The Mayo Clinic PGRN will apply modern pharmacogenomic techniques to help make it possible to "individualize" the drug therapy of breast cancer and depression.

National Institute of General Medical Sciences & Indian Health Service

Title: **Oklahoma Native American Research Centers for Health (NARCH VI)**
P.I.: **Gloria Ann Grim**
Institution: **Cherokee Nation**
Grant No.: **GM092238-01**
Award: **$100,000**

The purposes of this project are: to encourage competitive research linked to reducing health disparities; to increase the capacity of the Tribes and University of Oklahoma to work in partnership to reduce distrust by the Native American communities and peoples toward research; and to develop a cadre of Native American scientists and health professionals engaged in biomedical, clinical and behavioral research that is competitive for NIH funding. The sixth Oklahoma Native American Research Center for Health (0NARCH6) continues the productive research and training partnership with the University of Oklahoma Health Sciences Center (OUHSC) by the Tribes, especially the Chickasaw, Creek, Choctaw and Cherokee Nations. Population served consists of 42,749 Chickasaws and 121,680 Cherokees, 49,714 Choctaws and 30,181 Creeks for a total of 244,324 in North East and South Central Oklahoma. The research will include 1) the impact of infections on maternal and child health in Native Americans, 2) research to develop better diagnostic and prognostic tests for rheumatic disease in Oklahoma tribal members, and to examine the potential roles of environmental triggers for autoimmunity focusing on vitamin D levels, tobacco smoke exposure (through serum cotinine levels) and abnormal immune responses to common viruses, 3) research to prevent excessive gestational weight gain in otherwise healthy but overweight Native American women and consequently decrease the proportion of women who gain in excess of the guidelines has the potential to decrease the risk and costs of obstetric complications associated with excessive weight gain, and 4) to develop methods to understand attitudes, beliefs, and perceived barriers or motivators to organ/tissue donation among American Indians living off-reservation.

Title: **Research to Improve Preconception Health of Adolescent Women (NARCH VI)**
P.I.: **Sara Jumping Eagle**
Institution: **Oglala Lakota Oyate**
Grant No.: **GM087165-02**
Award: **$128,436**

The Oglala Sioux Tribe, in partnership with Stanford Research/University of South Dakota School of Medicine and the Oglala Lakota College, will be addressing priority health issues identified by the tribe and to support and expand the research capacity and infrastructure that will build on the research foundation that has been developed within the tribe over the past decade. Particular attention will be given to undertaking research to improve the preconception health of adolescent girls.

National Institute of Mental Health

Title: **Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia**
P.I.: **Deanna L. Kelly**
Institution: **University of Maryland, Baltimore**
Grant No.: **MH090071-01A1**
Award: **$99,833**

Risperidone is available generically and one of the most widely used antipsychotic medications; but is associated with elevated prolactin. This elevation is particularly pronounced in women and most recent studies show that the vast majority of women have elevated prolactin levels with approximately 50% also having the corresponding side effects of amenorrhea, oligomenorrhea or galactorrhea. Elevated prolactin may be associated with sexual dysfunction, decreased quality of life, medication nonadherence and decreases in bone mineral density over time. Lowering the dose or switching medications due to this side effect in stabilized patients is not a practical option in most cases. There is little evidence to guide treatment in this important area however dopamine agonists such as bromocriptine or amantadine may exacerbate symptoms, have lacking efficacy data and are associated with side effects. We have sizeable pilot data to suggest that a low dose of aripiprazole (10 mg/day), a dopamine partial agonist, added to Risperidone can improve symptomatic prolactin side effects. We will complete a double blind randomized 16-week control trial examining adjunct aripiprazole (10 mg/day with increase to 15 mg/day at 8 weeks if no response) vs. placebo in 70 women with symptomatic hyperprolactinemia and hypothesize it will be effective in the resolution of amenorrhea, oligomenorrhea and galactorrhea. We also hypothesize that aripiprazole will significantly improve quality of life, personal well-being and sexual function. And, we will examine improvements in positive, negative and depressive symptoms, sex hormone levels and measures of bone turnover. The significance and innovation of this application is high as this is a significant complaint and concern of women and very little evidence is available to guide treatment in women who are stabilized and doing well on antipsychotic treatments but develop these significant side effects. If funded, this important treatment research study of adjunct aripiprazole treatment will provide invaluable data and treatment options for thousands of women who suffer from schizophrenia and will help move the field towards better tailoring and personalizing antipsychotic treatment, particularly for women who suffer from these problems.

National Institute of Neurological Disorders and Stroke

Title: **Effects of Estrogen on Brain Morphology and Neuronal Integrity in Early Menopause**
P.I.: **Kejal Kantarci**
Institution: **Mayo Clinic**
Grant No.: **5R21NS066147-02**
Award: **$191,541**

Neuroprotective effects of estrogens offer the possibility of preventing or delaying Alzheimer's disease in menopausal women. Estrogen treatment in older women who were late into menopause in the Women's Health Initiative Memory Study, did not prevent dementia. The question remains as to whether or not estrogen can preserve neurological function and decrease the risk of dementia when administered early in menopause from 6-36 months of the last menses. This project is proposed as an ancillary to the Kronos Early Estrogen Prevention Study (KEEPS), which is a nationwide, multi-center, randomized blinded study designed to provide evidence on the benefits and risks of oral and systemic estrogen treatment in recently menopausal women. Our goal is to test the neuroprotective effects of estrogen treatment in early menopause, during the 48 months of the randomized clinical trial. We will determine the rates of hemispheric

atrophy on MRI, and the change in neuronal metabolite N-acetylaspartate (NAA) on proton MR spectroscopy (1H MRS) as a surrogate for the neuroprotective effects of estrogen treatment during the early postmenopausal years. In addition to the longitudinal serial measurements of whole brain, hippocampal and ischemic lesion volumes, we will use exploratory 3-dimensional voxel-based analysis of the serial MRI to determine the differences in the change in whole brain morphology in women who are taking estrogens compared to placebo. Our collaboration with the investigators of the KEEPS Cognitive and Affective Study will give us the ability to relate the change in neuronal metabolic integrity and brain morphology with the concurrent change in cognitive function in newly menopausal women. As an outcome of the proposed investigations, we expect to determine whether or not oral and transdermal estrogen treatment preserves brain structure and neuronal function during the immediate years after menopause. Several decades of follow-up are necessary to determine if estrogen treatment in newly menopausal women prevents Alzheimer's disease. This project will provide the necessary in vivo evidence on the neuroprotective effects of oral and transdermal estrogens in early menopause in the short term, for future large-scale, long term trials. The original contributions of this study to women's health research will include the demonstration of the effects of estrogens on longitudinal change in brain morphology and neuronal integrity, and the relationship between these biological changes and the concurrent change in cognitive function in recently menopausal women.

Title: **Modifiable Risk Factors in Stroke Incidence and Mortality Among Women**
P.I.: **Sophia Wang**
Institution: **Beckman Research Institute of City of Hope**
Grant No.: **1R21NS075608-01**
Award: **$243,441**

Stroke is the third leading cause of death in the United States (U.S.) and women account for 60% of all deaths from stroke. Major shifts in modifiable exposures over the past decade—increasing obesity and physical inactivity and decreasing menopausal hormone therapy (MHT) use—are changing the profile of women's health, but their effect on stroke among women is unclear. The California Teachers Study (CTS), a prospective cohort study that has actively followed 133,479 female California public school professionals for a broad range of health outcomes since 1995, is poised to evaluate how these societal transitions in modifiable exposures affect incidence of and mortality from stroke. The unique repository of life course exposure data on modifiable risk factors in the CTS cohort provides a near-singular resource for prospective assessment of women's health risks associated with long-term history of physical activity, longitudinal anthropometry data on body fat distribution, and detailed MHT use. Our specific aims address the impact of these shifting exposures both individually and together on stroke incidence and mortality, both overall and among the two major stroke subtypes (ischemic and hemorrhagic). In Aim 1, we will determine the impact of obesity and physical inactivity on the rates, risk, and population attributable fraction of incident and fatal stroke. Our detailed questionnaires permit us to evaluate the effect of lifelong and changing patterns of obesity phenotypes (defined as a combination of temporal changes in overall adiposity with adult body fat distribution) and physical activity, including by age and recency. In Aim 2, we will determine whether the effects on rates, risk and population attributable fraction observed from obesity and physical inactivity (Aim 1) become more pronounced in the years following widespread cessation of MHT use (after 2002). To accomplish these aims, we will calculate age-adjusted and age-specific annual incidence and mortality rates, standardized to the U.S. population in 2000. To calculate risk associations, we will use time-dependent exposure data on these key exposures from teenage years to old age and analyze associations with stroke risk and mortality using statistical approaches that account for missing data and secular changes in exposures. We will calculate the population attributable fraction for each etiologic risk factor, and by time period when MHT was widely used versus the recent sharp decline in use. Public Health Relevance: Successful completion of these aims will permit evaluation of the population impact of a decade

of profound transition in obesity, physical activity, and MHT use on women's stroke incidence and mortality, and provide insight into the interplay between these and other relevant exposures. This proposal focuses on the etiology of stroke incidence and causes of stroke mortality and emphasizes common, modifiable, behavioral risk factors in ways that can facilitate future population-wide stroke prevention efforts. PUBLIC HEALTH RELEVANCE: The California Teachers Study spans more than a decade of profound transitions in women's health behaviors, including increasing physical inactivity and obesity, and decreasing use of hormone therapy. By examining how exposures to these common, modifiable risk factors over a woman's lifespan influences rates and risk of stroke incidence and mortality, this study will provide critical new knowledge that can serve as the basis for behavioral public health interventions that benefit women on a population-wide scale.

Title: **Neuropathologic Abnormalities Define a Subgroup of Patients with CFS**
P.I.: **Benjamin Natelson**
Institution: **Beth Israel Medical Center**
Grant No.: **NS075653-01**
Award: **$189,405**

Chronic fatigue syndrome (CFS) is a debilitating multi-symptom disorder characterized by unexplained and prolonged fatigue, whose diagnosis is currently based on a relatively broad clinical case definition. Consequently, the pool of CFS patients included in clinical studies of the illness is greatly heterogeneous—a fact that might have impeded research progress to date. A major step forward in understanding the pathophysiology of CFS would involve reducing this heterogeneity by identifying one or more subgroups of patients with different pathophysiological causes of their illness, and then selecting one of these subgroups for inclusion into research studies. Over the past few years, we and others have provided substantial data supporting the existence of a subgroup of patients with a neurobiological cause for their illness, based on stratifying the sample according to the absence or presence of comorbid Axis I psychopathology (CFS-no psych or CFS-NP and CFS-psych or CFS-P, respectively). Compared to CFS-P patients, the CFS-NP patients had more cognitive dysfunction, a higher rate of abnormal cerebrospinal fluid (CSF) findings, lower regional cerebral blood flow (rCBF), and higher ventricular CSF lactate values. A further complication and limitation of these studies is that each had investigated only one brain-related variable, whose utility in separating CFS patients into subgroups was limited. The purpose of the present Exploratory/Developmental Research Grant (R21) proposal is to rigorously assess and confirm whether patients in the CFS–NP group have consistent abnormalities across several different neuropathological variables—an outcome that would be expected if this group, in fact, does have distinct neurobiological underpinnings. Specifically, in the same subjects, we will (a) assess cognitive function using objective neuropsychological testing; (b) conduct biochemical analysis of spinal fluid samples obtained by lumbar puncture; and (c) measure rCBF and ventricular lactate using magnetic resonance imaging and spectroscopy, respectively, in CFS-P and CFS-NP patients. This will allow us to test the hypothesis that CFS-NP patients have more abnormalities in these outcome variables than CFS-P patients. Our second Aim will use the results from the first Aim in a cluster analysis to attempt objective, data-driven classification of the CFS subjects into subtypes, and then compare the resulting subgroups based on membership into CFS-NP or CFS-P groups. This aim will test the hypothesis that the results of the cluster analysis will identify a group with abnormalities across the multiple brain-based variables studied, and this group will be constituted of significantly more CFS-NP patients than in other groups.

Title: **p38 MAPK as a Female-Specific Drugable Target in CNS Autoimmune Disease**
P.I.: **Cory Teuscher**
Institution: **University of Vermont and State Agricultural College**
Grant No.: **1R21NS076200-01**
Award: **$228,750**

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by myelin loss, varying degrees of axonal damage, and progressive neurological dysfunction. MS is the most common disabling neurologic disease of young adults and adolescents affecting ~350,000 individuals in the United States and more than 1 million individuals worldwide. Current MS disease-modifying therapies (DMTs) have limited efficacy and untoward toxicities, underscoring the need for new approaches based on targeting underlying disease mechanisms. The p38 mitogen-activated kinase (MAPK) is a central molecule in autoimmune/inflammatory responses in diseases such as rheumatoid arthritis (RA) and Crohn's disease, and inhibition of p38 MAPK is currently being explored clinically as a DMT for these diseases. However, the role of p38 MAPK in the pathophysiology of MS (or MS models) and its potential as a therapeutic target has not been investigated. Using experimental allergic encephalomyelitis (EAE), the principal autoimmune model of MS, we tested whether inhibition of p38 MAPK can influence EAE susceptibility and disease progression. Treatment of female mice with the pharmacological p38 MAPK inhibitor, SB203580, either completely prevented disease or halted disease if administered at the onset of clinical signs. Strikingly, male mice were completely unresponsive to treatment. These findings suggest that sex-specific factors contribute to SB203580 mediated inhibition of p38 MAPK activity and EAE susceptibility. In this application, we propose to: 1) determine the molecular and cellular mechanisms targeted by p38 MAPK inhibition in EAE and 2) determine the basis of the sexual dimorphism in the therapeutic response to SB. Understanding the mechanisms of drug action is likely to provide novel, more specific drug targets for MS therapy. The gender dichotomy with regard to efficacy of SB203580 is particularly important, since many autoimmune diseases, including MS, exhibit a female-specific sexual dimorphism in disease susceptibility. The finding that SB203580 is fully capable of selectively inhibiting disease in females provides for the possibility of a unique DMT that selectively targets the increasing female MS patient population. No study to our knowledge has evaluated the DMT potential of inhibiting p38 MAPK in MS, despite the fact that many compounds targeting this pathway are already approved for phase 2 clinical trials in other autoimmune diseases. Further, relatively few studies focus on the basis of sex differences in therapeutic responses in MS or its models. Inhibition of the p38 MAPK pathway may not only provide a novel DMT which selectively targets the increasing female MS patient population, but also will likely provide mechanistic insight relevant to development of additional DMTs for MS, by uncovering new targets for therapeutic intervention. PUBLIC HEALTH RELEVANCE: The objective of this proposal is to explore a new molecular pathway which is likely to be important in the pathogenesis of multiple sclerosis (MS), and understanding of this pathway can yield new therapeutic targets for treatment of this devastating disease. Further, this proposal explores the bases for sexual dimorphisms in efficacy of drug treatment in autoimmune disease. This point is highly salient today given the increasing female incidence of MS.

Title: **Sex Differences in the CNS During Disease**
P.I.: **Rhonda R. Voskuhl**
Institution: **University of California, Los Angeles**
Grant No.: **5R21NS071210-02**
Award: **$188,650**

Numerous neurological diseases are characterized by a sex difference. The neuropathology often includes infiltration of immune cells, with this immune infiltration potentially contributing to disease pathogenesis. Since it is known that sex differences exist in the immune system, this confounds investigations into sex differences in the CNS. Thus, we will use bone marrow chimeras

to investigate sex differences in the CNS. By varying sex chromosomes or sex hormones in hosts reconstituted with a common immune system, one can ascertain the role of sex chromosomes and sex hormones on the brain response to injury. We will use one of the most inflammatory of all CNS disease models, the multiple sclerosis model, experimental autoimmune encephalomyelitis (EAE), to show applicability of this approach to a variety of neurological diseases. We will employ mice which differ in the complement of sex chromosomes (XX vs. XY), while having the same gonadal type, to determine the effect of sex chromosomes in the absence of confounding effects of exposure to different types of sex hormones. Specifically, in aim #1 we will determine whether the greater severity of EAE in XX, as compared to XY-, mice is due to sex chromosome effects in the CNS. In aim #2, we will determine if the sex chromosome effect in the CNS during EAE is due to the dose of X or Y genes. Finally in aim #3, we will use mice which differ in gonadal type, female vs. male, while having the same sex chromosome complement (XX vs. XX Sry) to determine whether the greater severity of EAE in female, as compared to male, mice is due to sex hormone effects in the CNS. PUBLIC HEALTH RELEVANCE: This is an exploratory (R21) grant to determine the effect of sex chromosomes and sex hormones on the central nervous system's response to an immune attack using the multiple sclerosis model, experimental autoimmune encephalomyelitis. This proposal will establish a model system to determine the effect of sex chromosomes and sex hormones on a variety of neurological diseases characterized by a sex difference.

National Institute of Nursing Research

Title: **Advancing Transdisciplinary Translation for Prevention of High-Risk Behaviors**
P.I.: **Diana Hanna Fishbein**
Institution: **Research Triangle Institute**
Grant No.: **NR013623-01**
Award: **$50,000**

Scientific Meetings to Advance Transdisciplinary Translation for Prevention of High-Risk Behaviors Several cross-cutting, forward-thinking investigators on the leading edge of both the social (geospatial mapping, contextual behavioral science, developmental psychology, education, social media) and basic sciences (genetic epidemiology, epigenetics, neuroscience, chemistry) have recently made notable advances in identifying factors that influence emergence of high-risk behaviors. This information has potentially significant implications for the prevention of high-risk behaviors, given that etiological social and neurobiological risk factors may also operate as moderators and/or mediators of intervention outcomes. Transfer and application of this knowledge from the basic to the prevention sciences and back again is, however, lacking. This transfer is particularly needed to understand differences in individual response to interventions to prevent high-risk behaviors and develop new interventions tailored for an individual's risk factors. We propose to use the R13 mechanism to hold two round-table meetings that convene a core of 60 relevant experts and advisors to "connect the dots" across the translational spectrum by identifying pressing scientific questions in risk behavior prevention research, as well as the collaborations and capabilities needed to address them. These meetings are designed to facilitate the relevance, operational feasibility, and utility of a transdisciplinary translational program of research to gain a better understanding of the mechanisms underlying individual differences in intervention responsivity. Meetings will promote a cross-disciplinary integration of theoretical perspectives and empirical methods to: a) identify high priority scientific questions yet to be addressed in the prevention sciences that may be informed by a new generation of research suggesting that neurogenetic mechanisms correlate and interact with environmental conditions to promote or interfere with behavioral change in response to interventions; b) conceive of novel psychosocial and technological preventive intervention approaches and policy developments that incorporate transdisciplinary scientific findings, c) discuss an educational agenda for early career researchers to move into translational prevention; d) identify potentialities for new collaborations that will

facilitate the advancement of a Translational Network for prevention research, e) conduct a survey of participants for their perceptions before and after the conferences regarding team science, needs for translational competencies, and market analysis; f) address ethical issues arising from inclusion of genetic and neurobiological markers of risk for behavioral problems, g) publish an open-access monograph of the proceedings; h) publish two special journal editions authored by a subset of attendees who will reanalyze their clinical trials datasets using state-of-the-art statistical techniques to elucidate mechanistic effects of their interventions, and report progress and preliminary findings from new collaborations forged during the meetings.

Title: **The Science of Compassion: Future Directions in End-of-Life and Pallative Care**
P.I.: **National Institute of Nursing Research**
Institution: **National Institute of Nursing Research**
Grant No.: **OD-11-301**
Award: **$2,500**

This Summit brought together over 900 scientists, researchers, palliative and end-of-life care health professionals, educators, policy analysts, members of professional organizations, and members of the public. The objectives were to: examine the current status of palliative care and end-of-life research, practice, and policy; propose strategies to overcome barriers and ensure scientific and methodologic rigor in our research; delineate new action items that galvanize progress in these vital areas of science; and, envision and map pathways to ensure a future rich with scientific endeavor and achievements.

Fogarty International Center for Advanced Study in the Health Sciences

Title: **AIDS International Training and Research Program: University of North Carolina at Chapel Hill**
P.I.: **Adaora A. Adimora**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **TW001039-13**
Award: **$20,000**

This is the second competitive renewal application for the UNC AIDS International Training and Research Program. We propose to continue to provide training in three countries: The Peoples Republic of China, Malawi and Cameroon. Investigators at UNC have worked in China since 1979, Malawi since 1989, and Cameroon since 1998. The UNC AITRP has embraced several guiding principles. First, we use training to build strong ties to key in-country organizations. Trainees with guaranteed "return jobs" in these organizations are preferentially selected. Second, our training opportunities build on funded research projects and bridge many of the strengths of UNC. Wherever possible we combine basic, clinical and epidemiological training and research in order to build critical mass. Third, we have used the Fogarty training to promote international research, working with many collaborators and funding agencies. Fourth, we have developed south-to-south and international collaborations to facilitate training and ongoing research opportunities. For example, University of the Witwatersrand is a training site for Malawi personnel, and we have developed a strong collaboration with the London School of Hygiene and Tropical Medicine for training of physicians from Malawi (a former British protectorate). Fifth, we have looked for opportunities for evolution and innovation. Such efforts have been particularly important in the development of a new Department of Public Health at the Malawi College of Medicine (which has received dedicated Fogarty support), extensive research ethics and IRB training in China, and rapid technology transfer in all three UNC AITRP countries. Sixth, we are committed to in-country leadership and ongoing mentorship after the trainee has completed our program.

Title: **AIDS International Training and Research Program: University of Pittsburgh**
P.I.: **Lee H. Harrison**
Institution: **University of Pittsburgh**
Grant No.: **TW001038-13**
Award: **$20,000**

We propose to continue the AIDS International Training and Research Program (AITRP) at the University of Pittsburgh (Pitt). Our mission is to provide Brazilian, Indian, and Mozambican health professionals with multidisciplinary tools needed to conduct cutting-edge HIV prevention research in their countries. The Director and Co-Director are, respectively, Dr. Lee Harrison, Professor of Epidemiology and Medicine, and Dr. Phalguni Gupta, Professor of Infectious Diseases and Microbiology. An exciting change in our program is the addition of a site in Beira, Mozambique, which has striking training needs and where Pitt has established close collaborations with the Universidade Catolica de Mozambique. The addition of Mozambique and the training of a large cadre of well-trained Brazilian investigators over the past ten years allow us to dramatically reduce our training efforts in Brazil and shift resources to Mozambique. As a component of our training program, we will leverage the extensive training already provided to Brazil by conducting south-to-south training between these two Portuguese-speaking countries. Ongoing research in Brazil includes HIV vaccine trials, studies of effectiveness of antiretroviral therapy in public clinics, and changes in causes of death among HIV-infected patients. In India, ongoing projects include studies of genetic heterogeneity of Indian HIV strains, CDS suppression of HIV, HIV incidence studies to identify high-risk populations, and development of a novel Clostridium perfringens-based oral HIV vaccine. Research at our new site in Mozambique is currently limited and we will use the training provided by the Pitt AITRP to jump start a much-needed research agenda there. Trainees from all three countries will have access to the substantial HIV research activities at Pitt, including research in epidemiology, behavioral sciences, and laboratory sciences. During the next five years, we propose to establish an extensive training program in Mozambique; provide limited, selected training for Brazil; and provide laboratory and behavioral sciences training for India. Our successful track record during the first 10 years, the excellent training opportunities we propose, and collaboration with key institutions in our three countries assure that our program will continue to be highly productive.

Title: **China-Rochester Suicide Research Training Program (CRSRT)**
P.I.: **Eric D. Caine**
Institution: **University of Rochester**
Grant No.: **TW009101-01S1**
Award: **$10,000**

This D43 NCD-LIFESPAN application is entitled the China-Rochester Suicide Research Training Program (CRSRT). It is built upon the International Clinical, Operational and Health Services Research Training Award ("ICOHRTA") program that has been funded since 2001 (D43TW005814). The current proposal is written in response to PAR-10-257 for a Chronic, Non-Communicable Diseases and Disorders Across the Lifespan: Fogarty International Research Training Award (NCD-LIFESPAN). Suicide is a major public health problem in China. It is the fifth leading cause of death overall, and the leading cause of death for individuals in the 15-34 year old age range. It has a national rate of approximately 23 deaths per 100,000; during 1995-1999, approximately 287,000 died by suicide. In response, we now are systematically growing the CRSRT to encompass multiple complementary settings that serve to diversify the academic breath and geographical distribution of our initiatives, increase our committed mentors, and widen the pool of applicants. Our high rate of positive outcomes during the past decade reinforces the rewarding nature of our high-intensity mentoring strategy. The CRSRT involves the Center for the Study and Prevention of Suicide (CSPS) of the University of Rochester Medical Center (URMC), and six key collaborators in China who bring a diversity of skills and leadership to our growing collaborative efforts, with centers in Beijing, Shanghai, Chengdu, and Changsha.

Our proposal reflects an ongoing, self-scrutinizing process that has informed our efforts to: 1) build training and research infrastructure, focusing primarily on public health and population-oriented research and prevention efforts; 2) identify and train excellent future scientists; and 3) develop new research findings that will inform efforts to prevent suicide in China during the coming decades. The CRSRT involves a year of intensive training in the CSPS, followed by two further years of mentored research in China. We provide trainees with the skills to emerge as independent investigators through intensive one-to-one mentoring and engagement in a variety of peer-oriented training experiences. We will continue to systematically evaluate the effectiveness of our recruiting, training, and research efforts.

Title: **Emory AIDS International Training and Research Program**
P.I.: **Carlos Del Rio**
Institution: **Emory University**
Grant No.: **TW001042-13**
Award: **$20,000**

Located in Atlanta, the Emory AIDS International Training and Research Program (AITRP) has established itself as an interdisciplinary training environment, that is producing highly qualified HIV/AIDS researchers. The collaborating countries of the Emory AITRP proposed for this application are Mexico, Georgia, Vietnam, Rwanda and Zambia. The specific aims of the research training program include: 1. To build academic capacity in partner countries through the support of in-country education and training. 2. To build HIV/AIDS research human resource capacity through the support of degree-seeking, long-term training. 3. To fill identified gaps in partner country research training capacity through the provision of specialized medium and short-term training. 4. To build in-country capacity to conduct implementation science research that will allow our trainees to become involved in the evaluation of the impact of a variety of interventions that are currently occurring in our collaborating countries such as PEPFAR.

Title: **Enhancing Training, Research Capacity, and Expertise in HIV Care (ENTRÉE)**
P.I.: **Umesh G. Lalloo**
Institution: **University of KwaZulu-Natal**
Grant No.: **TW008863-02**
Award: **$60,000**

The broad aim of the Enhancing Training, Research Capacity and Expertise in HIV Care (ENTRÉE) program is to address the shortage of competent health care personnel to manage the increasing burden of HIV/AIDS in the Province of KwaZulu Natal that has numerous PEPFAR treatment programs. The specific aims are to: increase the competency of medical, nursing and pharmacy students in the management of HIV/AIDS through enhancement of undergraduate training and infusion of the curriculum with a program of a continuum of care approach to HIV/AIDS and improved clinical preceptorship; scaling up of an innovative parallel training track for selected undergraduate medical students in HIV towards a certificate / diploma / masters program; increase the competency of medical interns / house-officers through the development of a program that will create a cadre of master trainers to support and enhance the internship experience; create a supportive learning environment and in so doing attract medical trainees to return to these centers that include both urban and rural internship and academic and non-academic clinical service centers; develop and support a program of research to enhance skills, among undergraduates and faculty, in research methodology and research implementation with particular emphasis on HIV and related complications including individuals selected from Southern African Development Community (SADC) countries; develop a program to promote retention of academic and research staff by providing a research career pathway and research support; and develop a postgraduate medical resource center unit within the Nelson R Mandela School of Medicine (NMSM) with seed funding support from the Department of

Health training grant. At least 50% of the beneficiaries of the program will be women. The program will use and expand an established telehealth program and set up academic resource centers in HIV care sites in KwaZulu Natal. The project will harness the resources of the academic departments of the Nelson R Mandela School of Medicine, the Schools of Nursing and Pharmacy and the established HIV/AIDS research units in the University KwaZulu-Natal. The University of Columbia is the US partner in this project.

Title: **Haiti AIDS Research Training: Models to Implementation**
P.I.: **Jean William Pape**
Institution: **GHESKIO Center**
Grant No.: **TW006896-08**
Award: **$20,000**

The goal of GHESKIO-Cornell ICOHRTA training program is to increase capacity in integrated clinical, operational, and health services research in support of Haiti's national scale-up of HIV and tuberculosis services. Haiti is the poorest country in the Western Hemisphere and has the highest rates of both HIV infection and tuberculosis. It is estimated that 3% of the adult population is HIV-infected and that the prevalence of tuberculosis is 402/100,000 population (100xUS rates). In response to this epidemic, the Haitian Ministry of Health asked GHESKIO to form a national HIV and TB Network, a collaboration of 32 public and private health care organizations across the country that is charged with "scaling-up" to provide a standardized package of HIV and tuberculosis services to 500,000 persons by 2014. The services include voluntary counseling and HIV testing, management of tuberculosis and sexually transmitted infections, prevention of mother to child HIV transmission, and comprehensive HIV care of children, adolescents, and adults. The Haitian Ministry of Health has asked GHESKIO (Haitian Study Group for the Study of Kaposi's Sarcoma and Opportunistic Infections) to lead this network through training, supervision, monitoring and evaluation, and through the conduct of operational and health services research. GHESKIO is an international research and training institution that has benefited from 25 years of uninterrupted NIH funding and research capacity building with Cornell University, and support from the Fogarty International Center. GHESKIO is recognized as a center of research excellence, and is a member of the NIH HIV Vaccine Trials Network (VTN), the AIDS Clinical Trials Group (ACTG) and a recipient of support from the United Nations Global Fund for AIDS, TB and Malaria and the President's Emergency Plan for AIDS relief (PEPFAR). In the current proposal, GHESKIO will continue as the primary training institution and extend research capacity to other organizations in Haiti that are participating in the GHESKIO HIV and Tuberculosis Network. The program will continue to emphasize medium- and long-term training in Haiti. Since its inception four years ago the ICOHRTA has provided training to 120 Haitian biomedical personnel, all of whom are working in Haiti, providing HIV/TB services and conducting operational and health services research. GHESKIO, in collaboration with Haitian and International partners, will develop training curricula in clinical, operational, and health services research methodology and in ethics, program management, and scientific writing. A Masters in Public Health Degree program, established with ICOHRTA support, will continue to be offered in Haiti by Quisqueya University, in partnership with GHESKIO and Cornell University.

Title: **Medical Education for Services to All Ugandans (MESAU)**
P.I.: **Nelson K. Sewankambo**
Institution: **Makerere University**
Grant No.: **TW008886-02**
Award: **$60,000**

In Africa, HIV, infectious diseases and other severe health problems compounded by critical shortages of health workforce compromise effective health care delivery. In order to train the necessary number of medical doctors in Africa, medical schools need to produce more high quality doctors.

This proposal assembles a 5 Ugandan medical school consortium with JHU to catalyze capacity building and performance enhancements in medical education, research, and environment geared towards improved service delivery. Funding this proposal will facilitate Ugandan universities to strengthen countrywide south-south institutional collaboration as a strategy to enhance quality in medical education with an increase in the number of health workers trained and retained in the country, especially in rural areas. This funding will strengthen the capacity of the Ugandan medical schools consortium to realize their joint mission "to ensure the transformative innovative medical education built on strong sustainable systems to produce more health workers of consistently high quality to address health priorities like HIV/AIDS through service and research to improve health outcomes for Uganda." The specific aims of the proposal are to improve the quality and relevance of medical education and service training by developing learner-centered curricula to be implemented at standardized community-based platforms for education, service, and research which geographically cover the entire country. Well-trained on-site supervisors will teach competencies necessary to deliver locally relevant services in resource-limited environments. Next, incentives and support will be provided to faculty and students to undertake transdisciplinary research at the community-based sites. A series of grants will be offered that will give students the opportunity to initiate operational research at community sites, will increase the pipeline of basic science and family medicine advanced degrees, and encourage faculty development and retention through research grants with "twinning" opportunities with JHU faculty. Finally, support systems capacity building will be emphasized to facilitate the efficient conduct of education and research. PUBLIC HEATLH RELEVANCE: Improving medical education in resource-limited settings through Innovative curricula will result in a larger number of high quality health care workers with the competencies to address Ugandan health care priorities such as HIV/AIDS and non-communicable disease such as cardiovascular disease and cancer.

Title: **Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum* and *P. vivax* in Yunnan and Hainan, China**
P.I.: **Fangli Lu**
Institution: **Sun Yat-sen University**
Grant No.: **TW008151-03**
Award: **$50,000**

Malaria remains a serious public health problem in China. In the subtropical Yunnan Province and the tropical Hainan Island of China, malaria has been the most endemic with high transmission of both *Plasmodium falciparum* and *P. vivax*. However, most of the attention in terms of research and interventions has been focused in Africa and Southeast Asia, very few studies of malaria in China have been conducted. Because of extensive use, chloroquine (CQ) has now lost its efficacy due to the emergence of resistant strains in most parts of the world. Meanwhile, suspension of the use of CQ has resulted in reappearance of CQ sensitivity. However, there were differences in the evolution of CQ resistance between parasites from Yunnan and Hainan, the exact mechanism needs to be investigated. Sulfadoxine-pyrimethamine (SP) targets the dhfr and dhps genes of *P. falciparum,* and point mutations that confer resistance have been widely reported worldwide. Documenting the identity and extent of SP resistance is also critical for policy decisions regarding antimalarial drugs. In addition, *P. vivax* causes a large burden of morbidity in the world including China but traditionally has been understudied. Based on these, our long-term goal of this proposal is 1) to identify single-nucleotide polymorphism (SNP) and characterize the geographic distribution of genetic diversity, population structure, and haplotype variability at drug resistant loci of *P. falciparum* from Yunnan and Hainan, China, 2) to examine the geographic population structure, levels of genetic diversity of *P. vivax* using microsatellite and SNP, and 3) to yield valuable information for making more effective malaria control policies in China. In the past several years we have developed the molecular methods to study the genetics, population diversity, and evolution of malaria parasites, and have done some preliminary studies on malaria field isolates from Yunnan and Hainan using genetic markers, thus enabling us

to study the molecular epidemiology of these important malaria parasites in this proposal. The specific aims are to: 1. Determine genetic polymorphisms associated with CQ resistance (CQR) in *P. falciparum* field isolates from Yunnan and Hainan provinces, China. 2. Determine the point mutation prevalence in the dhfr (pyrimethamine drug resistance) and dhps (sulfadoxine drug resistance) genes associated with SP resistance in *P. falciparum* field isolates from Yunnan and Hainan provinces, China. 3. Assess the changes of *P. vivax* genotypes using pvcsp, pvmsp1, pvmsp3-α genes, and microsatellite markers and determine the geographic structure and specific epidemiological characteristics of *P. vivax* transmission in Yunnan and Hainan, China.

Title: **Programmatic: Expanding Innovative Multidisciplinary Medical Education in Zambia**
P.I.: **Yakub F. Mulla**
Institution: **University of Zambia**
Grant No.: **TW008873-02**
Award: **$60,000**

Zambia is one of the countries in the world most heavily impacted by the HIV epidemic with an estimated adult prevalence of 14.3%. While recent indicators suggest progress in the national HIV prevention and management response, this is not sustainable without substantial increases in health manpower. Health care worker (HCW) training will require investments at many levels, starting with the expansion of the capacity and quality of pre-service training programs. The University of Zambia (UNZA) is the sole training institution in Zambia for Medical Officers and other health care professionals including bachelors degree programs in Nursing, Pharmacy, Biomedical Sciences, and Physiotherapy, Masters in Public Health and Nursing, and Masters in Medicine for clinical subspecialties. UNZA also has active affiliation agreements with the only Clinical Officer training program at Chainama College of Health Sciences and with other training institutions for nursing and HCW training institutions throughout Zambia. UNZA is thus critical for addressing the needs to expand HCW training in Zambia. Critical shortages of faculty and instructors must be addressed in order to meet these targets. The overall goal of this programmatic application is to strengthen both the quality and quantity of HCW education across selected high-priority training programs at UNZA and its partner institutions. Expanding and retaining faculty will be critical to these goals long-term. To accomplish this goal, our Specific Aims are: Specific Aim 1: Improve substantially the capacity of UNZA to train more HCWs at the UNZA School of Medicine (SOM) and affiliated institutions. Specific Aim 2: Improve the overall quality of HCW training, emphasizing integrated HIV specific training at UNZA. Specific Aim 3: Enhance the MMed degree program for physicians to ensure that graduates have the capacity to conduct evidence-based research and program evaluation. Specific Aim 4: Enhance the academic environment at UNZA to better retain faculty. PUBLIC HEATLH RELEVANCE: The people of sub-Saharan Africa are the most heavily affected by the HIV epidemic. The Zambian programmes for expansion of HIV therapy and prevention services has been very impressive but can only be sustained if more health care workers are trained. The single center for most advanced health care worker training in Zambia is the University of Zambia (UNZA). We propose to enhance the training programs at UNZA to improve the quality of training allowing for training many more HCW throughout Zambia.

Title: **Programmatic: Novel Education Clinical Trainees and Researchers (NECTAR) Program**
P.I.: **James Gita Hakim**
Institution: **College of Health Sciences, University of Zimbabwe**
Grant No.: **TW008881-02**
Award: **$60,000**

This application for a MEPI Programmatic Award will establish the Novel Education Clinical Trainees and Researchers (NECTAR) program at the University of Zimbabwe College of Health Sciences (UZCHS). UZCHS is the centre of medical research and education for Zimbabwe. NECTAR will be a consortium of investigators based on the long history of strong and productive collaborations in education and research between faculty at UZCHS and faculty at Stanford University and the University of Colorado Denver. The NECTAR consortium will consolidate the unique education and research training experience and expertise available in each of the consortium institutions. UZCHS, is the applicant institution and the site of most NECTAR activities. The strategy of NECTAR is that improvements in the approach to medical education at the medical student and post graduate levels, coupled with programs to improve faculty training and support and investments in novel educational models and technologies, will lead to improved capacity of UZCHS to meet the healthcare training and research capacity needs of Zimbabwe. The goals of NECTAR are to: (1) Increase the number and improve the proficiency of UZCHS medical graduates in PEPFAR priority areas. (2) Improve the retention of UZCHS graduates in Zimbabwe and increase the proportion of recent graduates who practice in Zimbabwe, serve as faculty at UZCHS, conduct research and are engaged in PEPFAR health priority areas. (3) Improve the recruitment and retention of academic faculty at UZCHS by transforming the UZCHS academic environment, creating new and sustainable educational and clinical partnerships and research opportunities.

Title: **QUIPU: The Andrean Global Health Informatics Research and Training Center**
P.I.: **Patricia Jannet Garcia**
Institution: **Universidad Peruana Cayetano Heredia**
Grant No.: **TW008438-03S2**
Award: **$10,000**

The overarching goal of this proposal is to establish the "QUIPU: Andean Global Health Informatics Research and Training Center," a center of excellence for training and research in global health informatics (GHI) to serve as a hub for addressing the national and regional needs for high-quality training in the Andean Region (AR) at a fraction of the cost of similar training programs in the U.S. The specific aims of the proposal are: 1. To develop and implement short-term and long-term training opportunities in GHI within the AR; 2. To engage emerging investigators in regionally pertinent research in health informatics and bioinformatics; and 3. To expand and consolidate a research network to link researchers in the AR, promoting south-south collaborations, as well as with colleagues from partner universities in the U.S. and other institutions. The Center will expand from the Universidad Peruana Cayetano Heredia (UPCH) and the U.S. Naval Medical Research Center Detachment (NMRCD) in Lima, Peru, two universities from the AR, the Universidad del Cauca (UCA) in Colombia and the Universidad Andina Simon Bolivar (UASB) in Ecuador, and the University of Washington (UW); who will work together as a Consortium to collaboratively implement QUIPU. The proposed program builds on existing and emerging collaborations between the four institutions, as well as a long-standing training-centered collaboration between UPCH and UW through NIH-Fogarty funded programs which allowed the development of a critical mass of trained researchers at UPCH and in Peru. We envision GHI as an umbrella for integrating health informatics and bioinformatics into clinical, biomedical and behavioral research issues that are key to advancing the health of populations in the AR and around the globe. The proposed program includes training and a research component. The training component will offer courses, two Certificate programs

(health informatics and bioinformatics), as well as Masters and PhD programs for advanced students. We plan to offer 12 scholarships for short courses, 11 for Certificates, 14 for Masters and 2 for PhD degrees during the 5-year grant. Candidates will be selected from Andean countries with a focus on Colombia, Ecuador and Peru. Video conferences and internet-based courses will be used to expand availability to a broader pool of students. The component for research in health informatics will strengthen NIH and non-NIH funded research conducted in the region, by providing competitive research awards, opportunities within already established research projects, and links to other researchers within the networks of collaborating institutions, including a regional research conference.

Title: **Training Program on Operational and Health Services Research for Malaria in Mali**
P.I.: **Peter J. Winch**
Institution: **Johns Hopkins University**
Grant No.: **TW008652-02S1**
Award: **$16,743**

The training program's main aim will be to strengthen current malaria prevention and control efforts in Mali by providing training in Mali in relevant research and evaluation skills. A secondary aim will be to support public health graduate training in Mali at both the masters and doctoral levels. Each year during the first three years of the training program, two trainers will spend two months at the JHSPH, take two or three courses, and develop the detailed training curriculum for a course they will offer upon their return to Mali. One 5 to 10 day course on malaria prevention and control will be organized each year for approximately 25 participants. Participants will be drawn from Ministry of Health personnel and personnel working in control projects implemented by UNICEF, NGOs or other organizations. The Department of Public Health of the University of Bamako is initiating a 2-year Masters in Public Health Program during the 2009-2010 academic years. This training grant will support a first cohort of 5 students then 3 subsequent cohorts of 3 students per year. On-going collaboration with the Malaria Research and Training Center provides opportunities for students to be exposed to malaria research, and to carry out their field placements at MRTC field sites and laboratories. Two students will be supported to carry out doctoral studies at DPH during Years 3 to 5 of the training grants. Students will be recruited from among the first 5 students to complete the MPH, and students with MPH from other universities. During the fourth and fifth years of the training grant, the students will spend one term each year at JHSPH taking additional courses not offered at DPH and getting input from JHSPH faculty on their dissertation research.

Title: **The Universidade Eduardo Mondlane/University of California, San Diego Medical Education Partnership**
P.I.: **Emilia Virginia Noormahomed**
Institution: **Eduardo Mondlane University**
Grant No.: **TW008908-02**
Award: **$60,000**

Although the development of new curriculum and of new educational approaches has had a profound impact on medical education around the world, the biggest challenge to medical education in many sub-Saharan Africa countries continues to be that there are too few medical educators and that the institutions in which they teach are so poorly supported that they cannot fully apply their considerable skills and energy to medical education. Thus, the overriding goal of the Universidade Eduardo Mondlane-UCSD Medical Education Partnership is substantially increase the number of highly skilled medical school faculty in Mozambique. We will emphasize the development of a powerful but locally sustainable biomedical informatics infrastructure to enhance both teaching and learning. By strengthening the infrastructure for clinical, operational and epidemiological

research we will both provide additional avenues for faculty development and greatly enhance institutional stability. A major priority of this collaboration is to recruit trainees and junior faculty into lifelong careers in medical education and to provide them with the skills to make these careers sustainable. To this end, we will develop early and mid-career mentoring programs that are tailored to the goals of individual Mozambican faculty and trainees as well as to the needs of the UEM Faculty of Medicine. Although the partnership will be anchored in Mozambique by the Universidade Eduardo Mondlane, as the program develops we will provide active assistance to Mozambique's two new medical schools in Nampula and Tete to create a network of all three of Mozambique's publicly funded Faculties of Medicine in order to extend the impact of this MEPI to all of Mozambique. By substantially strengthening Mozambique's medical education infrastructure, we expect that our partnership will have a profound effect on Mozambique's ability to deliver better medical care to all of its citizens for the next several decades.

Title: **Vanderbilt University-CIDRZ AIDS International Training and Research Program**
P.I.: **Sten H. Vermund**
Institution: **Vanderbilt University Medical Center**
Grant No.: **TW001035-13**
Award: **$20,000**

The Vanderbilt University (VU) Center for Infectious Disease Research in Zambia (CIDRZ) AITRP, formerly the VU-University of Alabama at Birmingham AITRP, seeks renewal of its grant, now in its tenth year due to an NIH-initiated one-year extension. We contribute research training to both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care. The VU-CIDRZ training partnership with our international collaborators is designed to train foreign scientists and key research support staff to conduct independent research and training in their home countries, as well as perform at an internationally credible level in collaborations with local and foreign scientists. We now seek to renew our AITRP with a continued focus on Zambia (since 1998), Pakistan (since 1994), India (since 2000), China (since 2000), and our newest partnership in Mozambique (VU training partnership since 2006 and developmental AITRP engagement since 2007). We have completed our older training commitments in Mongolia, Jamaica, and Russia and will complete our training commitments for Bangladesh upon the graduation of a current doctoral training (anticipated in 2011). We have restricted our AITRP training partnerships to five focus cities in order not to dilute our impact to where we have funded overseas research and strong research training partners. At the same time, we have leveraged support in each of the five venues such that our AITRP resources will go much further than permitted by the grant's funding alone. We will continue to provide a diverse portfolio of long, medium, and short-term training options. To date 58 trainees have received graduate degrees, 97% of whom have returned to work in their home countries, 8 are currently in degree programs and over 2,000 have been trained through our in-country advanced short-courses. We believe VU remains an ideal university partner for this initiative for several significant reasons.The migration of the training program to VU offers the opportunity for trainees to receive the absolute highest quality of graduate training and exposure to innovative HIV/AIDS/STD/TB related research, resources, and faculty mentors. The program is uniquely positioned within the infrastructure of the VU Institute for Global Health (VU IGH),directed by Dr. Vermund with its "center-without-walls" philosophy that nurtures noncompetitive partnerships among and within VU and with partner institutions around the globe. We feel that the innovative features of our renewal and our proven track record address the unmet needs in international AIDS training.

Title: **Weight, Diet, Genes, and CVD Risk Factors (Hypertension and Diabetes)**
P.I.: **Nanette Requintina Lee**
Institution: **University of San Carlos**
Grant No.: **TW008288-03**
Award: **$50,000**

Cardiovascular diseases (CVD) are the leading causes of morbidity and mortality in the world (1-3). Hypertension and diabetes, two of the major CVD risk factors, are complex diseases caused by the combined actions of genetic and environmental factors (4-8). Few studies have examined the interaction of these factors and fewer, if any, have looked at their effects in populations of developing Asian countries that are plagued with increasing levels of obesity and rapidly changing food environments (9, 10). The information gap may be due to the lack of population-based studies with adequate depth and detail. There is a paucity of information on dietary and adiposity trends derived from longitudinal studies and there are inadequate genetic data, especially among Asians who tend to develop CVD risk factors at lower body mass index thresholds (11, 12). Aims and Methods: The proposed study aims to understand how weight history, dietary patterns, and genetic variants independently and jointly affect blood pressure and fasting glucose among adult Filipino women (ages 38 to 71 yr in 2007) using the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing community-based study of over 2000 women (and their infants) which began in 1983. This is a unique dataset that contains not only rich genetic information on these women but also dietary and anthropometric measurements obtained since baseline, recent blood pressure (1998-2007) and fasting glucose (2005) measurements, and other individual-, household-, and community-level data collected over a span of 24 years of rapid country-wide socio-economic changes. Specifically, using multivariate regression methods we will determine the: (a) effect of weight history (i.e. duration of overweight) on the risk of having hypertension and/or diabetes; (b) association between dietary patterns (identified through cluster analysis) and hypertension and/or diabetes; (c) independence and co-occurrence of hypertension and diabetes and how these relate to weight and dietary patterns; and (d) effects of genetic variants on hypertension and diabetes, focusing on gene variants that have been associated with hypertension or diabetes by previous association studies. Further, the study will explore significant interaction of effects among genetic variants, overweight history and dietary patterns in affecting hypertension or diabetes.

National Center for Complementary and Alternative Medicine

Title: **Acupuncture for Aromatase Inhibitor-Related Arthralgias in Breast Cancer Patients**
P.I.: **Dawn Hershman**
Institution: **Columbia University Health Sciences**
Grant No.: **AT006376-01**
Award: **$200,000**

Third generation aromatase inhibitors have been shown to be superior to tamoxifen in improving disease free survival, decreasing distant and local recurrence rates and decreasing incidence of contra-lateral breast cancer in women with early stage hormone receptor positive breast cancer. However, up to 50% of women on AI report symptoms of debilitating musculoskeletal pain and joint arthralgia that can lead to noncompliance and early discontinuation, thereby impacting survival. Our previous phase II randomized study (n=40) showed that acupuncture administered twice weekly for 6 weeks compare to sham acupuncture improve AI induced joint pain/stiffness as measured by modified Brief Pain Index short form (mBPI-sf) worse pain score by 50%. The proposed phase III randomized, sham controlled, blinded, multi-centered clinical trial will look at the effects of acupuncture on joint pain/stiffness that started or increased since initiation of AI in 200 women with Stage I-III breast cancer. Women will be recruited from four

institutions and randomized to either true acupuncture or sham acupuncture administered twice weekly for 6 weeks follow by maintenance weekly acupuncture or sham acupuncture for 6 weeks. True acupuncture sessions will consists of standardized full body and joint specific point prescription and the NADA auricular protocol. The sham acupuncture treatment will consist of superficial needling at full body and joint specific point prescriptions that do not correspond to any true acupuncture points. The primary hypothesis is that acupuncture administered twice weekly for 6 weeks then weekly for 6 weeks will reduce joint pain/stiffness in women with AI induced arthragia as measured by mBPI-SF scores at 6 weeks compared to sham acupuncture. Secondary endpoints will assess whether weekly maintenance true acupuncture from week 6 to week 12 will maintain the effects seen at week 6 as measured by mBPI-SF score at 12 weeks and whether true acupuncture will have a durable effect as measure by mBPI-SF score at 24 weeks, compared to sham acupuncture. Other secondary endpoint (to be evaluated at baseline, 6, 12 and 24 weeks) include 1) additional assessment of joint pain/stiffness and functional status via self administered questionnaires (Western Ontario and McMaster Universities Osteoarthritis (WOMAC), Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) and Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International criteria (OMERACT-OARSI), 2) quality of life assessment via the self administered questionnaire Functional Assessment of Cancer Therapy—Breast/Endocrine subscale (FACT-B/ES), 3) analgesic use, 4) functional testing (grip strength and "'timed get up and go' for lower extremity") and 5) exploratory hormonal and inflammatory biomarkers. This study will be the first large multi-center center intervention trial looking at the effects of acupuncture on AI induced arthragia in women with breast cancer.

Title: **Identification of Novel Phytoprogestins from Hops and Red Clover**
P.I.: **Joanna E. Burdette**
Institution: **University of Illinois**
Grant No.: **AT005377-02**
Award: **$194,287**

Hormone replacement therapy (HRT) is the most commonly prescribed medication for the alleviation of menopausal symptoms. Unopposed estrogen replacement therapy increases the risk of developing endometrial cancer by 120% for every 5 years of use. To eliminate this risk in women with a uterus, the addition of progesterone to HRT in the form of combined estrogen/progesterone replacement has been implemented. Considerable evidence now indicates that the addition of synthetic progestins to HRT increases the risk of breast cancer as well as many other deleterious side effects. In response to the problems associated with HRT, millions of women are exploring the use of botanicals and dietary supplements for the alleviation of climacteric symptoms. However, the use of botanicals with only plant-derived estrogens in the absence of progestins might increase the risk for developing endometrial cancer similar to estrogen alone. Two common supplements, hops and red clover, contain phytoestrogens that bind and activate estrogen receptors. Interestingly, when hops and red clover are given orally to ovariectomized rats, uterine weights are not significantly increased in animals treated with a crude extract but are significantly increased in animals given an equivalent dose of the pure phytoestrogen. The hypothesis of this grant proposal is that selective natural progesterone compounds can be identified from botanical extracts to generate a combined phytoestrogen-phytoprogestin alternative to traditional hormone replacement therapy. The presence of both estrogen and progesterone receptor agonists in one botanical extract may provide both the benefits of estrogens for alleviation of menopausal symptoms and the progesterone necessary to combat formation of uterine cancers. Selective and safer progestins might also be identified from botanical sources improving the overall behavior of the progestin used in HRT. In order to provide support for this hypothesis the following specific aims are proposed: Aim 1. Do botanical extracts contain phytoprogestins and what are the pure compounds responsible for the progesterone-like activity? Aim 2. Are phytoprogestins specific and selective for uterine progesterone receptors? Aim 3. Are

phytoprogestins protective against uterine hyperplasia in an ovariectomized rat model? These studies will provide a clear justification for the use of botanicals that have the possibility of providing both estrogen and progestin-like activity but with more selective and safer profiles for the treatment of menopausal symptoms. Women are already taking phytoestrogens for menopausal symptoms, and incorporation of progestins may prevent hyperplasia and cancer of the uterus.

Office of the Director, Division of Program Coordination, Planning, and Strategic Initiatives

Title: **Emotions Are Emergent Events Constrained by Affective and Conceptual Processes**
P.I.: **Lisa Feldman Barrett**
Institution: **Northeastern University**
Grant No.: **OD003312-05**
Award: **$192,431**

Emotional states are central to mental and physical health. NIH invests tremendous resources in research on emotion, much of it devoted to animal models. Ironically, this research is guided by a scientific paradigm that is grounded in human experience. People experience fear and see it in others, so scientists assume there must be a literal (modular) neural circuit for fear in the mammalian brain. Rats freeze when they hear a tone paired with a foot shock, so they are presumed to be in a state of fear (versus surprise, anger, or even a general state of alarm) and undergoing 'fear learning.' Scientists also presume that a map of the neural circuitry of freezing behavior will yield a neural mechanism for fear that is largely preserved in humans, and a decade of neuroimaging studies have focused on locating a homologous neural circuit in the human brain. In the last five years, I have traced the roots of this 'natural kind' model, conducted a comprehensive review of the literature to examine its veracity, and found it wanting (Barrett, 2006a).1 In response, I have fashioned a new systems-level model, called the Conceptual Act Model, grounded in the neuroanatomy of the human brain. My model parsimoniously incorporates neuroscience findings from rats, primates, and humans, and explains the mechanisms that produce the range and variety of behavioral and introspective instances that we call 'emotion' (Barrett, b, c; Barrett, Mesquita, Ochsner, & Gross, 2007; Barrett, Ochsner, & Gross, 2007; Duncan & Barrett, 2007). The Conceptual Act Model asks different—and perhaps better—questions about what emotions are and how they function in mental and physical health. The NIH Director's Pioneer Award will allow me the intellectual freedom and resources to continue building evidence for the Conceptual Act Model of emotion, thereby shaping a new paradigm to guide the scientific study of emotion.

APPENDIX B

ORWH-Cofunded Research Summaries, FY 2012

National Cancer Institute

Title: **Assisted Reproductive Technology and Risk of Childhood Cancer**
P.I.: **Barbara Joan Luke**
Institution: **Michigan State University**
Grant No.: **CA151973-02**
Award: **$18,750**

Use of assisted reproductive technology (ART) has risen steadily in the United States during the past two decades due to several reasons, including childbearing at older maternal ages and increasing insurance coverage. Studies have reported significantly higher risks of adverse perinatal outcomes in assisted—versus spontaneous—conception pregnancies, including an excess of prematurity, low birthweight, and birth defects. ART and/or infertility may influence the incidence of other conditions with prenatal origins, such as childhood cancer. In addition, the prevalence of imprinting disorders such as Beckwith-Wiedemann and Angelman syndromes is elevated among children conceived by ART; some of these disorders, in turn, drastically raise the risk of several embryonal cancers that occur in early childhood. Several cohort, case-control, and case-series studies of assisted reproduction and childhood cancer have reported null results, although all were limited by small sample size and could not differentiate specific cancer types. One study that focused specifically on hepatoblastoma found that use of infertility treatment or assisted reproduction was associated with a nine-fold increased risk of disease. Using the resources of the Society for Assisted Reproductive Technology (SART) and the birth and cancer registries in 20 States and New York City, we propose to conduct the largest study to date of ART and childhood cancer risk. SART maintains an ongoing national database of programs that provide ART services in the United States as mandated by the federal Fertility Success Rate and Certification Act of 1992 [PL 102-493]. As of 2006, the latest year of data available, this included comprehensive data (including identifiers sufficient for linkage) on 138,198 ART cycles from 483 clinics resulting in 41,343 pregnancies and 54,656 infants for a single year. We propose to link the data from the SART database from 2004-2013 to the birth and cancer registries of 20 states and New York City, including the five states with the highest numbers of ART births (California, New York, Illinois, New Jersey, and Massachusetts), to create a cohort of approximately 30 million children, including over 467,000 conceived by ART to evaluate the association between assisted reproduction and the risk for childhood cancer. The specific aim of this study is to compare the incidence of childhood cancer in children with assisted conception to that in the general population.

Title: **Bedside to Bench—Molecular Epidemiology of Postpartum Involution of the Breast: Demonstration of Tools for Understanding Influences of Pregnancy on Breast Cancer Risk**
P.I.: **Mark Sherman**
Institution: **City of Hope**
Award: **$90,000**

Experimental and observational data implicate postpartum breast remodeling in the pathogenesis of early onset aggressive breast cancers (reviewed, J Mammary Gland Biol Neopl June 2009), a disease that disproportionately affects African Americans. Recent studies of animal models suggest that an inflammatory wound response related to remodeling promotes progression of in-situ to invasive cancer, and that this effect can be blocked by anti-inflammatory drugs (Nat Med 2011). In addition, our collaborator, Dr. Kathleen Arcaro, has developed immunomagnetic

methods to isolate epithelial cells shed in milk and assess DNA methylation of tumor suppressor genes involved in breast cancer. Using this technique, she has preliminarily demonstrated detection of pregnancy associated breast cancers (AACR 2011).

This proposal would refine tools for studying women through the early postpartum period to understand the effects of pregnancy and lactation on the breast. These tools will include novel methods of sampling breast epithelial cells shed in milk and MRI imaging. We will preliminarily explore hypotheses related to specific candidate mechanisms and biomarkers that have been implicated in postpartum re-modeling or may predict breast cancer risk by comparing data from lower risk uniparous women, defined as younger or White, as compared to higher risk women, defined as older or African American. Bench aims will include: improved milk collection, fractionation and optimization of milk assays, including DNA methylation analysis and measurement of hormonal and inflammatory markers. Bedside aims include: collection of milk at two time points to assess molecular markers for comparison over time within subjects, and between subjects, stratified by race and age, and to assess a subset of the same subjects during this period by MRI at the NIH Clinical Center.

To pursue our aims, we will leverage a unique collaboration between CCR, extramural collaborators and NCI/DCEG investigators with broad interests in breast biology and cancer. The proposed collaboration will include: 1) Jane Balkam, R.N., Ph.D., an expert lactation consultant with the NIH Work Life program; 2) David Bluemke, M.D., Ph.D., Chief of Radiology at NIH who will develop MRI studies; 3) Kathleen Arcaro, Ph.D., a laboratory scientist at the University of Massachusetts who has developed methods to isolate epithelial cells from milk for analysis of DNA methylation in tumor suppressor genes and will work with Dr. Sherman to optimize fractionation and assays and 5) DCEG investigators with interests in breast cancer epidemiology, including early life events, genetics, breast density, hormones and molecular pathology. Dr. Hewitt will work with Dr. Sherman to prepare cells for pathologic analysis, Dr. Faupel-Badger will evaluate hormone assay data, Dr. Gierach will interpret MRI data and provide epidemiological expertise and Dr. Meeker will perform telomere assays. Dr. Sherman will serve as PI and will lead the project, as well as providing expertise related to breast biology, pathology and molecular epidemiology. Dr. Arcaro, as extramural PI, will provide unique expertise on milk processing and performing DNA methylation assays on cells shed in milk.

Title: **California Health Interview Survey**
P.I.: **David Grant**
Institution: **University of California, Los Angeles**
Grant No.: **N261200544000C**
Award: **$200,000**

California Health Interview Survey (The California Health Interview Survey (CHIS) is the largest and most comprehensive state health survey in the U.S. It provides valid local and state estimates for California. Conducted by telephone in English, Spanish, Chinese, Korean and Vietnamese, CHIS interviews a representative sample of over 40,000 adults in California households. Since its inception in 2001, NCI has supported cancer control items on CHIS, and ORWH provided funding for FY12. CHIS data are publicly released. CHIS data are widely accessible to policy makers, stakeholders and researchers via the AskCHIS calculator, public use data, and micro-data files (http://www.chis.ucla.edu/).

Title: **DCEG/EBP Intramural—Follow-up of DES Cohorts**
P.I.: **Jessica Mills**
Institution: **Boston University**
Grant No.: **261201000128C*3**
Award: **$18,750**

Since 1992, DCEG and other NCI investigators, along with collaborators from five field study centers, have been actively following diethylstilbestrol (DES) exposed and unexposed mothers, daughters and sons, and granddaughters for adverse health effects resulting from this exposure. As DES-exposed offspring are currently reaching the age when cancer rates begin to rise, it is important to continue to monitor long-term risk of cancer and other adverse health outcomes in this unique population. The study also provides a model for assessing a number of hypotheses that address concerns about prenatal hormonal influences on disease risk, both an intriguing area of science and an increasingly controversial environmental issue that affects a substantial proportion of the population.

To date the study has identified excess female breast cancer after age 40 that shows a dose-response effect, as well as increased risk for high-grade lesions of the cervix and vagina. Concern over other hormone-related cancers remains; though to date analyses have been limited due to small numbers of cases. In the sons, investigators observed an excess risk for urogenital anomalies and infertility, and a likely excess of testicular cancer. To examine the effects in the third generation (the daughters of the prenatally exposed daughters), investigators assembled a small cohort in 2000. Given their average age, there have been few relevant disease outcomes. However, investigators noted an elevated risk for infertility—though not statistically significant, this outcome was also seen in DES-daughters. In addition, there were three cases of ovarian cancer in the granddaughters, even though substantially less than one had been expected. While both of these observations remain difficult to interpret, they have added some urgency to expand the cohort and continue to follow-up.

Since 1992, DCEG and other NCI investigators, along with collaborators from five field study centers, have been actively following diethylstilbestrol (DES) exposed and unexposed mothers, daughters and sons, and granddaughters for adverse health effects resulting from this exposure. As DES-exposed offspring are currently reaching the age when cancer rates begin to rise, it is important to continue to monitor long-term risk of cancer and other adverse health outcomes in this unique population. The study also provides a model for assessing a number of hypotheses that address concerns about prenatal hormonal influences on disease risk, both an intriguing area of science and an increasingly controversial environmental issue that affects a substantial proportion of the population.

To date the study has identified excess female breast cancer after age 40 that shows a dose-response effect, as well as increased risk for high-grade lesions of the cervix and vagina. Concern over other hormone-related cancers remains; though to date analyses have been limited due to small numbers of cases. In the sons, investigators observed an excess risk for urogenital anomalies and infertility, and a likely excess of testicular cancer. To examine the effects in the third generation (the daughters of the prenatally exposed daughters), investigators assembled a small cohort in 2000. Given their average age, there have been few relevant disease outcomes. However, investigators noted an elevated risk for infertility—though not statistically significant, this outcome was also seen in DES-daughters. In addition, there were three cases of ovarian cancer in the granddaughters, even though substantially less than one had been expected. While both of these observations remain difficult to interpret, they have added some urgency to expand the cohort and continue to follow-up.

Title: **Definition of Microenvironment in Breast Cancer**
P.I.: **Mina Jahan Bissell**
Institution: **University of California, Berkeley, Lawrene Berkeley National Laboratory**
Grant No.: **CA064786-17**
Award: **$18,750**

One of the earliest manifestations of malignant progression is loss of tissue organization. This proposal continues to examine the hypothesis that architectural integrity is crucial for maintenance of normal breast function as well as for suppression of neoplasia. We have postulated that elucidation of a "signaling integration plan" that establishes and maintains polarity and structure within the acini and ducts of breast tissue will uncover prognostic and therapeutically-relevant markers of intermediary steps in malignancy. As such, we postulated and provided evidence that myoepithelial cells (MEPs) provide crucial structural and functional cues to luminal epithelial cells (LEPs) partly via production of, and signaling through, laminin-111 (Ln-1). We further postulated, and now provide additional evidence, that in traditional cell culture conditions, purified LEPs almost immediately develop a hybrid LEP/MEP phenotype acquiring aspects of MEP gene expression and in particular developing the tumor suppressor functions normally conferred in vivo by MEPs and an ability to make acini, which normally requires the presence of MEPs. Consequently, in order to make relevant models for the study of human LEP-MEP interactions we must identify the conditions that instruct these cell types to retain their original functions. Accordingly, we have developed new and versatile microenvironmental arrays (MEArrays) to probe how MEPs and LEPs become, and remain, determined. We now propose to expand our findings in 3 specific aims. We will specifically: 1- identify pathways that allow retention of MEP- and LEP- specific functions in culture using designer MEArrays and designer media. We then could probe the importance of desmosomal proteins and other regulatory molecules in addition to Ln-1 produced by MEPs, in how MEPs and LEPs interact to retain polarity, architecture and function. 2- complete the identification of Ln-1 signaling cascade components for mammary specific functions using inhibitory peptides, blocking antibodies, mutant cells and shRNA ablation in high throughput assays using Cellomics and other devices and designer 3D microenvironments. 3- identify and characterize central players and connections in the 'signaling integration plan' for structural integrity of acini using bioinformatics analysis of gene expression arrays, genome-wide methylation profiles and other changes in chromatin structure, identification of miRNAs affecting cellular architecture, and by positioning the new genes we identified using a unique 3D screen, on our integration map. Collectively these experiments address the importance of MEP/LEP interactions in maintenance of polar acinar structures in breast tissue, and could also provide a proof of principle for other tissues. Since loss of appropriate balance and/or integration of these signals leads to malignancy, our results will both advance fundamental knowledge and yield novel markers for early diagnosis and therapeutic strategies to limit and/or reverse breast tumor progression.

Title: **Feasibility of Community-Based Tampon Self-Sampling to Prevent Cervical Cancer**
P.I.: **Elizabeth H. Fontham**
Institution: **Louisiana State University Health Sciences Center New Orleans**
Grant No.: **CA157263-01A1**
Award: **$200,000**

Medically underserved women are generally at higher risk for many health problems including cervical cancer. Solutions can often be found by utilizing resources within the community. An academic-community partnership has been formed to develop a novel approach to screening for cervical cancer. High risk types of human papillomavirus (HPV), 16, 18 and others, are etiologically linked to cervical cancer. HPV can be detected from samples obtained from self-swabbing of the vagina, urine testing, or insertion of tampons. These methods could be performed in

the community or at home by women, which is useful for the group of women not visiting the gynecologist to receive recommended testing. This study will compare the effectiveness of home-based self sampling screening for cervical cancer with conventional Pap testing in a community-based setting. Given the ease of home use, it is hypothesized that home-based tampon testing for HPV DNA will be equal or superior to the annual Pap testing. For such home sampling to be effective, it must be: (1) used at least as much as current referral rates to the gynecologist; (2) acceptable to the woman as a means to prevent cervical cancer; (3) able to be performed at home; and (4) able to identify those women at risk for developing cervical cancer. The specific aims of this project are to: compare compliance with a home-sampling tampon HPV test to compliance with clinic Pap testing; assess a high risk population's acceptance of home use of a tampon for HPV testing in general and compared to traditional clinically administered Pap testing; assess a high risk population's ability to correctly follow instructions for home tampon sampling for HPV testing; and assess the accuracy of the home administered tampon HPV results. In order to achieve these aims, a group of women will be asked to administer the tampon sampling at home and return via mail. Another group will have conventional Pap testing for comparison. Surveys of satisfaction will also be conducted.

Title: **Feasibility of Virtual Agent Cervical Cancer Education for Hispanic Farmworkers**
P.I.: **Kristen Jennifer Wells**
Institution: **University of South Florida**
Grant No.: **CA167418-01A1**
Award: **$100,000**

Latinas experience higher cervical cancer (CC) incidence and mortality when compared to the general population in the United States. Many Latinas lack access to health care and experience literacy, communication, and knowledge barriers that prevent them from obtaining CC screening. Patient navigator (PN) and other similar interventions have been implemented to increase CC screening rates; however, few have focused directly on the needs of Latinas. Interactive technological interventions, like embodied conversational agents (ECA), are currently used in other populations, settings, and for other health topics, but no known initiative has used culturally and literacy appropriate technology to deliver Spanish-language CC education as part of a PN intervention. This study aims to create and conduct a preliminary evaluation of a Spanish-language Virtual Patient Educator (VPE) multimedia application to augment a PN intervention for increasing CC screening rates among Latinas in a rural agricultural community. Using the Social Cognitive Theory, the proposed project will be conducted in 2 phases. In Phase 1, the research team will engage community members to develop a low literacy Spanish-language interactive multimedia application consisting of an ECA. Using theoretical principles and drawing from our formative research, the project team will design the VPE through systematic and technical processes. Ongoing feedback (usability testing) from members of the intended audience will be carried out to ensure that patients (users) can perform intended system tasks efficiently, effectively, and satisfactoril. Once usability testing is complete, a series of learner verification interviews will be conducted t assess initial suitability of the VPE. Since the VPE will be the first known Spanish-language ECA used to augment a PN intervention, it is important to see whether patients accept the VPE and whether it is feasible to conduct a study of patient navigation augmented by the VPE. In Phase 2, a preliminary evaluation of 2 methods of patient navigation delivery (with and without VPE) will be conducted with 60 participants who are not up to date with recommended CC screening according to American College of Gynecologists and Obstetricians' guidelines. Cluster randomization will be used to randomize patients to 1 of 2 PN intervention conditions: (1) PN; or (2) PN plus VPE (PN+VPE) using date of clinic as unit of randomization. The preliminary evaluation will examine the feasibility of recruitment, randomization, data collection, and acceptability of VPE application. Exploratory data will also be collected regarding the potential impact of PN+VPE on behavioral capacity and self-efficacy

for obtaining CC screening, Pap test adherence, and satisfaction with care. The proposed project will advance our research towards the development of interactive technology interventions to disseminate health education to disparate populations.

Title: **HPV Vaccine Development and Evaluation**
P.I.: **Allan Hildesheim**
Institution: **NCI Intramural Division of Cancer Epidemiology and Genetics Research Project**
Grant No.: **N261200100007**
Award: **$400,000**

ORWH has collaborated with the NCI on the development and evaluation of the prophylactic virus-like particle (VLP) human papillomavirus (HPV) vaccine that was discovered by investigators at the NCI. In the late 1990s, ORWH supported efforts to conduct animal studies and an early phase I human trial in the United States that were critical to demonstrating the potential for this vaccine. Subsequently, ORWH supported the multiyear, community-based randomized, phase III trial of the HPV vaccine conducted by NCI in Costa Rica. This is the only publically funded trial of an HPV vaccine. Results from the study in Costa Rica, which is ongoing, have shown that 1) the vaccine is highly effective at preventing new infections with HPV types 16 or 18, 2) the vaccine confers partial protection against HPV types phylogenetically related to HPV 16 or 18, 3) the vaccine does not help treat existing infections, 4) fewer than 3 doses of the vaccine protects as well as the full 3-dose series for at least 4 years, 5) levels of antibodies achieved long-term following two doses (0 and 6 months) of the HPV vaccine are high and only slightly lower than those observed after three doses of the vaccine, likely explaining why fewer than three doses provided a high degree of protection , 6) the vaccine protects against HPV infection at the anus, 7) the vaccine protects against HPV infection in the oral cavity, 8) vaccine impact declines with increasing age at vaccination, 9) vaccination induces cross-neutralizing potential in sera of vaccinated individuals, and 10) modest levels of antibodies generated by natural HPV infection provide partial protection against re-infection. Efforts in Costa Rica are ongoing and completion of 10 years of follow-up of trial participants is expected within the next 4-5 years so that long-term effects of the vaccine (efficacy, safety and immunogenicity) can be fully evaluated. During the FY11-FY12 period, ORWH support enabled expansion of the work in Costa Rica to include 1) an assessment of vaccine efficacy at sites other than the cervix (anus and oral cavity) and 2) investigation of the immunological mechanisms/parameters that might explain why this vaccine is effective even when fewer than the recommended three doses are administered and against HPV types not included in the vaccine formulation.

Title: **International Pooling Project of Mammographic Density**
P.I.: **Valerie McCormack**
Institution: **International Agency for Research on Cancer**
Grant No.: **CA167771-01**
Award: **$49,267**

Women with a high percentage of fibroglandular tissue in their breast, as opposed to fatty tissue, have an increased breast cancer risk (up to 5-fold higher) in the subsequent 10 or more years. This attribute, known as mammographic density (MD), varies between women and can change within the same woman over time. Having both genetic and environmental determinants, between-country differences in MD may account for the over 6-fold international variations in breast cancer incidence rates. Only one study has investigated this to date, i.e. a US/Hawaii/Japanese comparison (Maskarinec et al. 2007). We aim to initiate a more widespread International Pooling Project of Mammographic Density to: (i) pool and obtain standardised comparable data on MD from countries spanning the breast cancer incidence range; (ii) describe international variations in overall and age-specific MD distributions and assess whether they

are explained by individual-level risk factors for MD; (iii) quantify the extent to which international variations in MD correlated with corresponding breast cancer incidence rates and Pike's proposed model of breast tissue ageing; (iv) assess a range of MD metrics (absolute/relative/age-specific/cumulative); (v) continue and expand this pooled resource into the future. The International Pooling Project of Mammographic Density would be the first such initiative for MD, which could later be expanded to include new methods of MD measurement, imaging modalities and a broader range of determinants. Being led by the International Agency for Research on Cancer, we emphasize an international perspective for this marker, especially urgent as breast cancer is now the most common cancer in women in almost every country worldwide. If MD does underpin international variations in breast cancer incidence, the monitoring of MD-distributions would become an important early indicator of changes in breast cancer risk.

Title: **Low-Dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction**
P.I.: **Melanie R. Palomares**
Institution: **Beckman Research Institute of City of Hope**
Grant No.: **CA140245-03**
Award: **$18,750**

Low-dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction Mantle radiation has been a cornerstone of HL treatment; however, female survivors of HL treated with mantle irradiation before age 30 have a 20- to 55-fold increased risk of developing breast cancer (BC)—a risk that is comparable to that of BRCA mutation carrierrs. Surgical prophylaxis is very effective in reducing the risk of BC, but such invasive strategies are not suitable for all women. Pharmacologic interventions exist, but only tamoxifen is approved for use in young women who have not yet reached menopause. Standard-dose tamoxifen (20 mg daily) is associated with undesirable side effects, but recent studies have laid convincing groundwork that tamoxifen at lower doses may be similarly efficacious in reducing BC risk with fewer side effects. We hypothesize that tamoxifen administered at a lower dose (5 mg daily) would be both an efficacious and safe non-surgical risk reduction intervention for female adult survivors of HL diagnosed during childhood or as a young adult. Thus, using a Phase IIb randomized, double-blind, placebo-controlled trial of low-dose tamoxifen (5 mg daily) in long-term female HL survivors treated with chest radiation, we aim to 1) Determine the impact of a two-year course of low-dose tamoxifen on well-established surrogate biomarkers of chemopreventive efficacy; 2) Establish the safety and tolerability of low-dose tamoxifen in this population; and, as an exploratory aim, 3) Examine the modifying effect of several well-defined demographic and clinical characteristics associated with radiation-related BC risk on the risk:benefit ratio from this intervention. Eligible subjects who provide informed consent will be randomized to 5 mg per day of tamoxifen versus placebo for two years. Outcomes will include several surrogate biomarkers of efficacy, including mammographic breast density (MBD, primary endpoint), breast cytomorphologic and proliferation measures, and insulin growth factors. Subjects will be carefully followed for safety and tolerability using patient-reported outcomes as well as lipid profiles, clotting factors, and markers of bone turnover as objective endpoints. Risk modifiers that will be examined include age, menopausal status, prior hormone use, body mass index, personal history of benign breast disease, and family history of cancer, as well as chest radiation dose, age at exposure, and latency from chest radiation. A sample size of 127 per arm will be able to detect a 20% reduction in MBD with low-dose tamoxifen relative to placebo with 80% power. We have identified over 900 potentially eligible subjects within our consortium of five institutions that have well-developed infrastructure to follow childhood cancer survivors long-term, thus demonstrating that we will have a sufficiently sized pool to draw the eligible patient population from and complete the study. At completion of this study, we hope to identify a well-tolerated risk reduction option for HL survivors that are at high risk for developing BC. Low-dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction Public Health Relevance: Survival from

Hodgkin lymphoma (HL) is excellent, but chest radiotherapy (RT) has been a cornerstone of treatment, and women with HL exposed to chest RT when they are young have a 20- to 55-fold increased risk of developing breast cancer (BC). Tamoxifen reduces the risk of BC by 50%, but at the cost of some undesirable side effects, while more recent studies suggest that lower dose tamoxifen may be similarly efficacious in reducing BC risk with fewer side effects. We believe that tamoxifen administered at 5 mg daily would be an ideal non-surgical risk reduction intervention for female HL survivors exposed to chest RT at high risk for BC; therefore, we plan to test this hypothesis in a Phase IIb clinical trial.

Title: **Molecular Mechanisms of BRCA1-Dependent DNA Damage Response and Tumorigenesis**
P.I.: **Xiaochun Yu**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **CA132755-05S1**
Award: **$18,750**

BRCA1 is a nuclear polypeptide to suppress familial breast and ovarian cancers. Accumulated evidence suggests that BRCA1 participates in DNA damage response. However, the molecular mechanisms by which BRCA1 participates in DNA damage response remain elusive. Recently, we have identified two new BRCA1 partners, RAP80 and CCDC98. Both RAP80 and CCDC98 associate with BRCA1 BRCT domain and participate in DNA damage response. Functionally, RAP80 and CCDC98 facilitate BRCA1's translocation to DNA damage sites. To search for the signals that recruit this BRCA1 complex to the DNA damage lesions, we have found that BRCA1-associated protein RAP80 recognizes ubiquitinated histone H2A and H2B. And both histone H2A and H2B are further ubiquitinated following DNA damage. In addition, we have identified two biallelic missense mutations and one truncation mutation of RAP80 gene in breast and ovarian cancer cells, suggesting that RAP80 could be another breast and ovarian tumors suppressor in BRCA1-dependent pathway. Thus, we hypothesize that recognition of ubiquitinated histone by RAP80 is the molecular basis that loads BRCA1 to DNA damage sites, which regulates proper DNA damage response, protects genomic integrity and prevents breast and ovarian tumor development. We propose following experiments to examine our hypothesis. Aim1: To examine the molecular mechanism by which RAP80 and CCDC98 target BRCA1 to DNA damage lesions. Aim2: To examine the functional defects of RAP80 mutations in BRCA1-dependent DNA damage response. Aim3: To examine the role of RAP80 in tumor prevention. In summary, studies outlined here will not only reveal the molecular mechanism by which BRCA1 participates in DNA damage response, but also identify the functional partners of BRCA1 in tumor suppression.

Title: **National Longitudinal Mortality Study**
P.I.: **Paul Sorley (NHLBI)**
Institution: **NHLBI, NIA, NCI, and Centers for Disease Control and Prevention/National Center for Health Statistics, in collaboration with the U.S. Census Bureau**
Grant No.: **0081-1998-005**
Award: **$200,000**

The National Longitudinal Mortality Study (NLMS) database is a population-based resource for studies of relationships between lifestyle factors, socioeconomic status (SES) and mortality. Advantages of the NLMS database compared to other large prospective studies include annual enrollment of nationally representative household samples with self-reported socioeconomic status. The study is designed to yield a sample reflecting the national population with respect to race, ethnicity and SES with precise estimates through weighting to adjust for under-sampling. ORWH contributed FY 2012 funding to update NLMS matches to the National Death Index through 2010. The updated match is an opportunity to advance understanding of factors

affecting women's health and mortality experience in the United States. The NLMS Steering Committee includes representatives of three NIH Institutes: the National Heart Lung and Blood Institute, National Institute on Aging, and National Cancer Institute and CDC's National Center for Health Statistics and the Census Bureau. The Steering Committee facilitates research proposals from intramural and extramural investigators. More than 130 collaborators have used the dataset to publish over 70 journal articles in JAMA, British Medical Journal, Lancet, American Journal of Epidemiology, Archives of Internal Medicine, Cancer, Stroke, and the American Journal of Public Health. Articles have also been published in Demography, Ethnicity and Disease, Gender Medicine, Journal of Aging and Health, Journal of Health and Social Behavior, Journal of Rural Health, Psychological Medicine, and Social Science and Medicine.

Title: **P3K, Retroviral Oncogene, and Homolog of PI 3-Kinase**
P.I.: **Peter K. Vogt**
Institution: **Scripps Research Institute**
Grant No.: **CA078230-14**
Award: **$18,750**

The goal of this project is to achieve a molecular understanding of the oncogenicity of phosphatidylinositol 3-kinase (PI3K). The proposed work will use two basic approaches: (1) a genetic analysis of the oncogenic functions of p110¿, the catalytic subunit of PI3K, and (2) genome-wide interrogations for novel regulators and targets of PI3K. The genetic analysis will concentrate on the interactions between p110¿ and Ras as well as p110¿ and p85. These interactions are critical to the oncogenicity of p110¿; they are fundamentally changed in the cancer-specific gain-of-function mutants of p110¿. The p110¿ protein carrying cancer-specific mutations in the helical domain (E542K, E545K) has requirements for p85- and Ras-binding that are opposite to those of the kinase domain mutant (H1047R). The helical domain mutants depend on Ras-binding but are largely independent of p85-binding. The kinase domain mutant does not require Ras but needs p85 to be active. We plan to analyze mutants of p85 and of Ras in which specific functions are disabled for their ability to activate wild-type and mutant p110¿. This genetic analysis will advance our understanding of the molecular mechanisms by which cancer-specific mutations in p110¿ induce a gain-of-function and make the protein oncogenic. The genome-wide interrogations for regulators and targets will take advantage of two new technologies. (1) A screen of expression libraries in the yeast Saccharomyces cerevisiae. This is a lethality screen based on the fact that expression of PI3K is toxic to Saccharomyces cerevisiae. The observed growth defect can be rescued by the expression of negative regulators of PI3K. Using this screen, we have identified several novel suppressors of PI3K. We will characterize these regulators and define the signaling chains that connect them to PI3K. (2) The second technology is a kinome screen that uses the two universally conserved lysines in ATP pockets of kinases to tag ATP-binding proteins by covalent linkage to biotin. We have used this method to reveal PI3K-induced changes in the kinome and, during initial studies, have identified three growth-regulatory kinases that are differentially expressed in PI3K-transformed cells. The roles of these and additional PI3K targets identified by the kinome screen will be analyzed and determined.

Title: **PET-MRI for Assessing Treatment Response in Breast Cancer Clinical Trials**
P.I.: **Thomas E. Yankeelov**
Institution: **Vanderbilt University Medical Center**
Grant No.: **CA142565-03S1**
Award: **$18,750**

We propose to develop integrated high field (3T) magnetic resonance imaging (MRI) and positron emission tomography (PET) methods for assessing the effects of molecularly targeted anti-angiogenesis and cytoxic treatments in breast cancer clinical trials. Our goal is to provide the breast cancer community with practical data acquisition and analysis protocols that facilitate

the translation of advanced imaging technologies into patient management and clinical trials. Dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted MRI (DW-MRI) can report on vascular status, tissue volume fractions, and cellularity, while fluorodeoxythymidine PET (FLT-PET) can report on cell proliferation. We propose to combine these MRI and PET data to provide anatomical, physiological, and molecular assessments of the response of breast tumors to novel anti-angiogenic and cytoxic treatments in clinical trials. To accomplish these goals we will pursue the following specific aims: 1. We will develop high field breast MRI protocols that measure tissue cellularity and vascularity. We will then develop methods for the rigorous registration of these MRI measures with quantitative PET characterization of cell proliferation. We will develop the algorithms and software architecture necessary for synthesizing the imaging data with (traditional) clinical data to assisting in clinical decision making. 2. In an ongoing Phase II study we will employ DCE-MRI, DW-MRI, and FLT-PET to assess the degree of tumor response after one and two cycles of Carboplatin and nab-Paclitaxel with or without Vorinostat in HER2-negative primary operable breast cancer. 3. In our planned Phase II study we will employ DCE-MRI, DW-MRI, and FLT-PET to assess the degree of tumor response after one and two cycles of neoadjuvant cisplatin, paclitaxel and the TOI inhibitor everolimus in patients with triple negative breast tumors. As the anti-cancer agents employed in these clinical trials are implicated in apoptosis and/or inhibition of cellular proliferation and/or inhibition of angiogenesis, we hypothesize that changes in metrics of cellular proliferation and vascularity, when merged with traditional clinical biomarkers, will provide significantly more accurate predictions on patient response than traditional methods of tumor response including RECIST. RELEVANCE: We propose to develop integrated magnetic resonance imaging (MRI) and positron emission tomography (PET) methods for assessing the effects of molecularly targeted treatments in breast cancer clinical trials. We hypothesize that the synthesis of imaging metrics reporting on vascularity, cellularity, and cell proliferation will provide predictive measurements of tumor response to treatment in appropriately selected clinical trials. Our goal is to provide the breast cancer community with practical data acquisition and analysis protocols that facilitate the translation of advanced imaging technologies into patient management and clinical trials.

Title: **Pharmacotheraphy Evaluation Tools for Improving Breast Cancer Outcomes in Rural Appalachia**
P.I.: **Rajesh Balkrishnan**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **CA168479-01**
Award: **$200,000**

Access to effective breast cancer care is a critical factor in Appalachia contributing to health disparities among this population. Poor adherence to adjuvant cancer treatment has been reported to increase risk of death and associated with increased medical costs in breast cancer. Patient medication use behaviors are critical to the cancer heath disparities in Appalachia, and research on essential medication use and quality in rural areas is scant. Data suggests that designing an effective intervention targeting determinants of access to cancer care in Appalachia will provide patients an opportunity to receive appropriate medical treatment to alleviate disparity in cancer morbidity and mortality. The major impact of this study will be the production of a concrete intervention design aimed at reducing cancer health disparities in Appalachia by targeting modifiable contributors such as accessibility of medical care, quality and quantity of pharmacological treatment delivery, and adherence behaviors and their determinants. The purpose of this application includes an innovative approach to model accessibility to cancer care resource influences guiding appropriate treatment delivery and medication use behaviors (persistence and adherence to prescribed treatment), and how such factors impact cancer survival. Our central hypothesis is that patients who are able to access adequate medical care are more likely to receive standard treatments and persistently follow recommendations which lead to better

therapeutic outcomes (such as survival). The strategies proposed will address the following specific aims: 1) Assess the complexity of the relationship between access to cancer care resources and patient prescribed guideline appropriate for adjuvant cancer treatments, 2) Delineate the manner in which specific social, system-specific, and individual determinants of access to cancer care affect patient medication use behaviors of persistence and adherence, and 3) Model cancer survival as a function of patient and system specific dimensions of access to cancer care, prescribing guideline appropriate adjuvant treatment and medication use behaviors. This study will use a unique NCI-funded linked dataset of 7,566 patients with breast cancer assembled from cancer registries, Medicare and Medicaid Services (CMS) Medicare claims data, US Social Security Administration's Death Master File (DMF), American Medical Association (AMA) Master file for information on physician and practitioners, American Hospital Dictionary (AHD) for healthcare facility characteristics. We hypothesize that there are modifiable individual and health-system related factors that impact the patient's receipt of optimal pharmacological treatment. The rationale for the proposed study is that, once medication access and utilization factors to which disparity in cancer survival can be attributed, are identified and accurately modeled, effective interventions targeting influential factors for breast cancer survival can be developed and tested in the same population and adapted to other populations burdened with similar inequalities, resulting in reducing health disparity in Appalachia and other regions.

Title: **Research and Studies on the Effects of Inflammation in Gall Bladder Cancer**
P.I.: **Ann Hsing and Jill Koshiol**
Institution: **NCI Intramural Research Project**
Grant No.: **N26100003**
Award: **$200,000**

Gallbladder cancer is one of the few non-gynecological tumors known to occur with higher frequency in women than in men. The highest rates of this cancer (particularly in women) are observed in Chile. Investigators in the Infections and Immuno-epidemiology Branch (IIB) are evaluating the feasibility of conducting a case-control study of gallbladder cancer in Chile to better understand the causes of this disease. As currently envisioned, the initial pilot effort will define whether such a study would be successful at identifying and enrolling cancer cases, controls with gallstones (an important precursor for this cancer) and controls form the general population. We are working with well established investigators in the region with a proven track record of conducting epidemiological investigations to maximize the likelihood of success. A case-control study of gallbladder cancer in Chile would permit us to elucidate the role of obesity (and metabolic syndrome more generally), diet, infections, immunological responses, and genetic susceptibility factors in the etiology of this tumor. This study could have important public health implications, since cholecystectomies are currently being recommended for women for the prophylaxis of gallbladder cancer in this high risk area. A better understanding of the causes of this disease could lead to the development of better and less aggressive preventative measures against this disease.

Title: **Roles of EGFR and miR-143/miR-145 in Western Diet-Promoted Colonic Tumorigenesis**
P.I.: **Bruce Marc Bissonnette**
Institution: **University of Chicago**
Grant No.: **CA164124-01A1**
Award: **$150,000**

While Western diets are implicated in increased colon cancer risk, molecular underpinnings of these dietary effects remain largely unknown. The azoxymethane (AOM) and Apc+/min mouse models mimic many features of human colon cancer, including tumor promotion by Western diet. We showed that Western diet up-regulated ligands for epidermal growth factor

receptors (EGFR). Furthermore, EGFR was required for tumor promotion. Several EGFR ligands are released from membrane-bound pro-ligands by the lipid-raft-associated metalloproteinase ADAM17. Our recent studies indicate that ADAM17 is down-regulated by microRNA-145 (miR-145), whereas K-ras, an EGFR effector is suppressed by miR-143. These co-transcribed miRNAs are down-regulated in human colon cancer. We recently showed that EGFR signals downregulate miR-143 and miR-145 in AOM and Apc+/min tumors. Furthermore, these miRNA reductions are necessary for EGFR mitogenic effects. Based on our data we hypothesize that ADAM17 up-regulation and miR-143 and miR-145 down-regulation play essential roles in Western diet-induced tumor promotion. We propose several aims to address this hypothesis: Aim 1: Elucidate the requirement for ADAM17 in diet-promoted colonic tumorigenesis. We hypothesize that ADAM17 inhibition or deletion will suppress diet-related tumor promotion. We will use 1a) the AOM model in conditional ADAM17-deleted mice; 1b) the Apc+/min model with a novel ADAM17 pharmacological inhibitor INCB3619 to dissect the role of ADAM17 in diet-promoted tumorigenesis; 1c) in vitro studies of lipid rafts to dissect fatty acid effects on ADAM17 in colon cancer cells. Aim 2: To determine contributions of miR-143 and miR-145 in diet-promoted colonic tumorigenesis. We hypothesize that loss of these miRNAs is necessary for diet-induced tumor promotion. We will employ Apc+/min mouse interbred with 2a) transgenic mice expressing villin-promoter regulated pre-miR-143 and pre-miR-145; or with 2b) miR-143 null mice or with 2c) miR-145 null mice to uncover the role of these miRNAs in diet-promoted tumorigenesis. In aim 2d), we will examine other miRNAs implicated in ADAM17 regulation and/or diet-related tumorigenesis, including miR-1, -31, -148, and -152. Aim 3: Determine the regulation of miR-143 and miR-145 by Western diet and tumorigenesis. We hypothesize that Western diet and malignant transformation suppress transcription, while neoplastic transformation also deranges processing. We will 3a) assess effects of ADAM17, diet and neoplastic stage on pri-, pre- and mature levels of miR-143, -145 in in vivo models; 3b) dissect EGFR and fatty acid effects on miR-143/-145 promoter activity using mutant deletions to identify cis regulatory elements; 3c) Determine proteins differentially co-associating with biotinylated miR-143 or miR-145 in murine processing-competent YAMC and processing-incompetent CT26 colon cancer cells to discover deregulated processing factors. Our proposal will clarify the role of ADAM17 and test a novel hypothesis that EGFR and these miRNAs form a self-amplifying loop that drives diet-promoted tumorigenesis.

Title: **Understanding and Preventing Breast Cancer Disparties in Latinas**
P.I.: **Beti Thompson**
Institution: **Fred Hutchinson Cancer Research Center**
Grant No.: **CA148143-03**
Award: **$18,750**

Breast cancer is the most common cancer among Hispanic women in the United States (US). The incidence of breast cancer among Hispanics (83.5 per 100,000) is lower than that among non-Hispanic Whites (147.3 per 100,000); however, as Hispanic women adopt the practices of mainstream US culture, their risk for breast cancer increases. Further, Hispanic women are at increased risk for breast cancers with poor prognosis. The overarching theme of this PSO application is to understand and prevent pre-cursors of breast cancer and to reduce breast cancer morbidity and mortality among Latinas. This will be done at multiple levels and will engage researchers across several disciplines. Projects have been carefully designed to contribute understanding to and preventing breast cancer in Latinas. It is the lonq-term goal of this PSO application to understand the antecedents of breast cancer in the Latina population, to understand the types of breast cancer found in the Latina population, and develop and implement a comprehensive program of screening to increase the opportunities for early breast cancer detection among Latinas. Our short-term obiectives are to: 1. Increase breast cancer screening among age-eligible Latinas; 2. Understand the processes by which ancestry, BMI, inflammation, and breast cancer are related in Latinas 3. To understand aspects of the etiology

of poor prognosis breast cancers by identifying risk factors related to triple negative (TN) and HER-2-overexpressing (H2E) tumors, which are more commonly found in Latinas compared to non-Hispanic whites 4. To understand the role of ancestry in breast cancer antecedents and incidence among Latinas. 5. To explore expression of genes involved in tumor-related pathways signaling. This application is committed to a comprehensive multi-level approach to reducing health disparities. Its projects range from the biologic and genetic to the social context within which people live. Through its four projects and cores, the proposed Center will cover a myriad of aspects of breast cancer, from biological processes and genetic pathways to individual determinants and social determinants of breast cancer.

Title: **Using Technology to Promote Activity in Women at Elevated Breast Cancer Risk**
P.I.: **Lisa Anne Cadmusbertram**
Institution: **University of California, San Diego**
Grant No.: **CA168450-01**
Award: **$67,371**

Obesity (i.e., excess energy intake and inadequate physical inactivity) is associated with increased risk of breast cancer among postmenopausal women. Effective and practical intervention strategies are needed to address the high prevalence of excess weight and sedentary lifestyle in middle-aged and older US women. Although web-based interventions to promote a healthy lifestyle are common, no studies have tested the use of web-integrated physical activity meters for promoting behavior change in this population. By leveraging innovative technology-based approaches, researchers and physicians may be able to replace intensive physical activity interventions with low-cost alternatives. OBJECTIVE: To test the feasibility of using a web-based self-monitoring technology (the FitBit) to promote physical activity among women at elevated risk for breast cancer (i.e., overweight/obese, inactive postmenopausal women). SPECIFIC AIMS: This pilot study proposes to use a 16-week randomized controlled trial of a novel intervention (FitBit activity monitor + training) vs. a pedometer to address the following aims: Primary aim: To investigate the effect of the FitBit-based intervention vs. provision of a pedometer on objective measures of physical activity and sedentary behavior. Secondary aim: To examine the acceptability and usage patterns of the device and website. METHODS: Fifty participants will be randomly assigned to receive (a) a FitBit monitor and training on use of the website or (b) a pedometer. The FitBit is a tiny physical activity tracking device that pairs with a website, wirelessly uploading activity data to provide the user with an easy-to-understand visualization of her daily activity patterns. Goal-setting features are used alongside simple graphs and charts to enhance self-monitoring of energy balance. Participants will be given a physical activity goal, trained in the use of the self-monitoring website, and asked to wear the FitBit clipped to their clothing every day for 16 weeks. The primary outcome will be change in MET-hours/day of physical activity, as measured by the ActiGraph GT3X accelerometer prior to randomization and at 16 weeks. Although this is a pilot study, we will have 80% power to observe an effect size of 0.7 at a significance level of $p<0.10$. Questionnaires will be used to measure intervention acceptability and direct data downloads will provide an objective assessment of usage patterns. CANCER RELEVANCE: Promotion of weight management and physical activity is an important aspect of breast cancer prevention because excess adiposity is associated with increased risk of postmenopausal breast cancer. As intervention research evolves, technology offers the potential for cancer prevention researchers to move away from costly traditional interventions toward easily disseminated interventions that can continue after the study has ended.

National Eye Institute

Title: **Broad Spectrum Molecular Therapy for Blinding Retina Disorders**
P.I.: **Jean Bennett**
Institution: **University of Pennsylvania**
Grant No.: **EY023177-02**
Award: **$150,000**

This proposal evaluates the translational potential of optogenetic therapy, an approach whereby visual function is achieved through the use of a molecular prosthesis that transmits its signals to downstream visual circuits. Studies in vitro and in vivo in animal models by our collaborators (and others) have demonstrated that light-activated chloride pumps or channels can be introduced into specific retinal cell types in diseased or atrophic retinas. There, these molecular prostheses can permit visual responses where before, there were none. The present program aims to address the knowledge gaps and technical limitations relevant to development of optogenetic therapy in two different paradigms: 1) Physiologically optimized forms of Halorhodopsin (NpHR) will be used to activate function of failing cone photoreceptors after the rod photoreceptors have degenerated; 2) Optimized Channelrhodopsins (ChRd) will be used to confer light responsiveness to second order retinal neurons in degenerated retinas. We will design and develop the appropriate vectors, delivery strategies and outcome measures for each paradigm, will carry out the prerequisite preclinical safety and efficacy studies, and will bring one of the studies (NpHR) to clinical trial. In the process, novel strategies of altering the transduction characteristics of adeno-associated virus (AAV) will be developed, new surgical approaches which could be applied to human eyes will be devised, and sensitive, noninvasive, clinically relevant outcome measures will be defined. Simultaneous with development of the technology, we will evaluate the bioethics of gene therapy-mediated delivery of molecular prostheses in humans. This comprehensive program benefits greatly from the wisdom and experience of many talented collaborators and advisors and takes advantage of the infrastructure that the PI has already developed for ocular gene therapy translational research.

Title: **Surveillance and Treatment of Community Newcomers and Travelers for Trachoma Control**
P.I.: **Sheila K. West**
Institution: **Johns Hopkins University**
Grant No.: **EY022584-01S1**
Award: **$40,000**

Infection with C. trachomatis has decreased substantially in trachoma endemic areas following repeated annual mass drug administration with azithromycin, although not as rapidly as anticipated. We propose to conduct a clinical trial to determine the added benefit for communities, which are now at low levels of infection, of a program to identify and treat new families who came after mass treatment, and travelers who return to the community, as they could be the source of re-emergent infection. The proportion of communities who are able to stop mass treatment will be compared in the group of communities randomized to mass treatment plus the newcomer treatment program compared to the communities randomized to mass treatment alone.

National Heart, Lung, and Blood Institute

Title: Avoiding Toxicity Associated with MTP Ablation
P.I.: M. Mahmood Hussain
Institution: SUNY Downstate Medical Center
Grant No.: HL095924-03S1
Award: $20,000

High plasma lipids and lipoproteins are risk factors for various cardiovascular and metabolic disorders. An approach to lower plasma lipids is to inhibit apoB-lipoprotein biosynthesis, a process critically dependent on an endoplasmic reticulum (ER) resident chaperone, microsomal triglyceride transfer protein (MTP). MTP inhibitors decrease apoB-lipoprotein secretion and lower plasma cholesterol. However, they increase plasma aminotransferases, such as ALT and AST, indicating liver injury. We hypothesize that increases in plasma hepatic enzymes associated with MTP inhibition are due to increases in microsomal free cholesterol, induction of ER stress and cell death. We further hypothesize that reducing cellular free cholesterol along with MTP inhibition might reduce hyperlipidemias and avoiding toxicities associated with MTP antagonists. In the first aim, Alb-Cre-MTPfl/fl or MTPfl/fl mice will be fed T-0901317, a LXR agonist to induce free cholesterol efflux; lovastatin, a HMG Co-A reductase antagonist to inhibit cellular cholesterol biosynthesis; or WY14643, a PPAR945; agonist to enhance 946;-oxidation of fatty acids, for 3 or 24 weeks. In another group, 937;-3 fatty acids, PPAR945;/948; agonists, will be injected intraperitoneally to reduce hepatic triglyceride and free cholesterol. In addition, Alb-Cre-MTPfl/fl mice will be fed a western diet and then treated with T-0901317, lovastatin, WY14643, or &-3 fatty acids. Experiments will then be performed in C57Bl/6J mice fed a western diet and fed daily with MTP inhibitors. Additionally, they will be fed olive oil alone or with other compounds described above to determine if toxicities associated with MTP inhibitors can be avoided by these treatments. Outcome measurements will involve changes in apoB-lipoproteins and hepatic enzymes in the plasma; hepatic triglycerides, esterified cholesterol, and free cholesterol; quantification of candidate mRNAs and proteins involved in cholesterol and triglyceride biosynthesis, ER stress, as well as AST/ALT isoforms. These studies will show that toxicities associated with MTP inhibition can be avoided by reducing hepatic free cholesterol. The second aim is to test the hypothesis that release of hepatic enzymes in the plasma is due to the induction of the ER stress and apoptosis. We will first demonstrate that MTP inhibition increases microsomal free cholesterol. Second, we will identify the ER stress pathways activated by MTP ablation/inhibition. Third, we will establish that MTP inhibition induces apoptosis. Fourth, a link between the ER stress and induction of apoptosis will be established. Fifth, importance of the ER stress pathways will be substantiated using ATF6-/-, CHOP-/- and Alb-Cre-Ire11fl/fl mice fed MTP inhibitors. Sixth, we will determine if induction of ER stress by tunicamycin increases plasma AST/ALT levels. At the completion of these studies, we will find out molecular mechanisms responsible for unwanted side effects associated with MTP therapy and suggest solutions to avoid these toxicities. These studies may lead to new therapeutic modalities for the treatment of various hyperlipidemias and have immediate potential for translational use.

Title: Endogenous Cardiac Repair in Humans
P.I.: Kenneth Ber Margulies
Institution: University of Pennsylvania
Grant No.: HL089847-04S1
Award: $72,000

Until recently, the heart has been viewed as a terminally differentiated organ with no capacity for new cardiac myocyte (CM) formation. This view appears to be incorrect, in that we and others have been able to isolate cardiac-derived progenitor cells (CDPCs) from human myocardium. Extending these results, our recent studies indicate that cells expressing the stem cell surface marker c-kit can be isolated from human hearts immediately after explantation and

subsequently induced to differentiate into CM via short-term co-culture with neonatal rat ventricular myocytes (RVMs). Though we typically find more c-kit+ cells usually in failing vs. nonfailing hearts, the need to replace these failing hearts via transplantation highlights the inadequacy of native cardiac repair mechanisms. Based on these findings, our broad working hypothesis is that increased c-kit+ CDPCs in failing human hearts include both lineage-negative c-kit+ and c-kit+/CD45(dim-moderate) cells that are each capable of new myocyte formation in vitro. In this context, the objective of this proposal is to quantify and characterize these distinct subpopulations of stem/progenitor cells within human hearts with an emphasis on elucidating their functional capacity for replication and CM differentiation. Our first aim is to identify what types of stem/progenitor cells are present in normal and failing human hearts. We will define distinct stem/progenitor subpopulations based on immunotyping of disaggregated myocardial cells with fluorescence microscopy and flow cytometry and perform complementary studies in tissue sections from the same hearts to define their distribution. Our second aim is to characterize replicative capacity of the selected CDPC subpopulations based on a combination of static assays (telomere length, telomerase activity and and p16INK4a expression) and functional assessment of proliferation rates. Our third aim is to characterize the cardiac myogenic potential of selected CDPC subpopulations derived from human hearts. These studies will define the rates and frequency of CM differentiation for sorted subpopulations under stardardized co-culture conditions, define whether cell contact is required for induction of CM differentiation by neonatal rat myocytes and identify secreted factors (chemokines or growth factors) that promote or augment rates of in vitro CM diffentiation in selected CDPC subpopulations. The clinical/therapeutic significance of this proposal is based on the premise that insights into the proliferative and cardiomyogenic potential of endogenous cardiac stem/progenitor cell subpopulations will promote progress towards therapeutic cardiac regeneration with or without cell therapy per se.

Title: **A Formative Examination of the Health and Safety of Female Firefighters**
P.I.: **Sara Anne Jahnke**
Institution: **National Development and Research Institutes, Inc.**
Grant No.: **HL119024-01A1**
Award: **$199,800**

Firefighters/EMS personnel are vital for public health safety, representing over two million individuals nationally. Because firefighters are required to respond to almost every domestic emergency, there is wide agreement that their health and readiness is of particular importance. Furthermore, a broad range of occupational exposures exist that negatively impact the health of firefighters. While the field of firefighter health has enjoyed growth over the past decade, the health of female firefighters remains largely unexamined. Similar occupational groups, such as the military, have developed focused programs to understand the unique work-related challenges to women's health; however, research in the fire service has remained relatively silent on the topic. This dearth of informatio likely contributes to the remarkably low rates of females recruited and retained by the fire service. While challenges such as harassment in the workplace have been identified as concerns for female firefighters, health concerns beyond emotional stress have received limited attention. Anecdotal evidence suggests that issues such as reproductive health, ill-fitting gear, and on-the-job injuries attributable to standard operating procedures and guidelines that do not accommodate differences in female characteristics are barriers to women serving as firefighters. The military, a similar population with regard to work task, environment, and a tradition of being primarily male, has been successful in making female health a priority through the development of a focused program of gender specific research. Despite significant cultural barriers, the armed forces have been successful in recruitment and retention of female personnel at a rate that far exceeds the US fire service. In this proposed project, we will use a multi-methods research design to examine health and safety issues among female firefighters.

In addition, this study will identify factors which serve as barriers to recruitment and retention of women in the fire service. Unique strengths of this R21 developmental application include strong support from the largest national fire service organization focusing on women and an investigative team with a documented history of successful research on the health of firefighters. Research for this formative research will be conducted in three phases including: 1) focus groups with a national sample of female firefighters, and key informant interviews with male and female fire service opinion leaders; 2) key informant interviews with female firefighters who have chosen early retirement to determine barriers to retention among this population and 3) an epidemiological survey of a sample of female firefighters to determine current health status and health concerns across a number of domains. This innovative study is a critical step in addressing gender inequity of the US Fire Service and identifying areas of intervention and prevention for this understudied occupational group.

Title: **Molecular Mechanism of Platelet Dense Granule Biogenesis**
P.I.: **Santiago Mauro Di Pietro**
Institution: **Colorado State University**
Grant No.: **HL106186-01A1S1**
Award: **$20,000**

Platelets play pivotal roles in both hemostasis and thrombosis. Platelet activation triggers secretion and the release of content from dense granules, a-granules, and lysosomes that in turn leads to the recruitment and aggregation of additional platelets and white cells. While impaired platelet function has been associated with disorders that manifest with moderate to severe mucocutaneous bleeding, excessive platelet aggregation is a major cause of morbidity and mortality due to its effect in myocardial infarction and stroke. In spite of the relevance of platelet dense granules for human health, little is known about their biogenesis. Therefore, our goal is to understand the molecular mechanism responsible for the biogenesis of platelet dense granules. Dense granules belong to a group of lysosome-related organelles (LROs). Formation of LROs involves two parallel protein transport pathways defined by Adaptor Protein-3 (AP-3) and Biogenesis of Lysosome-related Organelles Complex-2 (BLOC-2). AP-3 is an adaptor that selects proteins with specific targeting signals in early endosomes and packages them into vesicles for transport to LROs. BLOC-2 also localizes to early endosomes but its function is unknown. We have recently obtained preliminary evidence suggesting that BLOC-2 has adaptor-like properties but with the ability to bind new targeting signals in dense granule proteins, different from the signals recognized by AP-3. Moreover, we obtained substantial preliminary results indicating that five proteins are fundamental components and new players in the pathways to dense granules: two "molecular switches", two novel proteins containing vesicle scission domains, and a molecular motor. These findings have opened new avenues to study the biogenesis of platelet dense granules. We propose to: (1) establish new in vitro and in vivo systems to study the biology of dense granules, (2) test the hypothesis that new dense granule targeting signals exist in dense granule proteins and that BLOC-2 is an adaptor that recognizes these signals and packages the corresponding proteins into vesicles destined for dense granules; (3) test the hypothesis that tissue specific "molecular switch" proteins recruit AP-3, BLOC-2, and other ubiquitous components to endosomal membranes to specifically direct transport to dense granules; (4) test the hypothesis that new vesicle scission and molecular motor proteins mediate the formation and transport of vesicles loaded with dense granule membrane proteins to dense granules; and (5) test the possibility that numerous patients that present in the clinic with platelet type bleeding disease of unknown etiology may have deficiencies in these new molecular switches, scission, and molecular motor proteins involved in dense granule biogenesis.

Title: **Premenstrual Syndrome and Risk of Subsequent Hypertension**
P.I.: **Elizabeth R. Bertone-Johnson**
Institution: **University of Massachusetts Amherst**
Grant No.: **HL115357-01**
Award: **$195,117**

Hypertension is one of the strongest predictors of cardiovascular disease (CVD) in women. Despite extensive knowledge of the etiology of hypertension and the availability of effective treatments, prevalence remains high. There is a substantial need for novel strategies to identify premenopausal women at high risk for hypertension who would benefit from early intervention to reduce their long term risk of CVD. Up to 20% of premenopausal women meet clinical criteria for premenstrual syndrome (PMS), a disorder characterized by moderate to severe luteal phase symptoms that substantially interfere with normal life activities and interpersonal relationships. The pathophysiology of PMS is complex, and factors including dysfunction of the renin-angiotensin-aldosterone system and vitamin D insufficiency likely contribute. Importantly, these factors have also been implicated in the etiology of hypertension. Thus, moderate to severe PMS may be predictive of increased risk of hypertension later in life, and may serve as an early sentinel of CVD risk. The proposed project will extend work completed during the Principal Investigator's current career development award (K01MH07624) to explore the relation of PMS with hypertension and blood pressure in two populations of women. First, we will determine prospectively if PMS occurring in the middle reproductive years is associated with subsequent risk of hypertension and changes in blood pressure over time. We have developed a prospective study of PMS nested within the Nurses' Health Study II (NHS2) cohort; to our knowledge, this is the only prospective epidemiologic study of women with PMS in existence. The NHS2 PMS Sub-Study includes 1257 women meeting established criteria for moderate to severe PMS and a comparison group of 2463 women without PMS. As of 2013, participants will have been followed for 24 years for incident hypertension and changes in blood pressure, and women with PMS will have been observed for up to 20 years following their PMS diagnosis. Second, we will determine if common PMS treatments and dietary and behavioral factors modify the association of PMS and blood pressure, and thus may provide opportunities for women experiencing PMS to reduce their risk of hypertension and CVD. Finally, using data from a second study of young adult women (n=375), we will determine if differences in blood pressure are already evident in women experiencing PMS in their late teens and early 20's. Data from both studies have already been collected, thus providing a cost-effective way to address these novel and important questions. IMPACT: This life course study will be the first to evaluate whether moderate to severe PMS may serve as an early sentinel of long-term health outcomes. It may help identify a population of women at high risk for hypertension who would benefit from increased screening and early intervention. Furthermore, it may lead to clinical trials of novels strategies for treating PMS, no only to reduce morbidity and improve quality of life in women with the disorder, but also to reduce their long-term risk of cardiovascular disease.

Title: **Saturated Fat and Protein Effects on Atherogenic Dyslipidemia**
P.I.: **Ronald M. Krauss**
Institution: **Children's Hospital & Research Center Oakland**
Grant No.: **HL106003-02S1**
Award: **$200,000**

The overall objective of this project is to test the hypothesis that the effects of saturated fat (SF) on lipoprotein markers of cardiovascular disease (CVD) risk are influenced by food sources of dietary protein. There is growing epidemiological evidence that consumption of red meat is associated with greater incidence of CVD than either white meat or non-meat foods. Pathophysiological support for the validity of this association is provided by preliminary evidence from our group that a high beef diet has a more deleterious effect on lipoprotein measures of CVD risk than we have observed for mixed protein diets. Specifically, we have found

that a high protein, high SF diet with a moderate red meat content selectively induces increases in intermediate density lipoproteins (IDL) and larger LDL particles that have been found to be much more weakly associated with CVD risk than smaller LDL. In contrast, a more recent study from our group has found that, with a similar intake of SF, high beef consumption results in a preferential increase in levels of small and medium sized LDL particles, both of which are strongly related to incident CVD. To date however, no studies have directly compared the lipoprotein effects of red meats with other food sources of protein in the context of both high and low saturated fat intake. We specifically hypothesize that increases in plasma levels of LDL cholesterol (C), and apolipoprotein (apo) B, induced by SF are greater when the major food source of protein is red meat rather than either white meat (poultry) or non-meat foods, and that this is due to increased levels of small and medium sized LDL particles. We therefore propose a clinical trial in which 180 healthy men and women will be randomized to high SF (15%) or low SF (7%) diet groups, and within each group, consume diets with equivalent amounts of protein derived from red meat, white meat, and non-meat sources for 4 wk each in random order. Our Specific Aims will test whether: (1) with high SF, the red meat diet, compared to the other food sources of protein, will result in higher levels of LDL-C, apoB, small and medium sized LDL particles, and total/HDL-C; (2) with low SF, dietary protein source will not be related to any of these measurements; (3) with both the white meat and non-meat diets, increased LDL-C with high vs. low SF will be due primarily to increases in IDL and/or large LDL, whereas with red meat the additional increase in small and medium LDL will result in greater increases in apoB. In addition to these aims we will test for possible metabolic determinants of dietary effects on apoB-containing lipoprotein subclasses, including post-heparin plasma hepatic lipase activity, which is critical for production of smaller LDL, and LDL receptor activity as assessed in peripheral blood mononuclear cells, a system demonstrated to reflect physiologically relevant LDL receptor regulation. Finally, we will examine potential dietary influences on other metabolic biomarkers of CVD risk, including HDL subclasses and apoproteins, insulin sensitivity as assessed by HOMA-IR, measures of inflammation including CRP and multiple cytokines, and endothelial function using a non-invasive fingertip method.

Title: **Uterine-Specific Genetic Modification and Lymphangioleiomyomatosis**
P.I.: **Jose M. Teixeira**
Institution: **Massachusetts General Hospital**
Grant No.: **HL109935-02**
Award: **$50,000**

Lymphangioleiomyomatosis (LAM) is a rare disease primarily found in females and is characterized by a diffuse interstitial infiltrate of atypical smooth muscle cell lesions in the lung parenchyma resulting in airway restriction. The etiology of the disease is unknown but is thought to involve hormonal regulation because it usually presents between menarche and menopause. Additionally, LAM is often found in patients with mutations in tuberous sclerosis complex (TSC), suggesting that inactivation of TSC can contribute to its development. We are studying uterine development and associated pathologies by conditionally deleting and/or activating candidate genes in pathways critical for normal differentiation and function. We have created mice with uterine-specific leiomyomas (fibroids) by either constitutively activating ¿-catenin or by expressing a truncated allele of adenomatous polyposis coli (APC) and we have shown preliminary evidence that the leiomyomas develop as a result of vascular hemorrhaging and subsequent hypertrophic scarring. The Mullerian duct-derived internal female reproductive tract organs (uterus, oviduct, cervix, and cranial portion of the vagina) are the only structures from the bipotential mammalian embryo not found in males, suggesting that the hormonally responsive mesenchymal stromal cells of the uterus might be the source of the cells for pulmonary fibrosis and account for the female-specificity of LAM. We hypothesized that pulmonary LAM might be caused by uterine vascular pathologies that allow intravasation of uterine stromal cells that can subsequently lodge and proliferate in the lungs. Histological analysis of the lungs

from our mouse models with uterine hemorrhaging and leiomyomas showed fibrotic lung plaques similar to that observed in human LAM that were also HMB45-, aSMA- and desmin-positive, markers for human LAM. We propose to investigate this hypothesis further with the following Specific Aims: (1) confirm that cells in the lung lesions are derived from the uterus, (2) determine whether uterine mesenchymal cells can be detected in peripheral blood, (3) test the hormone responsiveness of the smooth muscle cells in the lung lesions, and (4) assess the marker profile of lung lesions for comparison with human LAM. The results from these studies will lay the foundation for continued investigation of the triggers and signaling pathways involved in the development of the LAM lesions as well as provide an in vivo model system for preclinical studies of therapeutics targeting those pathways.

National Institute on Aging

Title: **Effects of Aging on Visual Memory: Neuroimaging Studies**
P.I.: **Roberto Cabeza**
Institution: **Duke University**
Grant No.: **AG019731-10**
Award: **$200,000**

Aging is associated with substantial deterioration of the visual system and associated sensory-perceptual processes. This decline in visual processing is a strong predictor of cognitive decline in healthy aging and of Alzheimer's disease. Yet, the effects of aging on visual processing and cognitive functions, such as memory, have typically been investigated independently of each other. Filling this void, the proposed neuroimaging studies focus on the interactions between age effects on visual and memory processes, and the brain regions mediating these processes. This significant goal is combined with an innovative multi-measure methodological approach which assesses age effects (1) on visual and memory performance using behavioral tests; (2) on brain activity in occipito-temporal, medial temporal, prefrontal regions using functional MRI (fMRI); (3) on the interactions among these regions using functional connectivity (fCON); and (4) on the integrity of the white-matter fiber tracts connecting these regions using diffusion tensor imaging (DTI). Most importantly, these different measures are directly linked to each other. The multi-measure approach is applied to three specific aims. Specific Aim 1 is to investigate the role of peripheral and top-down modulation deficits in visual memory impairments in older adults. Older adults show reduced activity and selectivity (dedifferentiation) in occipito-temporal cortex, which may reflect peripheral or top-down modulation deficits. Study 1 compares the effects of divided attention, which interferes with top-down modulation, and stimulus degradation, which mimics age-related peripheral visual deficits. Study 2 employs overlapping face-house stimuli to examine selective attention deficits. Specific Aim 2 is to investigate the role of perceptual and conceptual processing deficits in visual memory impairments in older adults. Conceptual processing enhances memory for meaningful visual stimuli such as objects but, when combined with perceptual processing deficits, can lead to false memories. Study 3 investigates age effects on conceptual vs. perceptual processing during the encoding of meaningful objects. Study 4 examines age effects on encoding leading to true vs. false memory for objects. Specific Aim 3 is to investigate the role of retrieval reactivation deficits in visual memory impairments in older adults. Visual memory depends not only on visual cortex activations during learning but also on visual cortex reactivations when visual events are remembered. Study 5 investigates age effects on the reactivation of memories for familiar faces and objects. Linking with Specific Aim 2, Study 6 investigates the reactivation of perceptual and conceptual representations. The proposed studies will be the first to systematically investigate the neural mechanisms of age-related visual memory decline. Their results will have direct implications for the development of treatments for memory decline in healthy aging. Moreover, given that visual memory decline predicts Alzheimer's disease a decade before diagnosis, the results will also have implications for the early detection and treatment of this disease.

Title: **Hypertension, Angiotensin Receptor Blockers, and Cognition: Effects and Mechanism**
P.I.: **Ihab M. Hajjar**
Institution: **University of Southern California**
Grant No.: **AG042127-01A1**
Award: **$200,000**

Hypertension is associated with cognitive impairment even in the absence of dementia. These vascular-related mild cognitive impairments are undetected and are commonly characterized by executive dysfunction. To date, no specific treatment is available for executive mild cognitive impairment which is associated with poor outcomes in hypertension. The PI has recently completed, with support from a K23 award, a preparatory pilot study (n=47) to test the feasibility, safety and effect size of candesartan, an angiotensin receptor blocker, compared to hydrochlorothiazide and lisinopril, in individuals with hypertension and mild cognitive impairment characterized by executive dysfunction. Our preliminary analysis which was recently accepted for publication in the Archives of Internal Medicine, suggests that, independent of blood pressure, candesartan is superior to other antihypertensives in preserving executive function. Candesartan was also associated with an increase in cerebral blood flow velocity that only reached significance in those with low flow velocity at baseline (n=23). We hypothesized based on these data to further test the effect of angiotensin receptor blockers on cognitive function by conducting a 1-year double blind randomized active-control trial of candesartan vs. lisinopril in 160 individuals with hypertension and evidence of mild cognitive impairment in the executive domain. The specific aims of this proposal are to investigate the effects of candesartan on executive function decline and on change in cerebral perfusion, cerebrovascular reserve and microvascular brain injury. We also aim at Identifying potential underlying mechanisms related to vascular structure and function by which candesartan may affect the cognitive and cerebrovascular outcomes. Participants will be recruited from the greater Los Angeles Area and evaluated at the University of Southern California. Cognitive tests that assess executive function and other cognitive domains will be administered at baseline and 12 months after treatment. Neuroimaging which includes perfusion (continuous arterial spin labeling) and micro-structure (diffusion tensor imaging), carotid ultrasound (carotid intima-media thickness), and endothelial and vascular inflammatory markers will be performed at baseline and after 12 months of treatment. This trial will shed more light onto the potential therapeutic effects of angiotensin receptor blockers on executive dysfunction and related vascular brain injury. This project will also improve our understanding of the possible mechanisms of action of this class of antihypertensives.

Title: **Menopausal Symptoms Initiative—Finding Lasting Answers for Sweats and Hot Flashes**
P.I.: **Andrea Z. LaCroix**
Institution: **Fred Hutchinson Cancer Research Center**
Grant No.: **AG032699-05**
Award: **$200,000**

The long-term objective of NIA's RFA-AG-08-004 entitled, New Interventions for Menopausal Symptoms (U01) is to accelerate progress in identifying effective remedies for vasomotor symptoms (VMS) in women going through the menopausal transition. We have created a network of scientists who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials to fulfill this mission. This Data Coordinating Center (DCC) application is being submitted in conjunction with the network entitled, The Menopausal Symptoms Initiative-Finding Lasting Answers to Sweats and Hot Flashes (MSI-FLASH). Our DCC will be jointly led by Andrea LaCroix and Garnet Anderson who have served together as Co-Principal Investigators of the Women's Health Initiative Clinical Coordinating Center (Seattle) for more than a decade. The MSI-FLASH network has five clinical sites located in Boston (Lee Cohen and Hadine Joffe, PIs), Indianapolis, IN (Janet Carpenter, PI), Oakland,

CA (Barbara Sternfeld and Bette Caan, PIs), Philadelphia (Ellen Freeman, PI) and Seattle (Katherine Newton and Susan Reed, PIs). This multidisciplinary investigator group proposes five randomized controlled trials testing a range of behavioral, mind-body, hormonal and pharmacologic interventions to treat hot flashes. The specific objectives of the DCC are to: 1) Provide and coordinate all necessary leadership activities to facilitate collaboration and productivity among network scientists during all phases in the lifecycle of VMS clinical trials from hypothesis formulation to publication, dissemination, and data sharing; 2) Build upon 15 years of experience and well established human and operational resources to coordinate 5 or more multi-site randomized trials including support of protocol development, recruitment, intervention, data collection and management, and statistical analysis; and 3) Create the infrastructure to involve an expanded network of scientists from the US and worldwide to facilitate the development and use of common methodologies and measurements for VMS trials inside and outside of this trial network so that emerging new treatments for hot flashes can be rapidly identified and rigorously tested for efficacy and safety with comparable results.

Title: **National Social Life, Health, and Aging Project**
P.I.: **Linda J. Waite**
Institution: **National Opinion Research Center**
Grant No.: **AG030481-05**
Award: **$200,000**

The primary objective of the National Social Life, Health and Aging Project (NSHAP) is to establish an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally-representative sample of 3,005 community-dwelling adults ages 57-85 in 2005/6. We propose to collect a second wave in NSHAP to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. We propose to revisit respondents four years after their initial interview. Using these data, we can describe and model the distribution of changes in health, well-being, social networks, social participation and social context. In each case, we shall examine the distributions both for the entire sample and within subgroups defined by key sociodemographic characteristics such as gender, race/ethnicity, and socioeconomic status. We also propose to augment the sample by interviewing the spouse/cohabitating romantic partner. These data will allow us to characterize the impact of marital and romantic relationships on health by examining the effects of one person's characteristics and behaviors on the health of the other. We will also analyze the partnerships themselves, and assess the relationship between characteristics of the partnership, such as support, closeness and mistreatment, and the health of each of the partners. In sum, we will explore our overarching hypothesis that older adults with strong functioning intimate relationships will show more positive (or less negative) health trajectories that those who have weaker relationships or lack such relationships altogether.

Title: **The Role of Vascular Aging in Cognitive and Physical Function**
P.I.: **Lydia Bazzano**
Institution: **Tulane University of Louisiana**
Grant No.: **AG041200-01A1**
Award: **$300,000**

Maintaining optimal health, both physical and cognitive, throughout the aging process is critical to minimizing healthcare costs and morbidity and mortality associated with diseases of aging. The integrity of the vascular system is essential for healthy aging. Aging-related structural

and functional disturbances in the macro- or microcirculation contribute the development of cognitive dysfunction and declining physical performance. Early life factors, from birth through childhood and adolescence, may play an important role in successful cognitive and physical aging via the aging of the vascular system. In the proposed study we will examine the role of vascular aging in maintenance of cognitive and physical performance by recruiting 1,257 participants in the Bogalusa Heart Study cohort who participated in cardiovascular risk factors examinations at least twice in childhood and twice again in adulthood. Participants will undergo cognitive function testing, physical function assessments and vascular risk factor examination with noninvasive studies of vascular structure and function. Birth weight and childhood socioeconomic and risk factor data is available for all individuals. Longitudinal analysis will be used to examine the relationship of early life risk factrs to subclinical vascular disease markers, while linear models will be used to examine the role of vascular risk factors and subclinical markers in maintenance of cognitive and physical function. This study represents a unique opportunity because all vascular disease risk factors have been collected prospectively from early life to middle-age in this bi-racial (black/white), rural community, allowing for exploration of race and gender relationships with cognitive and physical function from mid-life. The proposed research will link vascular risk factors across the life span and subclinical vascular markers in early middle age with cognitive and physical performance in later middle age. In doing so, we will identify risk factors, timing and subpopulations for intervention that could reduce the incidence of cognitive and physical decline in old age and improve the rate of successful aging for persons across the nation.

Title: **Study of Women's Health Across the Nation—Coordinating Center**
P.I.: **Kim Sutton Tyrrell**
Institution: **University of Pittsburgh at Pittsburgh**
Grant No.: **AG012553-18**
Award: **$125,000**

The Study of Women's Health Across the Nation (SWAN) is a 7-center multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition. SWAN has amassed ten years of data about endocrinology of the transition and other factors relevant to midlife health and aging. As SWAN requests its fourth competing renewal, the study itself proposes to transition from a study of the menopause to a study of aging in women. The average age of participants at the beginning of the SWAN IV project will be 59 years (54 to 65) and SWAN IV will follow these women through the age range of 59 to 70. SWAN has the unprecedented capability to link the expansive biological, medical, social, behavioral, and demographic data it has collected during mid-life and the menopausal transition to the development of both positive and adverse health states in early oldage. The primary objectives of SWAN IV are to: 1) Characterize the endocrinology and symptomotology of the post-menopause (2 to 12 years after final menses); 2) Ascertain additional health outcomes (such as measured physical performance) that are relevant to the early old age range and that may be affected by the factors that we have studied in mid-life and 3) Understand the relations between the mid-life and menopausal transition experience of women and subsequent positive and negative health outcomes. To accomplish this, the investigators propose annual phone contact to closely track menopausal status, menopausal symptoms and selected health events. In addition, two in-person clinic visits are proposed to accomplish detailed physical measures of early disease. The major thematic areas of SWAN IV include 1) Physical Functioning; 2) Bone/ Osteoporosis; 3) Cognitive Function/ Symptoms/ Mental Health and 4) Cardiovascular. New areas for SWAN include physical performance and osteoarthritis, history of major depression, and carotid wall thickness. SWAN will continue to monitor symptoms, cognition, cardiovascular risk factors, endocrinology, bone density and fractures. SWAN IV will advance our understanding of how modifiable risk factors related to the menopause transition are linked to sub-clinical disease measures and hard outcomes. This may lead to improved strategies for the primary

prevention of disease in women. RELEVANCE: SWAN has compiled the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. Of particular public health importance is that the continuation of SWAN will permit the study to increase understanding of the effects of these menopause-related changes on subsequent health and risk factors for age-related diseases.

Title: **SWAN: Study of Women's Health Across the Nation**
P.I.: **Joel S. Finkelstein**
Institution: **Massachusetts General Hospital**
Grant No.: **AG012531-19**
Award: **$75,000**

The Study of Women's Health Across the Nation (SWAN) is a multi-center, multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. The goals of the original RFA were to answer the following questions: How do hormones change with the menopausal transition? What factors affect the timing of the transition? What are the symptoms that accompany menopause and who is at risk? How do cardiovascular risk factors change with the transition and is there ethnic variation? What are the rates of bone loss with the transition? When does bone loss begin and what are the risk factors? What are the health consequences of menopause and who is at risk? SWAN is compiling the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. SWAN is now poised to study the effects of these menopause-related changes on subsequent healthy aging and on age-related diseases in the post-reproductive period. SWAN I was first funded in September 1994 by the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the Office of Research on Women's Health (ORWH) in response to RFA AG-94-002, Menopause and Health in Aging Women. The first competing continuation of SWAN (SWAN II) was funded in 1999 and the second (SWAN III) in 2004. SWAN I, II and III have been supported by a cooperative agreement mechanism, with 9 funded components: 7 clinical centers, a central reproductive hormone laboratory (CLASS), and a coordinating center. A second central laboratory (MRL) was originally funded as a subcontract to the Coordinating Center (CC). In addition, a Core Repository of serum, plasma, and urine specimens and a DNA Repository were established in June 2000 under separate funding (U01 AG 17719, PI: Dr. MaryFran Sowers). For non-study-related reasons, site operations at New Jersey Medical School stopped in April 2004. The basis of this action was allegations made by two study employees who resigned abruptly. The SWAN PI and study coordinator were subsequently exonerated from these allegations. Please see Appendix 12 for a more complete report. The grant was transferred to the Albert Einstein College of Medicine in 2005. Since that time, the New Jersey PI and project director have worked tirelessly to overcome the obstacles to re-implement the study. As of June 1, 2008, a total of 155 women have successfully completed their clinic visit and five more visits are scheduled. We project that by the end of SWAN III, data will be available for 250 women. This has been very encouraging and thus Nanette Santoro, PI of the New Jersey SWAN site has been approved by the NIA to prepare a U01 application to cover further contacts for the Hispanic women. Please note that the SWAN IV project applications pertain to the remaining six sites only. Information relative to the New Jersey site is covered in the separate application submitted by Dr. Nanette Santoro. From over 16,000 women aged 40-55 years who were screened during 1995-1997, 3302 women aged 42-52 years were enrolled in SWAN's longitudinal cohort (approximately 450 at each of 7 clinical centers). They completed their baseline clinic visit during 1996-1997. Of the 3302 women enrolled, 1550 were Caucasian, 935 African American, 286 Hispanic, 250 Chinese, and 281 Japanese. A subset of 880 menstruating women was enrolled in the Daily Hormone Study (DHS) started in 1997, which is designed to examine cyclical daily hormone and symptom patterns during the menopausal transition.

National Institute on Alcohol Abuse and Alcoholism

Title: **Ethanol-Induced Conditioned Partner Preference in Mice**
P.I.: **Ruth I. Wood**
Institution: **University of Southern California**
Grant No.: **AA020575-01A1**
Award: **$205,000**

Drinking behavior and social context are intimately intertwined, particularly among young adults. Peer relations can promote drinking. At the same time, alcohol consumption promotes social bonding, as in the popular concept of a "drinking buddy". Ultimately, to combat unhealthy patterns of social drinking, it is important to understand how ethanol shapes the neurochemistry of affiliative behavior. We have developed a mouse model of conditioned partner preference, and we have obtained pilot data to demonstrate ethanol (EtOH)-induced social preference in female mice. Conditioned partner preference is similar to conditioned place preference, but it incorporates social aspects of approach, recognition, and affiliation. This has relevance to drinking behavior in humans. In our pilot studies thus far, female mice prefer conspecifics with whom they have previously been intoxicated. There is a further interaction of EtOH and estradiol to promote social preference, since EtOH-induced partner preference is enhanced in estrogen-treated ovariectomized females (OVX+E) vs ovariectomized females without estrogen (OVX). The proposed studies will use C57Bl/6 female mice to extend our initial observations. Aim 1a will determine the range of EtOH doses which facilitate conditioned partner preference in OVX, OVX+E, and OVX+E females with progesterone. Aim 1b will examine sex differences in EtOH-induced conditioned partner preference by testing orchidectomized males with and without testosterone. Aim 2 will expand the conditioned partner preference model to test the effects of other drugs of abuse (amphetamines, morphine) on social bonding. Finally, Aim 3 will begin to explore underlying mechanisms for EtOH-induced conditioned partner preference. In this regard, pair bonding and affiliative behavior are sensitive to vasopressin mediated through the vasopressin V1a receptor. Furthermore, the vasopressin system is sensitive to both EtOH and estradiol. Aim 3 will test the ability of a V1a receptor antagonist to block EtOH-induced conditioned partner preference. Together, these studies represent an essential first-step to understand substance abuse and social bonding in mice.

Title: **Pharmacokinetics and Pharmacological Effects of Alcohol After Bariatric Surgery**
P.I.: **Marta Yanina Pepino**
Institution: **Washington University**
Grant No.: **AA020018-01A1**
Award: **$258,709**

Today, millions of Americans have had bariatric surgery, and given the magnitude of the obesity epidemic, it is anticipated that this number will continue to rise. Despite the numerous health benefits of these procedures, there is a growing concern with the development of alcohol problems after gastric bypass surgery. We believe that changes in alcohol pharmacokinetics and subjective responses to alcohol that occur as a result of the anatomical and physiological changes caused by upper gastrointestinal tract diversion might be an important mechanism responsible for the association between gastric bypass surgery and postoperative alcohol abuse. The current proposal will be the first study that will investigate the effects of gastric bypass surgery on subjective responses to alcohol and alcohol pharmacokinetic using validated methods and controlling for the important confounding effect of changes in body weight. Patients who will undergo gastric bypass surgery and a group of patients undergoing banding gastric surgery will be evaluated 3 times before and 3 times 9 m after surgery following identical procedures. Unlike after gastric bypass, the anatomy of the intestine/stomach is intact after gastric banding. Thus, gastric banding subjects will allow controlling for changes in alcohol metabolism and

mood effects that could be caused by weight loss. Breath and blood samples will be taken before and at various times after a dose of alcohol (0.8 or 1.4 g/l of total body water) or non-alcoholic placebo control are consumed. Blood alcohol concentrations (BAC) will be determined by the gold standard technique of headspace gas chromatography and these concentrations will be compared with the BAC estimated from breath samples. Subjective ratings of alcohol effects will be measured by validated questionnaires extensively used in the field. The results from our study will lay the foundation for understanding the effect of gastric bypass and gastric banding procedures on alcohol kinetics and pharmacodynamics, which can help tailor counseling in patients undergoing these procedures and prevent alcohol misuse after surgery.

Title: **Role of MSK1, Era, and Brf1 in Alcohol-Associated Breast Cancer**
P.I.: **Shuping Zhong**
Institution: **University of Southern California**
Grant No.: **AA021114-01A1**
Award: **$205,000**

Alcohol is the dietary factor, which is most consistently associated with breast cancer risk. This association involves the estrogen receptor (ER), which is over-expressed (ER+) in around 80% of breast cancer cases. Alcohol-association is more pronounced in ER(+) breast cancer cases than in ER(-) breast cancer cases, however, the molecular mechanism remains to be determined. Cancer cells have a consistent cytological feature of nucleolar hypertrophy, where rRNAs are synthesized by RNA polymerases (Pol) I and Pol III. Pathologists have been using enlarged nucleoli as a diagnostic indicator of cell transformation and neoplasia. It indicates that transformation in situ is tightly linked to the deregulation of RNA Pol I and III gene transcription, because the size of the nucleolus reflects the levels of rRNA synthesis. RNA Pol III is responsible for the synthesis of a variety of untranslated RNAs, including 5S rRNAs and tRNAs. Deregulation of RNA Pol III-dependent genes (Pol III genes) would serve to enhance the translational capacity of cells, which is required to promote cell transformation and tumor development. Alcohol-induced deregulation of Pol III genes may be fundamental to the development of breast cancer. Our previous studies demonstrated that MAP kinases modulated Brf1 and TBP expression and Pol III gene transcription and mediated phosphorylation of histone H3 (H3ph). Our recent studies have demonstrated that ethanol activates MAP kinase and induces Pol III gene transcription through enhanced TBP and c-Jun expression by using cell culture and an animal model. Preliminary results have revealed that alcohol induces Pol III gene transcription in both normal breast and breast cancer cell lines. However, the induction in breast cancer cells (5-6 fold) is higher than i normal breast cells (2.5 fold). Further analysis indicates that the induction is ER dependent. The ER ligand, E2 (17b-estradiol) causes an induction (< 2 fold) of these genes, whereas ethanol works with E2 to create an additional increase (12 fold) in Pol III gene transcription, resulting i cell proliferation and transformation. Alcohol activated MSK1 (mitogen- and stress-activated protein kinase 1), a downstream component of MAP kinases, which mediates phosphorylation of histone H3 (H3ph) at serine 10 (H3S10ph) and serine 28 (H3S28ph) and modulates gene expression and cell transformation. Thus, we hypothesize that alcohol activates MSK1, which mediates H3ph. H3ph in turn upregulates Brf1 expression and Pol III gene transcription to enhance the protein synthetic capacity of cells, which can eventually lead to ERa-dependent breast cancer. This implies that the induction by alcohol may be an early event, contributing to the development of ER(+) breast cancer. By using cell culture and animal models, we will determine: 1) if alcohol-activated MSK1 mediates Brf1 expression and Pol III gene transcription, which in turn causes phenotypic changes, and if inhibition of MSK1 by its chemical inhibitor and shRNA or using a MSK KO mouse blocks alcohol-induced cell transformation and Pol III gene transcription; 2) if alcohol-induced H3ph modulates Brf1 and Pol III gene expression and cell transformation; 3) if alteration of ERa and Brf1 expression affects transcription of Pol III genes and if blocking Brf1 expression by its shRNA inhibits tumor formation in nude mouse upon administration of alcohol or alcohol plus E2. These studies are designed to determine the

molecular mechanism of alcohol-induced deregulation of Pol III genes in the development of ER+ breast cancer. Investigating the effects of MSK1 and Brf1 shRNAs on tumor formation may provide a new approach to inhibit tumor growth. Our overall objective is to investigate the role of MSK1 and Brf1 in the alcohol-induced response that may be critically important in ER+ breast cancer development.

National Institute of Allergy and Infectious Diseases

Title: **Airway Inflammation and Airway Remodeling**
P.I.: **David H. Broide**
Institution: **University of California, San Diego**
Grant No.: **AI070535-07**
Award: **$12,500**

Airway remodeling is the term applied to the structural changes observed in the airway in asthma. Although current NIH guidelines recommend maintaining a goal of normal lung function in asthma, current therapeutic strategies do not specifically target airway remodeling as the cellular and molecular mechanisms that result in remodeling are not well defined and thus therapeutic targets are not well understood. Thus, there is an important need to identify mechanisms by which airway remodeling is mediated so that potential novel therapies could be directed at these pathways. In addition, characterization of these pathways could lead to the development of non-invasive blood or sputum biomarkers to identify, monitor, and perhaps subset, patients with asthma and remodeled airways. This UCSD AADCRC proposal will be directed by David Broide (Professor of Medicine) and include three projects (Broide, Croft, Zuraw) that will investigate mechanisms of airway remodeling in asthmatics exposed to allergen and rhinovirus common triggers of asthma. Thus, the overall hypothesis that will be explored in all three projects is that exposure to allergen triggers expression of inflammatory and remodeling pathways in allergic asthmatics that are exacerbated by exposure to respiratory viruses such as rhinovirus. The specific hypothesis that will be explored in each project and that will be driven by samples from asthmatics, is that the innate immune response (airway epithelium, macrophages, natural helper cells) play an important role in initiating and perpetuating the inflammatory and airway remodeling response to environmental triggers in allergic asthmatics. The three interrelated projects will focus on Innate inflammation and airway remodeling (Broide, Project 1), TNF-R family members, inflammation and remodeling (Croft, Project 2), and Epithelial GILZ inflammation and remodeling (Zuraw, Project 3) and be supported by Administrative Core A, and Asthma Clinical Core B, which will be a source of sputum, BAL, endobronchial biopsy, and blood samples from asthma and control subjects provided by investigators in Core B (Ramsdell, Harrell, and Thistlethwaite, UCSD; Proud and Leigh, University of Calgary; and Hamid, McGill University). An lOFM Core is also proposed as requested by the RFA.

Title: **Airway Inflammation and HLA-G in Asthma**
P.I.: **Steven R. White**
Institution: **University of Chicago**
Grant No.: **AI095230-02**
Award: **$12,500**

Our program seeks to clarify cellular and molecular mechanisms that lead to chronic asthma in order to identify novel, more effective therapies. We concentrate on immune mechanisms that underlie chronic airway inflammation with a clear focus on one immune tolerance molecule, the class I major histocompatibility complex protein human leukocyte antigen (HLA)-G, that we believe has an important role in modulating airway inflammation that is critical to chronic asthma. The key premise of our AADCRC proposal is that understanding the role of HLA-G will lead to new and better therapies to alleviate the suffering caused by asthma. To this

end we propose three highly integrated and related projects: in Project 1, we will examine the presence and regulation of expression of HLA-G in asthmatic airways and in the airway epithelium, and relate presence to asthma severity and to the expression of regulating microRNA. We will examine the regulation of HLA-G expression by key Th2 cytokines such as IL-13 that are important to chronic asthma and relate expression back to airway cytokine concentrations in chronic asthma. In Project 2, we will exploit naturally occurring genetic variations in HLA-G and its LILRB receptors to understand how signaling through HLA-G and its receptors regulate the transition of CD4+ lymphocytes to the Th2 phenotype in mild/moderate asthma and to the Th17 phenotype in severe asthma. This project also will examine how genetic variation in the LILRB receptors modulate the effects of HLA-G on both T cell phenotype and on the SHP1 and SHP2 signaling pathways that modulate airway smooth muscle hypertrophy in chronic asthma. In Project 3, we will elucidate mechanisms that account for the higher risk of asthma among children of asthmatic mothers compared to children of non-asthmatic mothers. Using HLA-G as a model of the interactions of genotype and asthma status in mother and child, we will identify differentially expressed genes and the mechanisms for their differential expression in airway epithelium, CD4+ T cells and airway smooth muscle in subjects with chronic asthma. To complete these projects, each will interact with a robust Patient Recruitment and Data Analysis Core that will recruit 100 carefully phenotyped and genotyped asthmatic subjects and additional control subjects, and collect blood and airway biological specimens to be used in each project through a Lung Biological Specimens Core that will provide analytical and long-term storage. We believe that our current levels of productivity and collaboration combined with new, exciting and cutting-edge questions in this proposal will allow us to be successful in achieving our overall goal—identifying novel therapeutic targets for chronic asthma.

Title: **Autoimmunity Center of Excellence (ACE) at Stanford**
P.I.: **Charles Garrison Fathman**
Institution: **Stanford University**
Grant No.: **AI082719-04**
Award: **$30,000**

The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The major theme of the Stanford Autoimmunity Center of Excellence (the Center) is the study of the regulation of CD4 T cells in pathogenesis and treatment of autoimmune diseases. The Center will support and be supported by other ACE groups across the United States; and will take advantage of Stanford's documented leadership in basic and clinical research, technology development, and education in clinical immunology. Success of the Center will be supported by the interrelationships previously established at Stanford among clinician scientists from multiple departments studying autoimmune diseases in multiple organs and tissues. The Stanford ACE will be composed of outstanding basic and clinical investigators from multiple disciplines at Stanford Medical School and proposes both a basic Research Project, centered on CD4 T cell unresponsiveness, and a translational Research Project to study a new T cell lineage (termed Th17 cells) that is characterized by the ability of these lymphocytes to secrete high levels of the proinflammatory cytokine interleukin-17 (IL-17). Proposed clinical research projects encompass three different autoimmune diseases [diffuse systemic sclerosis (SSc), psoriatic arthritis and systemic juvenile idiopathic arthritis (SJIA)] that afflict adults and children, as well as organ systems including joints, skin, blood elements, and blood vessels, and will both test efficacy of therapy and develop tests to characterize the mechanisms of action of these therapeutics. The proposed Pilot and Feasibility Project proposes a two year research plan in Systemic Juvenile Idiopathic Arthritis (SJIA) patients to identify and validate urine peptide biomarkers that predict (a) response to TNF inhibition; (b) response to IL-1 inhibition; and (c) impending disease flare. In addition, this proposal will provide other ACE groups access to cutting edge reagents and technology platforms for studying human autoimmune diseases, and dissemination of Educational

Materials that can be used by other ACEs to teach clinical immunology concepts to high school, undergraduate, graduate, postgraduate, and clinical fellows and faculty. The Stanford ACE proposes to support integrated basic, pre-clinical and clinical research by proposing and then conducting basic and translational research into the mechanism of CD4 T cell unresponsiveness; two clinical trials that include novel therapies and mechanistic studies of these therapies for autoimmune diseases; and a pilot proposal that intends to develop new bi omarkers of disease. PROJECT 1A: Clinical Component (Genovese, M) CLINICAL COMPONENT DESCRIPTION (provided by applicant): Stanford University Medical Center (SUMC) has an extraordinary tradition of medical, translational, and basic science research. An outstanding array of resources, faculty, and facilities will be available to support the proposed ACE site at Stanford University. This proposal brings together a skilled group of translational researchers with a track record of productivity in both laboratory and clinical research focusing on human autoimmune mediated diseases. Stanford has brought together various disciplines to demonstrate both accomplishment and ability to work together with the following fields represented: Adult Rheumatology, Dermatology, Pulmonary Medicine, and Pediatric Rheumatology. The projects chosen for this submission highlight the significant collaborations that exist between Rheumatology (Adult and Pediatric), Dermatology and Pulmonary Medicine. Both clinical trials projects explore dermatologic and rheumatologic manifestations of diseases such as Psoriatic arthritis and Systemic Sclerosis. Clinical Trial Concept 1: The use of an anti-IL-17 mab in the treatment of active Psoriatic Arthritis Primary Hypothesis: The proportion of patients achieving the ACR 20 response from Baseline to Week 14 among active Psoriatic Arthritis (PSA) subjects treated with IL-17 mab is larger than the proportion achieving ACR 20 response from Baseline to Week 14 among active PSA subjects treated with placebo Objectives: The goal of this study is to determine the safety and efficacy of a monoclonal antibody to lnterleukin-17 (IL-17 mab) in the treatment of PsA with active skin and joint disease. Clinical Trial Concept 2: The use of CTLA-4lg (abatacept) in subjects with diffuse systemic sclerosis Primary hypothesis: Given several lines of evidence supporting the role of activated T cells in affected skin, we hypothesize that inhibiting T cell activation may lead to significant clinical improvement in skin manifestations in patients with diffuse systemic sclerosis (dSSc), and that changes in tissue and blood autoantibody and cytokine profiles will be associated with clinical response. Objectives: The primary goal of this study is to determine the safety and efficacy of CTLA-4lg (Abatacept) for the treatment of cutaneous manifestations of dSSc RELEVANCE (See instructions): The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune (Al) disease. The Stanford ACE proposes clinical research projects that encompass three different autoimmune diseases (SSc, psoriatic arthritis and SJIA), and proposes to study the MoA of therapeutics for preventing or treating different Al diseases.

Title: **Cervical/Vaginal Mucus and Microbicides**
P.I.: **Thomas Hope**
Institution: **Northwestern University at Chicago**
Grant No.: **AI094584-02**
Award: **$18,750**

To develop a functional microbicide it is critical to know how it will interact within HIV in the context of the female genital tract. This is a critical issue as previous clinical trials have indicated that microbicides do not function as expected in the presence of semen. Likewise, other factors, such as cervical/vaginal mucus, might also modulate microbicide function. To date, little is known about how HIV interacts with these fluids and how the interaction of these fluids changes the local environment. Even less is known about how microbicides interact with HIV within this milieu. For example, the vehicle delivering the microbicide might interact with the biological fluids of sexual transmission to either increase or inhibit HIV acquisition or microbicide potency. The Hope laboratory has recently developed methods that allow the transport of

HIV with cervical and cervical/vaginal mucus to be analyzed and quantified. These studies have revealed that mucus can perturb HIV transport and is pH sensitive. At acidic pH, as is found in the lactobacilli influenced environment of the vaginal vault, HIV transport is greatly reduced. At neutral pH, such as when semen is introduced into the system, HIV transport is reduced 10-15 fold relative to what is observed in media (water). Additionally, we have found, but not yet published, that virus-binding antibodies can further reduce transport in neutral pH cervical mucus. These antibodies do not need to be neutralizing as any antibody binding to the virus can decrease virus transport. Semen also contains mucins and other components that have the potential to alter HIV transport as we have observed in cervical mucus. How HIV is transported within semen and how this changes when mixed with mucus or microbicides is not defined. How this process influences HIV transport and interaction with mucosal barriers is not understood. In the first phase (R21) of this proposal we will define how HIV is transported in semen alone and mixed with mucus and/or microbicide vehicles such as carbopol gel and hydroxy ethyl cellulose (HEC). In the second phase (R33) of this proposal we will extend our studies into the environment of the rhesus macaque female genital tract to determine how biological fluids and microbicide vehicles alter the way that virus interacts with the mucosal barriers of this environment and how these changes can increase or decrease SIV acquisition. These studies will lead to a better understanding of how virus interacts with biological fluids and how these interactions might alter microbicide efficacy.

Title: **Designing Optimal Microbicide Delivery Integrating Rheology and Acceptability**
P.I.: **John Edward Hayes**
Institution: **Pennsylvania State University**
Grant No.: **AI094514-02**
Award: **$18,750**

This year perhaps 2.5 million people will be added to the approximately 35 million already infected with HIV/AIDS, 50% of whom are women. Topical microbicides offer these women a means to prevent sexually transmitted infections (STIs), including HIV. However, in addition to concerns about the biological efficacy of current microbicides, user acceptance of and adherence to their use is suboptimal. It has been estimated that a single microbicide with even limited efficacy could prevent millions of new HIV cases annually. The design of vaginal microbicide dosage forms has challenged formulation scientists. Safe and efficacious products are necessary, but not sufficient to assure adherence. User acceptability depends both on the physical properties of the material and behavioral factors. Constraints that drive acceptance must be identified and addressed early in development. The acceptability of the product to women must be evaluated preclinically. We propose the rational preclinical design and development of a dosage form that delivers an immediate efficacious dose of active pharmaceutical ingredient (API) followed by the slow release of API over a period of 1-3 days to maintain efficacy. This dosage form can be thought of as a temporal vaginal ring/diaphragm that releases API(s) as it slowly erodes away. These products will be an adaptation of current softgel capsule technology. However, unlike current gelatin capsules, we will develop a range of non-gelatin capsules varying in shape and firmness (texture). Human perceptual data will be assessed throughout and guide the design process. Carrageenan will be used for the development of heat-stable softgels that, unlike current gelatin capsules, will not melt in tropical environments. The two-phase nature of softgels ('ovules') will permit the inclusion of a second component. Our R21 goals provide for proof-of-concept of this new delivery system, and the R33 goals will optimize both acceptability and biophysical functionality. The R33 will also explore potential higher-order functionality, like mucoadhesion or delivery of probiotics. Here, we propose a new microbicide delivery system, designed to overcome both biological (insufficient HIV neutralization) and behavioral (poor acceptability and adherence) deficiencies of current products. By designing formulations that function for optimal efficacy and optimal use (acceptability / adherence), microbicides

produced via these methods are likely to have a greater impact on the HIV/AIDS pandemic than those currently in the development pipeline. Also, by developing a methodology for design of vaginal products where multiple factors (shape, texture, size, and multi-stage delivery) play a central role, we increase the options women have in microbicide use. Critically, our product type is flexible—allowing for multiple textures, sizes, shapes and antiviral strategies—to accommodate a range of user preferences.

Title: **Development of an HIV-1 Entry Inhibitor Pre-drug as a Microbicide**
P.I.: **Min Lu**
Institution: **University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School**
Grant No.: **AI094555-02**
Award: **$18,750**

With no vaccine in sight, there is an urgent public health need to develop an effective topical microbicide that can reduce the number of new HIV-1 infections in women. The potential role of virus-cell fusion inhibitor-based microbicides in preventing mucosal transmission of HIV-1 has been clearly identified. However, none of the reported gp41 fusion inhibitors has made significant progress toward clinical trials. HIV-1 infection requires fusion of the viral and cellular membranes, driven by association of two heptad-repeat regions in the gp41 ectodomain to form a highly stable six-helix bundle structure. Whereas this postfusion motif comprising native N36 and C34 peptides has no inhibitory activity, the isolated peptides inhibit HIV-1 entry by binding to their cognate sites on gp41. Our goal in this MIP VI application is to develop an inexpensive, potent, structured 'pro-drug' form of the N- and C-peptide fusion inhibitors that exhibits significant microbicidal activity upon use in situ. Our development effort will be based on preliminary data obtained with a truncated six-helix bundle that inhibits in vitro infection by primary HIV-1 isolates with low nanomolar IC50 values. We propose a comprehensive, interdisciplinary approach that combines high-resolution structural determination, recombinant protein production and mutagenic analyses, virology, and animal model efficacy studies. In this project we seek to conduct in vitro and in vivo preclinical and animal model-based research intended to facilitate the development of new HIV-1 gp41 peptide fusion inhibitor as a practical microbicide. The Specific Aims are: 1. To optimize and identify HIV-1 peptide fusion inhibitors for development as a vaginal microbicide. (a) To identify and incorporate specific amino-acid residue substitutions that optimize both potency and solubility of fusion inhibitor peptides. (b) To develop and optimize robust procedures for the large-scale bacterial expression and purification of select fusion inhibitor peptides. (c) Investigate the mechanisms of resistance to peptide inhibitors so as to avoid eliciting resistance. 2. To characterize the specificity, potency and toxicity of optimized peptide fusion inhibitors and their in vitro synergistic interactions with the CCR5 inhibitor CMPD167 and the entry inhibitor BMS-378806. (a) Determine the virucidal activity of optimized fusion inhibitor peptides against a diverse set of primary HIV-1 isolates. (b) Evaluate their toxicity, immunogenicity and drug stability in the rabbit model. (c) Study antiviral synergy in vitro in order to make rational predictions for lead inhibitor combinations for in vivo efficacy testing. 3. To test the effectiveness of the fusion inhibitor peptides to protect against mucosal HIV-1 infection. (a) Characterize the specificity and potency of effective peptide inhibitors in an in vitro model of HIV-1 infection of human cervical and vaginal tissue. (b) Use the NOD/SCID-hu BLT mouse vaginal transmission model to assess the in vivo potency and breadth of activity of highly effective peptide inhibitors alone and in combination with the small-molecule CCR5 inhibitor CMPD167 and the small-molecule entry inhibitor BMS-378806.

Title: **Epithelial Barrier Programs in Asthma and Allergic Disease**
P.I.: **Michael J. Holtzman**
Institution: **Washington University**
Grant No.: **AI070489-07**
Award: **$12,500**

The overall goal of this AADCRC proposal is to define the role of the epithelial cell barrier in the pathogenesis of asthma and allergic disease and to use that information to prevent this type of disease. We combine expertise in airway as well as gut and skin epithelial cell biology, and we use cell and mouse models with high fidelity to directly translate our findings to humans. The AADRC therefore consists of three interrelated Projects that ask, first, how airway epithelial cells mediate effective antiviral defense under one condition but asthma under another (Project 1), second, how airway epithelial cells remodel towards an overabundance of mucous cells in post-viral and allergic asthma (Project 2), and third, how epithelial injury in the skin triggers the march from atopic dermatitis to asthma (Project 3). Each project addresses the respective question with a novel but overlapping molecular approach to mechanism and takes advantage of a breakthrough discovery to set a new scientific paradigm for the system under study. Thus, Project 1 unravels a new IFN signaling pathway that offers improved protection against viral infection and post-viral asthma and is specific to the airway epithelial cell barrier; Project 2 dissects a new pathway for autophagy proteins to support proper mucous cell function and prevent mucous cell metaplasia in the airway in a manner reminiscent of the intestinal epithelial barrier; and Project 3 defines a new TSLP production and secretion pathway that drives airway inflammation based on its expression in the skin epithelial barrier. Each Project is constructed so that the first aim will establish a basic pathogenic mechanism using cell and mouse models that are shared among projects and supported by the Cores for tissue and cell processing (Core C) and mouse models (Core D). In turn, each Project will conduct a second aim to validate and translate its findings using samples from children and adults with asthma and/or atopic dermatitis supplied by the Core for human subjects and data analysis (Core B). Sharing samples and overlapping scientific goals among projects create a synergistic program that can be coordinated by a common Administrative Core (Core A). Project and Core interactions are based on the overall principle that each Project begins with molecular hypothesis building in cell and mouse models and translates findings from these models to studies of humans with asthma and/or allergy. In each project, we aim to validate a clinically useful biomarker of the disease process and lay the groundwork for the future development of biological and/or small molecular weight compounds that might influence the process as a therapeutic strategy.

Title: **Epithelial Genes in Allergic Inflammation**
P.I.: **Gurjit K. Khurana Hershey**
Institution: **Cincinnati Children's Hospital Medical Center**
Grant No.: **AI070235-07**
Award: **$12,500**

Allergic disorders are a major global health concern affecting 150 million people worldwide. Recently, epithelial cells have emerged as central participants in the pathogenesis of allergic inflammation: (1) they interface with the environment and initiate the response to environmental triggers; (2) the mucosal epithelium in the lung, skin, and gut functions as a physical barrier against pathogens and environmental exposures including allergens; and (3) epithelial cells have been directly implicated in Th2 responses, serving as a critical interface between innate immune responses and Th2 immunity. The overall objective of these studies is to elucidate the mechanisms by which epithelial cells contribute to the pathogenesis of allergic disorders. The overarching hypothesis of this Center proposal is that epithelial cell genes play a central role in the pathogenesis of allergic disorders. This hypothesis will be tested by three integrated projects that use the Center for coordination and synergistic extension of the projects beyond the scopes and capabilities of the individual projects. This Center will provide important insights

into the genes and pathways that may be Important in epithelial driven allergic inflammation and provide a basis for the design of novel therapeutic strategies aimed at the epithelial surface, i.e. lung (asthma), skin (atopic dermatitis), or gut (food allergy or eosinophilic esophagitis). Furthermore, integration of data across projects will provide novel insights into a key question in allergy—What are the mechanisms underlying tissue specific disease manifestations of allergic inflammation? Each project in the Center is focused on distinct epithelial cell genes and their roles in allergic disorders. Project 1 will examine the association of epithelial genes with allergic diseases that target distinct mucosal surfaces. Project 2 will dissect the role of epithelial desmoglein-1 in the pathogenesis of the allergic disorder eosinophilic esophagitis. Project 3 will focus on delineating the mechanisms by which epithelial-derived IL-33 is regulated by trefoil factor 2 (TFF2) during the early innate immune events that initiate allergy and asthma; and better define the role of the TFF2/IL-33 pathway in the pathogenesis of allergic disorders.

Title: **Host and Viral Determinants of Infant and Childhood Allergy and Asthma**
P.I.: **Ray Stokes Peebles**
Institution: **Vanderbilt University Medical Center**
Grant No.: **AI095227-02**
Award: **$12,500**

The long term objective of this application is to define the relationship between infant respiratory syncytial virus (RSV) infection and the host response that enables asthma inception. There is abundant evidence that children who experience severe RSV bronchiolitis during infancy are at greater risk for developing asthma later in childhood; however the host and viral determinants of severity of illness are not fully defined. Also unknown is whether mild RSV-induced illness in infancy may protect against the subsequent development of childhood asthma. In Project 1, we utilize the ReSPIRA (Respiratory Study for Protection of Infants from RSV to Asthma) cohort of 2000 infants to focus on host immune responses to RSV infection and the subsequent risk of recurrent wheezing and childhood asthma. Specifically, in Project 1 we will a) establish the relationship between the host phenotypic response to RSV infection in the first 6 months of life and the risk of recurrent wheeze and asthma, and b) identify the host genetic and immune response determinants of the RSV infection phenotype that affect the development of early childhood wheezing and asthma following RSV infection. In Project 2, we will focus on the contribution of specific RSV strains to early childhood wheezing and asthma development. RSV strains isolated from the ReSPIRA cohort will be genotyped and clinical parameters such as bronchiolitis severity score, as well as mediators of the host immune response measured in respiratory secretions will be studied to determine how RSV genotypes impact the host response. In Project 3, we will utilize a mouse model of RSV infection to examine the role of the prostaglandin 12 (PGI2) on airway dysfunction of an RSV strain (01/2-20) that has been associated with severe infant bronchiolitis and which induces airway pathology in the mouse. We previously reported that PG12 and signaling through its receptor (IP) is a critical determinant of severity of illness in RSV strain A2 infection. This project will determine the role of host PGI2 in RSV airway pathogenesis and also determine if a PGI2 analog currently used in the treatment of human disease is a target for RSV bronchiolitis. Further, in Project 3, we will use RSV strains isolated from ReSPIRA in Project 2 to determine the generalizability of PGI2 as a therapeutic target.

Title: **Mechanisms of B Cell Responses in Autoimmune Disease**
P.I.: **Eugene William St. Clair**
Institution: **Duke University**
Grant No.: **AI056363-09**
Award: **$30,000**

This application is a competitive renewal of the Autoimmunity Center of Excellence (ACE) at Duke. Its research focus will continue to be modulation of B cell responses in autoimmune disease. The ACE will be under the leadership of Dr. E. William St. Clair, Professor of Medicine

and Immunology. For the past 5 years, Duke has been a productive member of the ACE network, contributing new insights into the developmental pathways of B cells and the mechanisms of B cell directed therapy. The proposed ACE builds on these discoveries and will support 2 new basic science projects, 5 ongoing and 2 new clinical trials, and an Administrative Core, and continue to emphasize a strong and fluid integration between the bench and the bedside. Tedder and colleagues have recently found that a phenotypically unqiue subset of B cells secreting IL-10 (called B10 cells) serve as critical negative regulators during adaptive CD4+ T cells responses, and dramatically suppress Th1 immune responses and autoimmune disease in mice. For Basic Research Project 1, they will examine the hypothesis that antigen-specific regulatory B10 cells modulate autoimmune responses in mice and man and that they can be manipulated for therapeutic gain. A picture is gradually emerging about the precursors of self-reactive B cells in autoimmune disease. Kelsoe and coworkers in Basic Research Project 2 will investigate developmentally regulated expression of activated cytidine deaminase (AID) in human fetal and neonatal pre-, pro, and immature/transitional B cells and its relationship to the generation of self-reactive B cells in human autoimmune disease, potentially eludidating another pathway of B cell self-reactivity outside the confines of normal tolerance mechanisms. We propose two new clinical trials to investigate lymphotoxin-beta receptor fusion protein as a treatment for primary Sjögren's syndrome, and rituximab therapy for bullous pemphigoid. A Pilot Research Project is also proposed to engineer tetramers of self-antigen enabling the identification and characterization of self-reactive B cells, which will have implications for the goals of the clinical and other basic research projects. Overall, the Duke ACE will bridge these basic and clinical studies to advance our understanding of autoimmune disease. The B cell is a type of immune cell essential to autoimmunity. The goal of the proposed Autoimmunity Center of Excellence at Duke is to improve our understanding of the roles played by B cells in human autoimmune disease. The projects are designed to be highly integrative between the bench and the bedside, with collaborations between basic and clinical scientists. These studies may lead to better treatments. CLINICAL COMPONENT: Clinical Component (ST CLAIR, W) CLINICAL COMPONENT DESCRIPTION (provided by applicant): The Clinical Research Component of the Autoimmunity Center of Excellence shares with the Basic Research omponent an overall goal of advancing our understanding about the role of B cells in the pathogenesis of autoimmune diseases. This component will be directed by Dr. E. William St. Clair. During the past 5 years, the Duke ACE has brought 3 new clinical trial concepts to the ACE Steering Committee, resulting in 1 completed trial, 1 ongoing trial, and 1 protocol in development. We are also participating in 3 other ongoing ACE-sponsored clinical trials. Therefore, substantial clinical research activity will carry over to the next funding cycle. Our center is organized to support clinical trials in rheumatology, dermatology, gastroenterology, hematology, and neurology. We have access to several large patient populations, including patiens with rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome, scleroderma, autoimmune blistering disease, psoriasis, inflammatory bowel disease, autoimmune hepatitis, anti-phospholipid antibody syndrome, and myasthenia gravis. Each of these disease areas has leadership from one or more physician-investigators with significant clinical trial experience, including an example of a productive inter-institutional collaboration. The physician leadership is supported by an ample infrastructure that provides clinical research space, infusion facilities, experienced clinical coordinators, and an Immune Monitoring Component. The Clinical Research Component aligns with the ACE at a thematic level, with substantial collaborations between basic and clinical scientists. To this end, the proposed clinical trial concepts will focus on B cell directed therapy. In one case, we propose to examine the clinical efficacy of lymphtoxin-beta receptor fusion protein in the treatment of primary Sjögren's syndrome, and have already secured commitment from the industry sponsor to provide study drug for this trial. The other application will investigate rituximab as initial therapy for bullous pemphigoid. The mechanistic studies for these proposed trials as well as current trials are highly integrated with the basic research projects. The Clinical Research Component will make a significant contribution to the ACE enterprise during the upcoming funding cycle. The Clinical Research Component will support clinical trials sponsored by the Autoimmunity Centers of Excellence

in several disease areas, including rheumatology, dermatology, gastroenterology, hematology, and neurology. It has been productive during the current funding cycle, and has the capability, as shown in this application, to generate new ideas for clinical trials that can be translated into well-designed studies.

Title: **Mucosal Tissue Explants as Surrogates for In Vivo Efficacy of Microbicides**
P.I.: **Carolina Herrera**
Institution: **University of London, Imperial College of Science, Technology and Medicine**
Grant No.: **AI094515-03**
Award: **$18,750**

The HIV microbicide field is dependent upon testing in non-human primates (NHPs) as the only relevant model to study infection. However, the predictive accuracy of NHP studies of efficacy in humans has not been validated and as such the economic value is unknown. Hence, refinement of this model and development of a novel correlate of efficacy in humans that will reduce the potential use of NHPs is key for the global progress of microbicides and specifically of the Microbicide Innovation Program's mission. This proposal addresses these issues by testing the hypothesis that ex vivo tissue explant cultures can provide a potential surrogate of in vivo efficacy through measurement of intra-tissular drug pharmacology and ex vivo infection/protection. This will be investigated using combined expertise in modeling mucosal tissue infection and measurement of antiretroviral (ARV) drug pharmacokinetics and pharmacodynamics in tissue. The proposal will focus on a reverse transcriptase inhibitor, PMPA (tenofovir), and an entry inhibitor, maraviroc, used alone and in combination as candidate microbicides. In the R21 component of the proposal we will demonstrate the robustness of our ex vivo explant models for analysis of pharmacological parameters and ex vivo infection independently of the origin (human or NHP) and the type of mucosa (cervicovaginal or colorectal). This will be investigated through two Specific Aims: 1) to define ex vivo pharmacological dose-responses (pharmacokinetics and pharmacodynamics) in human and rhesus macaque mucosal tissue explants; 2) to define whether the viral backbone affects pharmacological correlates of activity. The next step of our proposal in the R33 component will involve validation of the model as a surrogate for prediction of in vivo efficacy of ARV drugs as vaginal and colorectal microbicides. Here the two Specific Aims are: 3) to assess whether activity of drugs titrated in vivo can be predicted with ex vivo challenge models: 4) to correlate ex vivo and in vivo protection and drug dosing in NHPs. The iterative design of the overall proposal will allow us to assess correlates between intra-tissular pharmacological dosing and efficacy at all levels: tissue type, origin of tissue, route of dosing and challenge, and nature of experiment (ex vivo, in vivo). These correlates will define conversion factors of microbicides efficacy between the NHP model and in humans, which will be key for the rational development of existing and future candidate microbicides.

Title: **Mucus-Penetrating Particles for Rectal Microbicides**
P.I.: **Justin S. Hanes**
Institution: **Johns Hopkins University**
Grant No.: **AI094519-02**
Award: **$18,750**

For reliable protection against STD transmission, rectal microbicides must be formulated in a way that will deliver the active agent to all the surfaces that are susceptible to infection. These include the entire rectum as well as a large fraction of the colon (due to peristaltic stirring of colonic contents). Colorectal surfaces are columnar epithelia that are mechanically and osmotically fragile, and are highly susceptible to STD transmission. Although continuous mucus secretion by these susceptible surfaces helps protect against trauma and pathogens, this continuously secreted mucus also poses a significant barrier against effective delivery of microbicides to the epithelial surface. Recently we developed novel mucus penetrating nanoparticles (MPP) that

can overcome this barrier and provide sustained, well-distributed delivery of drugs to mucosal surfaces. Our hypothesis is that MPP will significantly increase the protective efficacy of rectal microbicides by achieving more uniform and complete colorectal distribution, sustained drug activity, and thus longer duration and more complete protection compared to drug delivered in gels (free drug) or drug delivered in conventional nanoparticles, CP, that adhere to mucus and fail to penetrate mucus barriers. In the R21 phase, we will determine optimal MPP properties for penetration of mouse colorectal mucus, and we will characterize the uniformity of MPP distribution and retention times in the mouse colorectum compared to CP and free drug. We will then prepare drug-loaded biodegradable and biocompatible MPP that provide sustained release of antiviral drugs (valacyclovir for HSV and UC-781 for HIV). We will deliver these MPP in both a rectal enema format and a rectal lubricant gel format since both formats are frequently used for enhancing rectal intercourse. Moreover, an enema may deliver MPP to large regions of the colon unlikely to be reached by a gel. The key milestone for the R21 phase will be development of valacyclovir-MPP and UC-781- MPP that provide more complete and persistent coverage of the rectal epithelial surface, with minimal toxicity, compared to CP formulations or free drug. In the R33 phase, we will extensively test these MPP formulations for safety and protective efficacy in our mouse/HSV rectal model and in the hu-BLT-SCID mouse/HIV model (via a subcontract with Dr. J. Victor Garcia-Martinez at UNC).

Title: **Nanoparticle Microbicides for Delivery of Combination Antiretroviral Drugs**
P.I.: **Kim A. Woodrow**
Institution: **University of Washington**
Grant No.: **AI094412-02**
Award: **$18,750**

Sexual transmission through the genital tract or rectal mucosa is the most common route for acquiring new HIV infections and accounted for ~70% of the 2.7 million people worldwide who became newly infected in 2007. A cure or effective vaccine that would contain the global spread of this epidemic is not expected in the near term, and new HIV infections continue to outpace advances made in treatment with antiretroviral drugs. There is consequently an urgent need to develop agents that can be applied topically to mucosal surfaces to prevent the sexual transmission of HIV. However, several large-scale clinical trials testing the efficacy of agents that disrupt the integrity of the viral envelope (detergents) or prevent adsorption or fusion of the virus with its target cells (polyanions) have failed to protect against HIV infection. The success of highly active antiretroviral therapy (HAART) provides a paradigm for developing the next generation of microbicides, raising the possibility that a combination of potent and broadly active inhibitors that exhibit multiple and complementary mechanisms of action may be vastly superior to the delivery of single compounds. To fully realize the potential of these potent antiretroviral (ARV) drugs, the challenges of formulating and delivering compounds with markedly different chemical stability and aqueous solubility in a topical combination product must be overcome. This research plan is designed to evaluate nanoparticle-based vaginal drug delivery systems for HIV prevention. The experimental focus is to achieve protection against vaginal transmission of HIV-1 by topical delivery of a combination of antiretroviral drugs using mucus- and tissue-diffusing nanoparticle microbicides. This research would be the first to control the temporal and spatial co-delivery of a combination of antiretroviral agents that have different mechanisms of action against HIV-1 (Aim 1). If successful, our studies would be the first to determine the size range and penetration depth accessible for nanoparticulate drug delivery systems in the vaginal mucosa (Aim 2). Our proposed research will also provide valuable data on the transport, biodistribution, and pharmacokinetics of encapsulated and released antiretroviral agents that are administered topically to the vaginal mucosa using nanoparticle microbicides (Aim 3). Finally, we will conduct preclinical safety and anti-HIV efficacy studies to rapidly advance our nanoparticle-based microbicides to human safety and efficacy trials (Aim 4). The outcomes from our proposed research may highly impact the field of microbicide research for HIV and other sexually-transmitted infections.

Title: **Oklahoma Autoimmunity Center of Excellence**
P.I.: **Judith A. James**
Institution: **Oklahoma Medical Research Foundation**
Grant No.: **AI082714-04**
Award: **$30,000**

The Oklahoma Medical Research Foundation is home to outstanding clinical and basic science investigators who have research interests in the etiology and pathogenesis of autoimmune diseases and seek to identify novel therapeutics for more effective patient treatments. The scientific expertise, extensive clinical trial experience, access to geographically distinct patient populations, as well as unique patient registries, repositories and core technologies provide a solid foundation for the Oklahoma Autoimmunity Center of Excellence (ACE) application to which we have added a multidisciplinary team of clinical and basic science investigators. The focus of the Oklahoma ACE application is on expediting the translation of scientific discoveries in autoimmunity to clinical application in the diagnosis and treatment of systemic autoimmune diseases. To accomplish this, the Oklahoma ACE comprises two research projects, a proposed pilot research project, a Clinical Center (Joan Merrill, PI) and an administrative core (Judith James, PI). The research projects focus on thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and Sjögren's syndrome, which are also focuses of the Clinical Center. Multiple sclerosis, rheumatoid arthritis, pediatric arthritis, insulin-dependent diabetes, idiopathic thrombocytopenia and pediatric lupus are other key disease emphases of the Clinical Center. Two complimentary, but unique, research projects focus on understanding early events in the development of lupus autoimmunity and in defining targetable genetic associations in Sjögren's syndrome. The pilot project uses complimentary methods to address roles of elevated interferon activity in patients with TTP and a novel animal model of thrombocytopenia. In addition, two clinical trials are proposed; both of which enhance or build upon the basic science projects. The first studies efficacy and mechanistic affects of anti-IFN in select SLE patient subsets by applying a patient centric, dose optimization strategy. The second tests the efficacy and early MRI changes of a novel MEK1/MEK2 inhibitor in RA with additional mechanistic studies. The Administrative Core will provide leadership and management through acting on behalf of the Oklahoma ACE members within the ACE Network and NIH Program, ensuring fiscal responsibility for the ACE, and providing an educational foundation for a multi-disciplinary approach to autoimmune disease research. Thus, the Oklahoma ACE will unite Oklahoma-based clinical and basic science experts to facilitate access to unique patient populations for participation in clinical trials and to understand basic mechanisms of etiology and pathogenesis. The Oklahoma ACE brings together adult and pediatric rheumatologists, neurologists, endocrinologists, dermatologists, hematologists, dentists, ophthalmologists, geneticists, immunologists, molecular biologists, epidemiologists and biostatisticians to provide a multidisciplinary approach to discovering and applying novel therapeutics in systemic autoimmune diseases. Through strong basic science projects paired with clinical expertise the Oklahoma ACE will provide unique research and clinical opportunities to the ACE Network. CLINICAL COMPONENT: CLINICAL CENTER (Merrill, J) CLINICAL COMPONENT DESCRIPTION (provided by applicant): The Oklahoma ACE Clinical Center brings together disease-specific and interdisciplinary clinics in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, thrombotic thrombocytopenic purpura, insulin dependent diabetes mellitus, pediatric SLE and juvenile inflammatory arthritis to forward translational research in autoimmunity. Patients from each of these disease populations are available and committed to participate in potential national ACE investigations. With adult and pediatric rheumatologists, adult and pediatric endocrinologists, neurologists, hematologists, dermatologists, ophthalmologists and dentists, as well as basic scientists from various areas of immunology, molecular biology, genetics, epidemiology and biostatistics, our investigative team is poised to make basic advances regarding disease pathogenesis and to help translate these discoveries to the clinic. The Clinical Pharmacology program at OMRF will serve as the primary home for the SLE, RA, Sjögren's syndrome and TTP clinics. Currently leading or participating in more than 20 active clinical trials, this clinical center

is accustomed to participating in clinical trials, managing confidential patient information, and providing multidisciplinary care. In addition, the Clinical Pharmacology space provides investigators access to state-of-the-art research tools directly adjacent to the patient care unit. Pediatric IDDM and rheumatology clinics are housed across the street at OUHSC and a large, community based multiple sclerosis clinic will participate for MS patient investigation. Joan Merrill, MD serves as the leader of our Clinical Center. She is the current medical director of the Lupus Foundation of America and a leader in SLE clinical trial development. She has served as the lead investigator on large, multi-site trials. Combining her extensive knowledge of clinical trial design and the known heterogenic presentation of SLE, she proposes to devise patient-centric clinical trials that use biomarkers of disease to optimize therapeutic doses. Our Clinical Center proposes two potential clinical concepts. Based upon our basic science investigation regarding pivotal roles for increased interferon activity in pre-clinical SLE, Sjögren's syndrome and potentially TTP, our first trial examines the efficacy and biologic impact of anti-INF alpha in SLE patients with arthritis and select dermatologic manifestations. The second trial proposes use of a first-in-class target of MEK1/MEK2 inhibition in RA to assess impact on MRI progression of disease and on select biomarkers. Both of these trials have mechanistic studies proposed to address key scientific questions regarding pathogenesis and response. The Oklahoma Autoimmunity Center of Excellence Clinical Center will provide interdisciplinary investigators with unique populations of well-characterized patients to participate in ACE network autoimmune disease clinical trials. With our rich Native American heritage and large rural populations, the patients provided by the Oklahoma ACE will be previously understudied and provide unique insights for therapeutic trials.

Title: **Pathophysiologic and Therapeutic Mechanisms of Aspirin Exacerbated Respiratory Disorders**
P.I.: **Joshua A. Boyce**
Institution: **Brigham and Women's Hospital**
Grant No.: **AI095219-02**
Award: **$12,500**

This Proposal for support of an Asthma and Allergic Disease Cooperative Research Center (AADCRC) grant is focused on the mechanistic basis of aspirin-exacerbated respiratory disease (AERD), a distinctive clinical syndrome that accounts for a disproportionate percentage of individuals with severe asthma and recurrent nasal polyps. AERD is associated with both characteristic clinical reactions to ingestion of nonselective inhibitors of cyclooxygenase (COX), persistently elevated generation of the cysteinyl leukotrienes (cys-LTs), especially during reactions to aspirin, and selective airway hyperresponsivness to leukotriene E4 (LTE4), the most stable and abundant of the cys-LTs. We have discovered a molecular pathway through which LTE4 induces pulmonary inflammation (requiring P2Y12 receptors and platelets) and vascular leak (requiring a putative novel LTE4 receptor, GPR99). We have also discovered that leukocytes from individuals with AERD display a defect in expression of COX-2 and COX-2-dependent generation of prostaglandin E2 (essential to maintain homeostasis in AERD), and that this reverses with desensitization to aspirin. We have also found that platelets and leukocytes from individuals with AERD lack the EP2 receptor for PGE2. A team of highly accomplished investigators with complementary skills will apply cellular, molecular, and whole animal strategies, combined with a proof-of-concept clinical trial to determine the cellular and molecular basis for these findings, their relevance to disease pathophysiology, and their amenability to therapy. Project 1 (J. Boyce, PI) focuses on the physiologic and functional consequences of EP2 receptor deficiency, and determines its epigenetic basis. Project 2 (Y. Kanaoka, PI) will verify the identity and function of GPR99 and determine its susceptibility to desensitization and its requirement for downstream effectors (platelets, P2Y12, and thromboxane) to elicit physiologic responses. Project 3 (E. Israel, PI) will determine the efficacy of P2Y12 antagonism on the severity of clinical reactions to aspirin, and the mechanism by which aspirin treatment restores COX-2-dependent PGE2 generation. The coordination of the AADCRC is enhanced by an administrative Core.

Title: **Role of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin in Asthma**
P.I.: **Joel Barry Baseman**
Institution: **University of Texas Health Science Center at San Antonio**
Grant No.: **AI070412-07**
Award: **$12,500**

The San Antonio Asthma and Allergic Diseases Cooperative Research Center (SA-AADCRC) represents a tightly focused, integrative and innovative effort to understand the role of Mycoplasma pneumoniae and its unique ADP-ribosylating and vacuolating toxin, designated Community Acquired Respiratory Distress Syndrome ToXin (CARDS TX) as important mediators of acute and chronic airway diseases, including new onset asthma and exacerbations, as well as persistent pulmonary dysfunction in children and adults. The basic science and clinical investigators who comprise the SA-AADCRC team share broad expertise and are highly collaborative. The SA-AADCRC's broad strategy of attack interlinks basic science and clinical research projects and cores. Project 1 uses the murine model and human materials to address fundamental questions on how CARDS TX induces asthma-like disease and exacerbates allergic pulmonary inflammation. Project 2 focuses on identifying CARDS TX ADP-ribosylating airway protein targets, delineating functionally important CARDS TX domains and essential amino acids that mediate CARDS TX binding to human surfactant protein A (SP-A) and airway cells, and generating antibody reagents that block/neutralize CARDS TX. Project 3 applies state-of-the-art biophysical techniques to uncover the structure and action of CARDS TX by using single crystal X-ray diffraction to determine CARDS TX three dimensional structure in the presence and absence of its cofactor NAD; neutralizing monoclonal antibody Fab fragments; and surfactant protein-A (SP-A). Clinical Core will collect human material from subjects with well controlled asthma, poorly controlled asthma and healthy controls and help in evaluation and follow-up of patient-related studies. Diagnostic Core will process clinical and experimental samples for diagnostic analysis by providing highly sensitive and specific diagnostic assays for rapid detection of M. pneumoniae CARDS TX. Pathology Core will provide necessary biopsy and necropsy procedures, lung pathology interpretation, histochemical and immunocytochemical evaluations, and qualitative and semiquantitative histopathologicai analyses. Administrative Core will oversee all SA-AADCRC-related activities and coordinate interactions and collaborations between projects and cores. Therefore, the SA-AADCRC represents a network of collaborators/colleagues who continuously ask fundamental and translational questions about asthma, airway-related pathologies, immunopathogenesis, and M. pneumoniae/CARDS TX biology and virulence mechanisms.

Title: **The Semen Enhancer of HIV Infection as a Novel Microbicide Target**
P.I.: **Stephen Dewhurst**
Institution: **University of Rochester**
Grant No.: **AI094511-02**
Award: **$18,750**

We will also test whether our lead molecules have efficacy in a cervical explant model for HIV-1 infection, and whether they have a synergistic or additive effect on the ability of other candidate microbicides to inhibit HIV-1 infection in the presence of semen. In the final Aim, we will assess the toxicity and inflammatory effects of the most promising candidate molecules, using beneficial Lactobacillus strains and cervical explants. The R33 phase will culminate with an evaluation of the safety and tolerability of the most promising compound in the rabbit vaginal irritation (RVI) model. The overall goal of these studies is to carefully determine whether small molecules that target SEVI have potential utility as a novel class of microbicides.

Title: **A Systems Biology Approach for Pediatric and Adult Autoimmune Diseases**
P.I.: **Maria Virginia Pascual**
Institution: **Baylor Research Institute**
Grant No.: **AI082715-04**
Award: **$30,000**

We propose to create an Autoimmunity Center of Excellence that will incorporate the efforts of clinicians, human immunologists (both basic and translational), physician-scientists with clinical expertise and research experience in autoimmunity, bioinformaticians, and geriomics/systems biologists. Together, the assembled group has an extensive background in clinical trials and a proven track record for merging basic and clinical science. This team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. Within this collaborative setting, a systems biology approach is proposed to focus on both pediatric and adult autoimmune diseases. The goals of the Center are: 1) To assess the efficacy of novel targeted therapies, 2) To develop simple and robust biomarkers using state-of-the-art genomic approaches, 3) To understand the role of recently identified T cell subsets in disease pathogenesis, and 4) To assess antigen-specific responses in pediatric and adult autoimmune diseases. These projects will provide a better understanding of the pathogenesis of specific autoimmune diseases and allow us to develop a strategy to assess disease activity based on novel transcriptional markers as well as to identify autoantigen-specific immune responses. The Center will deliver: 1) Innovative clinical trials targeting specific cytokines in psoriasis & dermatomyositis. 2) Development of biomarkers for dermatomyositis, psoriasis, lupus and multiple sclerosis. 3) Identification of novel therapeutic targets in dermatomyositis. 4) Development of assays to test autoantigen-specific immune responses. 5) Development of a unique microarray database of human autoimmune diseases. CLINICAL COMPONENT (Cush, J) CLINICAL COMPONENT DESCRIPTION (provided by applicant): Baylor Institute for Immunology Research aims to bring together a distinguished team of clinical investigators to conduct cutting-edge clinical trials on specific autoimmune diseases. This unique group of investigators and clinicians has appointments at Baylor University Medical Center, UT Southwestern Medical Center, Texas Scottish Rite Hospital in Dallas and Northwestern University. These talented individuals have been enlisted from diverse programs with subspecialties in dermatology, rheumatology, neurology, pediatrics, and human immunology. They provide a set of inimitable resources for clinical trials and have a proven track record for merging basic and clinical science. Indeed, this team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. With such outstanding collaborative players, a systems biology approach is proposed here which investigates both pediatric and adult autoimmune disease. To this end, two Phase II randomized, double-blind, placebo-phase controlled clinical trials are proposed. The first trial investigates whether blocking IL-1 with Anakinra will result in objective disease improvement for patients with Juvenile Dermatomysitis. The trial design will demonstrate: 1) if the time to improvement for patients receiving Anakinra early in the study will be earlier than those who receive later treatment; and 2) if the proportion of patients improved at week 8 of the blinded phase will be significantly greater in the early treatment group. Mechanistic studies will utilize gene expression profiling assays to find a novel diagnostic test for JDM as well as disease activity measures and biomarkers to follow and predict patients' response to therapy. The second clinical project proposes to use a-IL-17 in patients with plaque psoriasis as well as psoriatic arthritis. Specifically, this study will assess the safety and efficacy of a-IL-17 in these patients and determine both the time to achieve endpoints of a PASI 75 or ACR20 and sustainability of such responses at 24 weeks. Associated studies will establish blood transcriptional markers to predict clinical responses in patients treated with a-IL-17, determine if transcriptional scores can be used to assess disease activity, and analyze the effect(s) of IL-17 blockade on B and T cell subsets. A dynamic team of clinical investigators assembled at BUR to conduct state-of-the-art clinical trials on autoimmune disease would be of great value and accelerate the process of bringing research from the laboratory bench to the bedside. This team proposes two important trials that will assess a-IL-1 treatment in Juvenile Dermatomyositis and IL-17 blockade in psoriatic diseases.

Title: **T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy**
P.I.: **Andrew D. Luster**
Institution: **Massachusetts General Hospital**
Grant No.: **AI095261-02**
Award: **$12,500**

The Massachusetts General Hospital/Harvard Medical School AADCRC entitled T cell effector and regulatory mechanisms in asthma and food allergy seeks to gain a better understanding of the role of allergen-specific effector and regulatory T cells in determining the physiological response to an allergen at mucosal surfaces. It is becoming increasingly clear that the net outcome of an inflammatory response is the balance of allergen-specific effector T cell activity and opposing regulatory T cell activity. Antigen-specific effector and regulatory T cell numbers and activity are in large measure determined by the outcome of allergen-loaded dendritic cell (DC) interactions with antigen-specific T cells. The MGH/Harvard AADCRC will explore the balance of effector and regulatory activity in asthma and food allergy and the ability of tolerogenic DCs to affect this balance. The Center will focus on two allergic conditions relevant to the mission of the NIAID, namely allergic asthma and food allergy, and utilize two clinical models [endobronchial segmental allergen challenge (SAC) and oral immunotherapy (OIT)] as a foundation for its studies. Project 1 focuses on the role of antigen-specific effector and regulatory T cells in determining airways inflammation and airways hyper-reactivity by correlating the numbers, phenotype and function of these cells in allergic asthmatics (AA) and allergic nonasthmatics (ANA) using innovative imaging techniques; Project 2 focuses on correlating the numbers, phenotype and function of these same T cell subsets with clinical outcomes of milk allergic patients undergoing milk OIT; and Project 3 focuses on the ability of tolerogenic DC therapy to manipulate the balance between these two opposing T cell populations in favor of regulatory T cells and tolerance in both asthma and food allergy. The three interrelated projects will be supported by Cores that will recruit, enroll and characterize allergic subjects for SAC and OIT, provide MHC class II tetramers to specifically identify and study allergen-specific T cells, and perform sophisticated transcriptome phenotypic analysis on T cell and DC subsets. The goal of this Center is to understand the balance of effector and regulatory allergen-specific T cell activity that determines clinical disease in asthma and food allergy and to establish the utility of using tolerogenic DCs to manipulate this balance to induce allergen-specific tolerance. This would pave the way for new therapeutic approaches to treat these and other allergic diseases.

Title: **Thermostable Vaginal Probiotic Microbicide**
P.I.: **Victor Bronshtein**
Institution: **Universal Stabilization Technologies, Inc.**
Grant No.: **AI094508-02**
Award: **$18,375**

Recently revised statistics show the number of individuals living with HIV at over 33 million worldwide, with 68% being in sub-Saharan Africa. Current HIV prevention methods, such as condom use, monogamy and abstinence, are not always feasible. The need for improved HIV preventative technologies remains urgent. The development of topical microbicides represents a new and exciting field in the prevention of sexually transmitted diseases. Of these, application of live probiotic bacterial microbicides (PBM) represents a promising preventative method. Our ultimate goal is to develop potent optimized multistrain thermostable and easily deliverable probiotic vaginal topical microbicides. To achieve this goal we will stabilize vaginal probiotics for long-term storage at high ambient temperatures and short term survival at temperatures required for quick dissolve film manufacturing (60¿C and above). The cornerstones of this proposal are: 1) Preservation by Vaporization (PBV)—an innovative, patent pending method of dry-stabilizing probiotics bacteria and other fragile biologicals at high ambient temperatures, and 2) Quick-dissolve thin film technology that is being optimized to deliver conventional vaginal microbicides. The strategy can be described briefly as, to occupy the vaginal epithelium and

provide a long lasting protective environment against HIV, BV, and STI acquisition small (10-50 ¿m) glassy sugar particles containing PBV vaginal probiotic bacteria will be formulated into thin films which utilize a water soluble polymer base. Thin films offer a unique delivery platform which has a number of advantages over other dosage forms. In a recent study comparing women's preference between films, tablets and ovules, the film dosage form was shown to have greatest acceptability among women studied. We believe that women will prefer using a vaginal film over other potential methods of probiotic microbicide delivery especially if a long-acting effect of the bacteria colonizing vaginal epithelium allows for less frequent use. Biologic properties of PBM after long-term storage at ambient temperatures will be characterized using cell culture models of vaginal and cervical epithelium.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Title: **NIH Osteoporosis and Related Bone Diseases—National Resource Center**
P.I.: **NIAMS (coordinating center)**
Institutions: **NIAMS, in cooperation with NIA, NICHD, NIDCR, NIDDK, ORWH, and HHS/OWH**
Grant No.: **268200800001C*42**
Award: **$50,000**

The National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases ~ National Resource Center, a part of the U.S. Department of Health and Human Services, provides patients, health professionals, and the public with an important link to resources and information on metabolic bone diseases, including osteoporosis, Paget's disease of the bone, and osteogenesis imperfecta. The NIH National Resource Center is dedicated to increasing the awareness, knowledge, and understanding of physicians, health professionals, patients, underserved and at-risk populations (such as Hispanic and Asian women, adolescents, and men), and the general public about the prevention, early detection, and treatment of osteoporosis and related bone diseases.

Title: **Osteoarthritis Initiative**
P.I.: **Michael Nevitt**
Institutions: **University of California, San Francisco (coordinating center); Ohio State University; University of Pittsburgh; University of Maryland; Memorial Hospital of Rhode Island**
Grant No.: **AR022258, 26820120031C*1**
Award: **$650,000**

Knee osteoarthritis (OA) is the most common cause of disability in adults. The "Osteoarthritis Initiative (OAI): A Knee Health Study" is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and follow participants who have knee OA or are at high risk for developing knee OA for at least a four-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual follow-up visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee

OA. Levels of knee pain and physical disability will be assessed at study start and at each of the follow-up visits by questionnaire and examination.

Title: **Predictors of Pregnancy Outcome in SLE and APS**
P.I.: **Jane E. Salmon**
Institution: **Hospital for Special Surgery**
Grant No.: **AR049772-10**
Award: **$200,000**

Pregnancy complications in women with the antiphospholipid syndrome (APS) and/or SLE include recurrent miscarriage, preeclampsia, placental insufficiency, and intrauterine growth restriction (IUGR). The mechanisms leading to placental and fetal injury in vivo are incompletely understood and treatment remains sub-optimal. We have identified complement as an early effector in pregnancy loss and/or IUGR associated with placental inflammation in a mouse model of APS and shown that complement activation causes the release of anti-angiogenic factors and abnormal placental development. The PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) is a first-time effort to translate our novel findings in mice to humans and determine if elevations of complement split products predict pregnancy complications in patients with antiphospholipid (aPL) antibodies and/or SLE. In the first 4 years of this prospective, observational study of pregnant patients grouped and analyzed according to the presence or absence of aPL antibodies and preexisting SLE, we have enrolled 342 pregnant patients in 7 centers, obtained detailed medical and obstetrical information monthly, and serially collected plasma, serum, DNA, RNA, and urine. Preliminary data suggest that elevated levels of complement activation products antecede and predict poor fetal outcome, consistent with our hypothesis that complement is a proximal mediator of fetal loss and IUGR. We propose to increase our target sample size from 400 to 700 pregnant patients to maintain study power given lower than expected outcome rates, and to leverage the infrastructure and rich collection of patient data and samples by expanding the array of biomarkers and scope of adverse pregnancy outcomes. Specifically, in Aim 1 we will determine whether elevations of split products generated by activation of complement pathways predict poor fetal and/or maternal outcome in patients with aPL antibodies and/or SLE and, in Aim 2, whether the balance of circulating angiogenic and anti-angiogenic factors predicts preeclampsia or delivery of IUGR infants. In Aim 3, a new direction, we will use the PROMISSE cohort to affirm in humans our recent findings in mice, that certain anti-DNA antibodies cross-react with N-methyl D- aspartate receptors (NMDAR) and cause neuronal death with ensuing cognitive and behavioral impairment. We propose to quantitate anti-NMDAR antibody levels throughout pregnancy in PROMISSE SLE patients and test the hypothesis that in utero exposure to maternal anti-NMDAR antibodies alters behavior and cognitive development in offspring by evaluating cortical function tasks in 12 month and 3.5 year old children. This competitive renewal and extension of the PROMISSE Study provides an outstanding opportunity to translate knowledge from mouse models to patients, define pathogenic mechanisms, identify predictors of poor pregnancy outcome in APL and/or SLE, and define novel therapeutic targets to prevent such outcomes.Patients with systemic lupus erythematosus (SLE) and/or antiphospholipid (aPL) antibodies are at increased risk for miscarriage, preeclampsia and fetal growth restriction—major causes of maternal, fetal, and neonatal morbidity and mortality in the US and worldwide—whose etiology and mechanism remain unknown and for which therapy is limited. In addition to causing placental dysfunction, maternal autoantibodies may also directly impair fetal brain development. Identification of biomarkers that predict poor pregnancy outcome in these patients will elucidate mechanisms of disease, define targets for treating patients, and generate clinically applicable indicators to permit initiation of interventional trials in patients at greatest risk for pregnancy complications.

Title: **Role of B Cells and DCs in Lupus Pathogenesis**
P.I.: **Mark J. Shlomchik**
Institution: **Yale University**
Grant No.: **AR044077-15A1**
Award: **$200,000**

Breaking T cell tolerance is arguably a critical step in the pathogenesis of SLE. Activated T cells provide help to autoantibody-secreting B cells and also infiltrate target organs. Therefore it is important to identify how, where and when such T cells are activated and how this is maintained. In fact, the latter is critical because any therapy will have to interrupt ongoing disease. Lupus-prone mice lacking B cells from birth have markedly reduced disease and much less T cell activation. This suggested that B cells are upstream in T cell activation and also that they would be good therapeutic targets. However, in lupus mice B cell depletion was difficult to achieve using standard anti-CD20 mAb and effects, particularly on T cell activation, were not striking. Similarly anti-CD20 failed to show clinical effect in SLE patients, though anti-BLyS did. These findings raise the question of what the role of B cells really was in ongoing disease, and whether, if efficient depletion were possible, would T cell activation and disease be reduced. They also suggested that other cell types such as DCs could be as or more important both for initiation and propagation. In this proposal we will use genetic approaches to target key cells and molecules-including deletion during disease rather than from birth-in order to unravel the complex interplays of disease mechanisms in vivo. To this end, we recently deleted cDC and pDC in lupus-prone MRL.Faslpr mice from birth. Surprisingly, we found little effect on T cell activation in secondary lymphoid tissue (SLT), but there were striking reductions in nephritis and skin disease, decreased proteinuria and longer survival. These data suggested that DCs might be required to activate T cells in target tissues-a novel role rather than to initiate activation, as might have been assumed. We propose a new model in DCs have non-redundant roles in tissue infiltration in lupus but that B cells are the most upstream APC in SLT. To address this model, we will first deplete both B cells and DCs during ongoing disease, rather than from birth. This will validate DCs as therapeutic targets and help resolve the controversial role of B cells. We will also distinguish the roles of cDCs from pDCs, as whether pDCs are important for SLE has not been tested experimentally. Second, to understand how B cells and DCs might be activating T cells, we will block APC function by deleting MHCII from each. Further, we will investigate the role of ICOS signals, which are linked to lupus in a number of ways, including emerging data that ICOS specifies T follicular helper (TFH) and T extrafollicular helper differentiation, cells that help autoreactive B cells. We also have exciting preliminary data that ICOSL on DCs specifically is required to promote infiltrating T cells in kidney, and that such cells express Bcl6 and thus may be related to TFH. To further investigate the roles of ICOS signals, we will specifically delete ICOSL on B cells and on DCs. Together these experiments-organized around Aim 1 focusing on B cells and Aim 2 focusing on DCs-will test our model; determine if B cells/DCs or both are important as APC; validate B cells, cDCs, and pDCs as therapeutic targets; and elucidate the role of ICOS signals in the development of pathogenic T cells.

Title: **Sex-Specific Movement Differences in Young Adults with and Without Hip Pain**
P.I.: **Cara L. Lewis**
Institution: **Boston University**
Grant No.: **AR061690-01A1**
Award: **$184,162**

Acetabular labral tears are an increasingly recognized source of hip pain in young adults, especially females, and have been linked to the premature development of hip osteoarthritis (OA). Recently, femoroacetabular impingement (FAI) has been implicated as a cause of labral injury and OA. In FAI, hip pain occurs in the presence of a structural abnormality of the acetabulum or femur which results in early contact between the bones during hip flexion and internal rotation. Current treatment for FAI includes surgical procedures to resect or reorient the femur

or acetabulum or both. While structure does contribute to hip pain, increasing evidence suggests that movement patterns may also play an important role. The long-term goal of this line of research is to improve treatment for hip pain, especially in young adults, which will prevent or slow the progression of chondral damage and thereby reduce the need for hip arthroplasty. The purpose of this project is to assess the movement patterns of people with FAI compared to people without hip pain and to test for sex- and limb-specific differences in these patterns. Identification of differences in movement patterns which may contribute to hip pain can improve non-invasive treatment for people with hip pain. To test for these differences, we will assess movement patterns using kinematic data collected during movements including walking, stepping down, supine straight leg raise and prone hip extension on subjects with FAI and subjects without hip pain. We hypothesize that subjects with FAI will display movement patterns which are closer to their end-range hip motion than subjects without hip pain. We believe that these movement patterns contribute to a subject's hip pain. We also hypothesize that females with FAI will display different movement patterns than males with FAI. We anticipate this sex difference in movement patterns because there is an unequal distribution of the structural abnormalities among females and males, and because a sex effect has been noted in other lower extremity injuries (e.g. ACL tears, patellofemoral pain). Furthermore, as subjects often have unilateral pain despite bilateral structural abnormalities, we hypothesize that subjects with FAI will display different movement patterns of the painful hip than the unimpaired hip. The knowledge gained from this research has the potential to redirect treatment for people with FAI by identifying sex-specific movement patterns which could be targeted by inexpensive and non-invasive therapeutic interventions. It also could be used to develop prevention programs focused on neuromuscular retraining.

National Institute of Biomedical Imaging and Bioengineering

Title: **Steroid-Based Contrast Agents for Magnetic Resonance Imaging of Endocrine Disease**
P.I.: **Thomas J. Meade**
Institution: **Northwestern University at Chicago**
Grant No.: **EB014806-01**
Award: **$250,000**

The objective of this research proposal is to develop a series of steroid-based magnetic resonance imaging (MRI) contrast agents to facilitate molecular characterization of the status and function of steroid receptors in hormone-dependent disease and development. The ability to detect the location of cell receptors and their concentration throughout a living organism is of vital importance as it allows for further understanding of cell signaling mechanics. Progesterone and estrogen are steroid hormones that bind to their receptors and function as a transcription factors in the nucleus. A non-invasive means of determining the hormone receptor status of hormone-dependent tumors and benign lesions could assist with treatment options, identification of the size and exact location of the tumor, and provide additional tools when traditional imaging strategies miss or confuse lesions of the breast and uterus. Unlike fluorescence and optical microscopy, MRI is not limited by depth or transparency of the specimen. MRI does not use ionizing radiation or radioactivity like positron emission tomography (PET) and X-ray/CT, and it allows for 3D reconstructions and high resolution imaging over time without the need to sacrifice the organism. It is the hypothesis of this grant proposal that gadolinium(III) conjugated hormone-based contrast agents can target and accumulate in hormone receptor positive cells to non-invasively image receptor status. Our preliminary studies have identified gadolinium (Gd)-conjugated progesterone derivatives as compounds capable of traversing the cell membrane, binding to progesterone receptors, initiating gene transcription, and enhancing contrast in mammalian tissues and tumors imaged in vivo using magnetic resonance, the most promising of which is termed "ProGlo". This proposal focuses on the application and expansion of ProGlo

to enhance the imaging of steroid receptor tumors and tissues in vivo. AIM 1. To synthesize and test a series of CAs that targets the estrogen receptor. Estrogen-based contrast agents will be designed and synthesized with varying polarities, charges, and water solubilities that will selectively probe membrane bound receptors or receptors located inside the cells and tumors. AIM 2. To investigate if hormone receptor disease of the breast and uterus can be classified as receptor positive using functional hormone MR agents. AIM 3. To chemically modify CAs to enhance in vivo relaxivity and reduce toxicity by developing and testing bio-orthogonal, water-soluble, and multi-chelated hormone CAs. Steroid receptors have emerged as attractive targets for molecular imaging due to their role in promoting the growth of breast and uterine lesions. This proposal will develop steroid contrast agents that could provide a molecular profile of hormone receptor status in cells, validate responsiveness to therapy, and improve diagnoses. Functional contrast agents will provide valuable tools for use in humans and for immediate use in animal models of hormone receptor dependent development and disease without the need to euthanize the animal thereby increasing knowledge about developmental biology, disease etiology, and progression.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Title: **Achieving a Critical Mass of Women Biomedical Faculty: Impact of Three U.S. Programs**
P.I.: **Deborah Lynne Helitzer**
Institution: **University of New Mexico**
Grant No.: **HD064655-04**
Award: **$175,144**

Although there are numerous career development programs for women faculty, women continue to leave academic medicine at alarmingly high rates. This study will examine the impact on retention and career success of individual women faculty who participated in three long-standing national programs, each of which targeted a separate career stage, as compared to women and men, at the same career stages, who did not participate in these programs. This research also aims to elucidate the patterns and processes that contribute to the experience of individuals and their institutions as a means to identify the barriers and facilitators—historic and new, individual and institutional—that face women faculty in attaining positions of leadership at academic health centers (AHCs) and transforming institutional culture. Informed by the guidance of an Advisory Board composed of highly respected female and male senior leaders in academic medicine, the goal of the research is to assess the impact of participation in intensive career development training programs on individual women faculty at early and mid-career stages and their institutions, in terms of retention and promotion, while verifying and illuminating the ways in which participation in these programs affect career trajectories. We will attempt to discover how the findings on retention, academic promotion and administrative advancement are influenced by (i) individual dynamics and personal/professional development factors addressed in leadership development programs; (ii) organizational factors in institutions that send their women faculty to such programs; (iii) how these factors may have led to enhancement of leadership development and gender experience for women participating in these programs; and (iv) how the interaction of these factors has or can lead to a change in organizational culture to ensure the ability of institutions to capitalize on the intellectual capital of women science faculty members. Along with this retrospective analysis, we will prospectively identify new emerging challenges that affect women Assistant and Associate Professors attending intensive career development programs, and create an infrastructure for future research on retention and promotion. Additionally, this study will provide a comprehensive set of findings which can serve as the basis for a future design of an innovative women-focused leadership program as well as providing helpful information on the culture change needed to improve recruitment and retention of America's leading scientific minds.

Title: **Brown/WIH Pelvic Floor Disorders Network Site**
P.I.: **Deborah Lee Myers**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **HD069013-02**
Award: **$25,000**

The mission of the PFDN is to identify optimal diagnosis and management strategies for women with pelvic floor disorders (PFDs) and this is directly in line with Women and Infants Hospital (WIH)/Brown's mission and commitment. WIH is a women's hospital, focused solely on advancing women's health and research and our extremely high volume, stable patient base, expertise of our multi-disciplinary collaborative and established research infrastructure provide the ideal environment to conduct large-scale, clinical research at the highest level. The aim of this application is for WIH/Brown to become the first PFDN site in New England by demonstrating: 1)our academic productivity and experience in multi-site, collaborative surgical, pharmaceutical and non-surgical clinical trials; 2)highly committed investigators with expertise in research methods and a specialized research team qualified to conduct multiple protocols, manage high quality data, and maintain high recruitment and retention; 3)a long-standing, formal relationship with multi-disciplinary collaborators committed to advancing the care of women with PFDs led by Urogynecology (including Urology, Colorectal surgery, Women's Gastroenterology, Women's Physical Therapy, and Women's Radiology); and 4)our high clinical volume (In 2009, the Division of Urogynecology evaluated 1211 new patients and performed 583 PFD surgical procedures; vaginal, abdominal, laparoscopic and robotic approaches are all represented). We present a concept proposal describing a 3-stage, randomized trial of a combined non-surgical and surgical approach to treatment of mixed urinary incontinence (MUl) in women who have failed conservative therapy and/or elect surgical treatment. Women suffering from MUl are at high risk for failure of segregated treatments and are often excluded from clinical trials focused on either stress or urge urinary incontinence alone. Clinical management of MUl remains a challenge and trials targeting this population are urgently needed. WIH has a long-standing history of supporting network collaboratives and our goal is to participate and become a leader in the PFDN in terms of protocol development and completion, data interpretation and quality, recruitment and retention and high quality dissemination of findings. RELEVANCE: Female pelvic floor disorders including urinary incontinence, pelvic organ prolapse and fecal incontinence are common, disabling conditions and are a significant public health issue. Although a variety of treatment options exist, high quality evidence to guide clinical management and to improve treatment specificity is still needed. Through the PFDN, WIH/Brown is committed to advancing high quality scientific evidence to help improve the care of women and reduce the burden of these disorders.

Title: **Cleveland Clinic Clinical Site**
P.I.: **Matthew Barber**
Institution: **Cleveland Clinic Lerner College of Medicine**
Grant No.: **HD054215-07**
Award: **$25,000**

The goal of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with pelvic floor disorders (PFD) using the highest quality research methods available. The Cleveland Clinic offers a stable academic and research-oriented environment for the conduct of PFDN studies including experienced investigators with complementary clinical and research backgrounds that have a particular interest and a successful history of conducting clinical trials evaluating both surgical and nonsurgical therapies for women with PFD. The specific aims of this application are: 1) to demonstrate that the Cleveland Clinic (CC) Clinical Site has contributed substantially to the academic, administrative, and clinical aspects of the PFDN since joining in its 2nd 5-year cycle; that it possesses the personnel, patient, clinical and administrative resources needed for successful participation; and that continued

participation would be advantageous to the successful attainment of the Network's scientific goals and 2) to present a concept proposal for potential conduct by the PFDN. We propose evaluating the comparative effectiveness of sacrospinous hysteropexy (SSH), the most well-studied uterine-sparing pelvic organ prolapse (POP) surgery, relative to total vaginal hysterectomy with sacrospinous ligament fixation (TVH/SSLF), a commonly used hysterectomy-based vaginal uterovaginal prolapse procedure. The specific aims of the concept proposal are: 1) compare the anatomic, functional, sexual and health-related quality of life outcomes of SSH to TVH/SSLF in women undergoing surgery for Stage 2-4 POP uterovaginal prolapse 2 years after surgery; 2) compare surgical recovery and short- and long-term morbidity of SSH and TVH/SSLF in these same women and 3) determine the incremental cost-effectiveness of SSH compared to TVH/SSLF for the treatment of Stage 2-4 POP. Enrolled subjects will be randomized in the operating room on the day of surgery to receive either SSH or TVH/SSLF (1:1) using a random permutated block design. Randomization will be stratified by surgeon to account for the varying experience and expertise. Subjects and study coordinators will be blinded to treatment assignment until completion of the study. RELEVANCE: Nearly one quarter of all women report symptoms of at least one PFD, including prolapse. POP is the most common indication for hysterectomy in postmenopausal women and it is unknown whether the addition of hysterectomy to POP surgery is integral to successful surgical outcome. The results of our concept proposal could justify or eliminate the need for as many as 70,000 hysterectomies in the US each year.

Title: **A Collaborative Workshop Across the Scientific Disciplines**
P.I.: **Sally T. Hillsman**
Institution: **American Sociological Association, Inc.**
Grant No.: **HD010988-01**
Award: **$10,000**

It is well-recognized in the scientific community that data-driven, scientifically rigorous tools are needed to stimulate and enhance efforts to use the talents of all our citizens, including underrepresented minorities and women. There is an additional need to look beyond individual efforts to begin to pursue a system-based analysis. This workshop proposes to address the recommendation from a 2008 National Institutes of Health (NIH)-supported (additional funding provided by the National Science Foundation (NSF)) leadership retreat, "Enhancing Diversity in Science: A Leadership Retreat on the Role of Professional Associations and Scientific Societies," regarding the need to establish a common standard for measuring and evaluating success of diversity-enhancing programs. The workshop further addresses the need to establish a more comprehensive and cohesive effort needed to track the many and various efforts of government (federal, state, and local), foundations, universities, scientific societies, and professional associations. Systematic data collection would allow possible answers to broad and important questions such as: To what extent research training should be supported collaboratively? What are the best practices that could be adapted that would allow for a maximum increase on the return on investment?

Title: **Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team**
P.I.: **Pamela A. Moalli**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **HD061811-04**
Award: **$66,666**

Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team Each year roughly 200,000 U.S. women undergo a surgery to repair pelvic organ prolapse (6, 7). Biologic and synthetic meshes are widely used in prolapse repairs to improve anatomical outcomes over native tissue repairs which currently have a failure rate of over 30%. To date, however, there is

little scientific data to guide surgeons in the selection of a particular product. As a result, meshes are used based on the recommendations of a local vendor and consequently, are placed in women on a trial and error basis. There is growing evidence, however, that the complications associated with prolapse meshes cause unacceptably high rates of morbidity including infection, mesh shrinkage, mesh erosion, mesh exposure, pelvic, rectal and bladder pain and dyspareunia. Such complications have become significant enough for the FDA to recently release a warning about mesh use, especially when it is placed transvaginally. In this proposal, we therefore, aim to establish an interdisciplinary team of scientists dedicated to the comprehensive testing of previously or newly marketed prolapse meshes and for the development of the next generation of graft materials based on specific scientific criteria. In the first phase of the study, we determine how biochemical and structural changes in the prolapsed vagina impact passive and active mechanical behavior so as to develop a mesh in which these deficiencies are repaired or compensated for, allowing us to restore the prolapsed vagina to the nonprolapsed condition. In the second phase, we hypothesize that the shortcoming of current prolapse meshes is that they are too stiff. While this results in a repair with increased tensile strength, it occurs at the expense of tissue function with accelerated tissue contraction, decreased elasticity and compliance, and deterioration of smooth muscle function. To test our hypothesis, we implant commonly used synthetic prolapse meshes into the vagina of nonhuman primates with prolapse using the gold standard surgical procedure (the abdominal sacrocolpopexy) and then define the cellular, biochemical and biomechanical impact on the vagina at 6 months post implantation. Eventually, we will implant meshes transvaginally to characterize the distinct host response to this surgical approach. In the third phase, we explore the development of future grafts for prolapse surgery. We hypothesize that because of its bioinductive effects, a combined biologic/synthetic mesh will be superior to a synthetic mesh alone in restoring vaginal structure and function. We propose that a key yet poorly developed component of prolapse repairs is the re-establishment of smooth muscle reactivity and therefore, test the use of a temporary biologically active scaffold in achieving this process. In this way, this grant proposal provides a mechanism to establish the first team of scientists dedicated to the comprehensive unbiased evaluation of prolapse meshes as a means of educating both current and future prolapse surgeons, and the public regarding potential problems associated with certain materials. Indeed, the development of such a group is imperative for protecting the health of women.

Title: **Consortium to Evaluate a Novel Violence Prevention Program on College Campuses**
P.I.: **Corrine M. Williams**
Institution: **University of Kentucky**
Grant No.: **HD069897-01A1**
Award: **$180,193**

Up to 25% of women may be sexually assaulted during college, and one-third of college students have experienced physical aggression from dating partners. While most students neither participate in nor condone violence, many respond passively to a campus culture that may tacitly support violence, as evidenced by violent media images, jokes trivializing violence against women, and sexual harassment. Growing awareness that all members of the campus community can play a significant role in ending dating and sexual violence (DV/SV) has led to an increase in violence prevention interventions for college students. However, very few of these programs have been empirically evaluated. A significant barrier to progress in intervention research is the infrastructure required to implement and evaluate interventions across multiple sites. For this project, the intervention will be Green Dot, an innovative primary prevention intervention to reduce DV/SV among college students, which was developed at the University of Kentucky. The intervention consists of one-hour persuasive speeches, followed by a six to either hour bystander intervention training called Students Educating and Empowering to Develop Safety (SEEDS). In addition, we are creating booster sessions that will be provided to all students who have

completed SEEDS training to assist with additional skills-building that may be required. As a developmental project, the proposed research will consist of three phases: 1) pilot work to create survey modules, resulting in a questionnaire that contains measures which are standardized across campuses to evaluate the effectiveness of the intervention and is a manageable length; 2) data collection at UK to streamline data collection procedures when other colleges are brought on; and 3) recruitment of additional implementation and control college sites. The University of Kentucky will operate as the coordinating center for the multi-site evaluation and will continue to serve as the pilot site or data collection and refinement of study methodology. The University of South Carolina has agreed to serve as an implementation site and the University of Cincinnati has agreed to serve as a control site. We will recruit an additional eight colleges (four control and four intervention sites) during the project period. By beginning with this R21 to conduct developmental work and begin problem solving, we can help to ensure the success of subsequent projects. If Green Dot is then determined to be effective across multiple campuses in preventing violence and the associated sequelae of adverse academic, as well as physical and mental health outcomes, experienced by so many college students, then the potential impact of this study is indeed groundbreaking. Additionally, the lessons learned from establishing a multi-site public health intervention trial, with one coordinating center responsible for all data collection via online surveys, has implications for the study of other health issues.

Title: **A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response**
P.I.: **Candace S. Brown**
Institution: **University of Tennessee Health Science Center**
Grant No.: **HD065740-02**
Award: **$200,000**

Approximately 14 million U.S. women have provoked vestibulodynia (PVD), a type of localized vulvar pain which causes major disruption in the everyday lives of up to 60% of affected women and negatively impacts sexual function in 45%. The financial burden imposed on the health care system is also significant, as these women visit multiple clinicians and specialists, and try numerous, unproven treatments. To date, few randomized controlled trials (RCTs) have been conducted to establish evidence based protocols for PVD management. The first immediate goal is to conduct a multicenter RCT of gabapentin treatment for PVD. Gabapentin was selected because of its efficacy in treating other neuropathic pain conditions and the promising, preliminary data on its use in PVD. This is a significant research project because PVD is a highly prevalent, chronic pain condition that is costly to the health care system and that currently has limited management options available to affected women. The second immediate goal is to define psychophysiologic measures of gabapentin response and to define mechanistically-based PVD subtypes, which may be related to abnormalities in central sensitization, muscle hypertonicity, and autonomic dysregulation. Identifying predictors of treatment response in PVD would have clinical applicability to other chronic pain syndromes, and is consistent with NIH's mission to investigate coexisting pain conditions in order to identify common etiological pathways and develop therapeutic targets. The specific aims are (1): to test the prediction that pain from tampon insertion (primary outcome measure) is lower in PVD patients when treated with gabapentin compared to when treated with placebo. Additional outcome measures include reported intercourse pain and 24-hour pain, and (2) to test the prediction that gabapentin treatment will reduce mechanical allodynia, reduce area and duration of hypersensitivity induced by intradermal capsaicin, reduce vaginal muscle pain to palpation, decrease the number and intensity of somatic tender points, and increase cardiac beat-to-beat variability. This 16-week, randomized, double-blind, placebo-controlled, crossover study will enroll 120 women between 18-50 years of age who report tenderness localized to the vulvar vestibule, pain with tampon insertion, and, when sexually active, insertional dyspareunia. Electronically entered daily diaries will be used to determine if pain is lower in PVD subjects when treated with gabapentin (up to 3600 mg/d)

compared to when treated with placebo. The approach is innovative because it focuses on an understudied condition, in a multicenter setting, using a novel outcome measure (the tampon test), and a newly developed web-based recruitment and patient-reporting tool. Data management will include a mechanism-based analysis of drug effectiveness. These study outcomes will ultimately lead to our long-range goal of identifying underlying pathophysiologic mechanisms of PVD in order to create evidence-based differential diagnoses of subtypes of PVD for more effective and cost-effective management options.

Title: **Effect of Feeding Buddies on Adherence to WHO PMTCT Guidelines in South Africa**
P.I.: **Kiersten Ann Israel-Ballard**
Institution: **Program for Appropriate Technology in Health**
Grant No.: **HD075090-01**
Award: **$300,000**

The 2010 revised WHO recommendations to provide antiretroviral (ARV) prophylaxis or treatment to mothers or infants during the breastfeeding period indicate a paradigm shift in PMTCT care and treatment programming. Yet despite South Africa's adoption of this guidance, myriad challenges currently exist. Confusion in the public health care system related to mixed messaging around safe infant feeding and the provision of-and now withdrawal of-free formula milk have made adherence to exclusive breastfeeding a challenge in South Africa. Cultural, social, and psychological factors influence the ability of women to follow PMTCT guidelines, which include exclusive breastfeeding for six months, adherence to ARV prophylaxis or treatment, and early infant diagnosis. Facility-based interventions alone are often inadequate to effect sustained behavioral changes in the face of multiple contextual factors. Community- and home-based support are needed, yet cost and systems constraints make these infeasible in many PMTCT programs. Our previous data suggest that a feeding buddy strategy could fill this gap and provide a home-based support system for the mother. The feeding buddy, who is selected by an HIV-positive pregnant woman to support her in overcoming sociocultural challenges to adhering to various aspects of PMTCT programs, is not an employed health care worker, but rather an individual known to the mother, making the intervention extremely cost-effective, and requiring minimal resources to implement. PATH is proposing a comprehensive evaluation of the feeding buddy concept in one health district of South Africa. The goal of the proposed study is to evaluate the effect of a feeding buddy to support mothers to adhere to PMTCT recommendations in order to establish feasible models of promoting HIV-free infant survival in resource-limited settings. We hypothesize that mothers who choose a feeding buddy will have increased rates of exclusive breastfeeding and adherence to ARV prophylaxis or treatment, as well as improved rates of early infant diagnosis and stigma reduction. A prospective cohort intervention study, set within a comprehensive ongoing national program addressing maternal and child health will be conducted with the following aims: (1) to determine the effect of a feeding buddy on adherence to exclusive breastfeeding and (2) to determine the effect of a feeding buddy on adherence to ARV prophylaxis or ART regimens. Secondary aims are: (1) to determine the effect of a feeding buddy on adherence to infant HIV testing at 6 weeks and (2) to determine the effect of a feeding buddy on disclosure and stigma. HIV-infected pregnant women (n=600) will be given the opportunity to choose a feeding buddy at an antenatal care visit to support infant feeding and PMTCT recommendations; follow-up will be to six months postpartum. Feeding buddies could be a simple, low-cost strategy for strengthening existing facility-level efforts to implement the new PMTCT guidelines, and ultimately could contribute toward improving HIV-free survival.

Title: **Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women**
P.I.: **Brahim Aissani**
Institution: **University of Alabama at Birmingham**
Grant No.: **HD064398-03**
Award: **$83,333**

Uterine leiomyomas (ULs) are the most common pelvic tumors in women of reproductive age, accounting for over 600,000 hysterectomies annually in the United States. Several lines of evidence support a genetic liability in the pathogenesis of ULs, yet no susceptibility gene is known. Advances in research on the genetics of ULs (fibroids) have so far been limited by the paucity of genetic epidemiologic studies and infrastructure to conduct them. The goal of this epidemiologic study is to evaluate the contribution of a region of Chr.1q43 that predisposes to uterine fibroids but remains inadequately investigated. Genetic predisposition to ULs has been studied primarily in the context of two rare inherited autosomal-dominant conditions, the hereditary leiomyomatosis and renal cell cancer (HLRCC) and the multiple cutaneous and uterine leiomyomatosis (MCUL1) syndromes, where germline mutations were found in the gene on Chr. 1q43 encoding the tricaboxylic acid cycle (Krebs cycle) fumarate hydratase (FH) enzyme. However, a direct role of this important metabolic housekeeping gene in tumorigenesis remains to be proven. Inactivating FH mutations have rarely (< 1-2% of the tumors analyzed) been observed in nonsyndromic (common) ULs; however, loss of FH appears to be a significant event in the pathogenesis of a subset of these tumors. Furthermore, several observations support the existence of an alternative or additional candidate gene on Chr.1q43 acting alone or interacting with FH to increase the risk of ULs in susceptible individuals: 1) the absence of FH genotype-phenotype correlations, 2) the marked genetic heterogeneity in ULs, and 3) the failure to observe ULs or multiple leiomyomatosis in siblings or parents of cases with fumarase deficiency, a severe recessive disorder. Taken together, these observations underscore the importance of exploring an extended FH region in a population-based study of ULs. To this end, we will generate a high-density single nucleotide polymorphism genotyping data across a 2-Mb region spanning FH in subsets of African American (n=582) and Caucasian (n=455) women enrolled in the NIEHS-Uterine Fibroids Study. This is a well designed cross-sectional study of ULs that includes data on most potential confounders. Our study is not intended to shift any paradigm about the origins of ULs; rather it will extensively investigate the role of FH in nonsyndromic ULs, dissect the intricate genetic correlates of Chr.1q43 markers in the expression of the disease phenotype and evaluate their effects in two populations with a marked difference in disease risk. Recent updates in the genome databases have revealed new potential candidate genes for tumor growth and important structural variations including a large (~ 308 Kb) copy number variation in the vicinity of FH; these new findings further justify a study with the proposed depth and extent of genetic coverage. This study will likely open new avenues for research and may ultimately redirect current preventive and therapeutic approaches or enhance their efficacy.

Title: **Identification of Genes Predisposing to Pelvic Floor Disorders**
P.I.: **Lisa Cannon Albright**
Institution: **University of Utah**
Grant No.: **HD061821-04**
Award: **$66,667**

The investigators propose a unique and powerful collaboration between basic and clinical scientists in Utah to identify genes affecting predisposition to pelvic organ prolapse (POP). The co-PIs both have significant experience, Dr. Norton in Pelvic Floor Disorder (PFD) genetics and Dr. Cannon-Albright in predisposition gene identification. The investigators will access the Utah Population Database, a computerized genealogy of Utah combined with decades of medical data from the two largest healthcare systems in Utah (serving 90% of the state), to identify and recruit surgically treated cases of POP (1,250 cases in 5 years). All POP cases sampled will be

genotyped with the Illumina 610Q SNP marker set. The PIs will apply multiple different genetic analyses to this resource of genotyped POP cases to aid in the identification of predisposition genes. The record linkage of medical procedure codes (identifying surgeries performed on each patient) to individual genealogy data allows us to identify all genetic relationships among the POP cases. We will perform genome-wide association analysis, using software we have developed which allows inclusion of both independent and related cases. We will identify all genetic relationships between the sampled POP cases and perform linkage analysis in informative, high-risk POP pedigrees. We will identify chromosomal regions shared Identical by Descent (IBD) in very distantly related cases in these pedigrees, and we will identify IBD sharing within the small subset of POP cases (2%) who are inbred. Initial collaborative analysis of data obtained by Dr. Norton's NIH funded study of affected PFD sib-ships has already provided significant evidence for a predisposition gene localization on chromosome arm 9q, and suggestive evidence for at least one other locus on chromosome 1. In summary, we will create a population-based resource of surgically treated POP cases, we will pursue established and new methods to identify and localize predisposition genes affecting POP, and we will begin a detailed search for the chromosome 9 gene we have localized.

Title: **Mothers and Others: Family-Based Obesity Prevention for Infants and Toddlers**
P.I.: **Margaret E. Bentley**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **HD073237-01**
Award: **$100,000**

Despite increases in obesity among infants and toddlers, few published interventions promoting healthy diet and decreased sedentary behaviors among this age group exist. To fill this gap, we propose a randomized controlled trial among 468 Non-Hispanic black women, their families, and their child caregivers to test the efficacy of a multi-component, tailored intervention versus an attention control (child safety) in promoting healthy weight gain patterns during infancy. The proposed intervention, Mothers and Others: Family-based Obesity Prevention for Infants and Toddlers will be one of the first to meet the unique needs of individual families by delivering anticipatory guidance on infant care, feeding and growth through multiple channels and to multiple caregivers. Primary modes of delivery for the intervention arm will include face-to-face counseling through 9 home visits (1 by a certified Lactation Consultant), 6 tailored health newsletters for mothers and 6 targeted health newsletters for "other" caregivers deemed influential by mothers, as well as ~160 cue-based text messages for mothers and "other" caregivers. The control group will receive messages on child safety delivered through general newsletters and text messages. Our main outcome is infant/toddler growth, captured by mean weight-for-length z-scores (WLZ) at 18 months, mean change in WLZ between 0-18 months, and likelihood of overweight (WLZ e 95th percentile) at 18 months. Differences between groups are expected to be achieved through uptake of targeted health behaviors, including a greater likelihood of breastfeeding initiation, exclusivity and duration; after 6 months, higher dietary intakes of whole fruits and vegetables and lower intakes of energy-dense snack foods; longer durations of infant and toddler sleep and fewer night awakenings; and, lower levels of television and electronic media exposure. We further hypothesize that these targeted health behaviors will be achieved through modifiable risk factors underpinning the intervention, namely more positive breastfeeding attitudes; higher levels of parenting and breastfeeding self-efficacy; higher levels of perceived social support; higher responsive feeding style scores; improved accuracy in perceiving infant/toddler weight status; and, diminished parental perceptions of infant fussiness. We believe Mothers and Others is highly significant and innovative, as it targets a minority population at high risk of early life obesity, it begins during pregnancy, a "teachable moment" for establishing healthy behaviors, it actively engages multiple child caregivers, and it utilizes novel intervention platforms, including tailoring and text messaging. We have assembled a strong, interdisciplinary team of researchers, each with an outstanding record for implementing and publishing research relevant to this

intervention. Collectively, we have experience conducting similar interventions in this population; designing, implementing and evaluating the proposed tailoring and novel technology components; recruiting and retaining a similar cohort; and measuring and analyzing relationships between the proposed modifiable risk factors, targeted health behaviors and outcomes of early life growth.

Title: **ORWH/NICHD Leiomyoma Tissue Bank**
P.I.: **James Segars**
Institution: **NICHD Intramural Research Program**
Award: **$50,000**

Uterine fibroids represent a health disparity and affect an average of one-in-four reproductive age women in the U.S. (1). The effect on reproduction is considerable as fibroids are estimated to add $34 billion annually to cost of health care in the U.S. In response to a need identified by the research community, the ORWH-NICHD Fibroid Tissue Bank was established to serve as a repository source of well-characterized fibroid and matched control tissues for NIH-funded investigators pursuing basic research on fibroid growth and pathogenesis. The overarching objective of this collaborative initiative between ORWH and NICHD is to improve understanding of the mechanisms and pathophysiology of fibroid disease. The improved understanding of fibroid-related cellular change is expected to serve as a foundation for development of new and novel treatment approaches. Since the establishment of the tissue bank, we have collected a total of 933 tissue specimens; 851 from fibroids and 82 from control-matched myometrial tissue. The samples are well characterized and preserved in order to permit RNA, DNA, metabolomics, and protein analysis. Patients from minority populations are well represented: 36% of patients were African American, 44% were Caucasian, and 19% had unknown or unreported race or ethnicity. Of note, the bank reflects the unusual diseases unique to the NIH: 57% of patients have rare conditions including HLRCC (14 patients), MEN-I, tuberous sclerosis, and Birt-Hogg-Dubé syndrome. This patient group represents 40% and 50% of the total fibroid and myometrial specimens, respectively, and 41% of the total specimens.

Title: **Pelvic Floor Disorders Network**
P.I.: **Charles William Nager**
Institution: **University of California, San Diego**
Grant No.: **HD054214-07**
Award: **$25,000**

The objectives and aims of this application are for the San Diego site to continue its work In the Pelvic Floor Disorders Network (PFDN). The unique strength of our application is our proven two site model, which combines the strengths of 7 academic investigators at both a tertiary medical center and a large volume HMO. We would like to provide leadership, continuity, innovation, academic expertise, a captured diverse patient population, and a proven research infrastructure to the network. We have a track-record of being the top 2 recruitment in surgical trials for pelvic floor disorders and we want to continue that into the third cycle of the PFDN. As noted in the RFA, "In many cases, clinicians caring for women with pelvic floor disorders have adopted principles of care and surgical techniques before rigorous, objective, controlled evaluation has taken place. New devices and techniques have had a dramatic influence on surgical practice…". Our study addresses this concern. Vaginal mesh is probably the most controversial topic in pelvic floor disorders and a strong argument can be made that the PFDN is the best group to study it. A growing-trend of women is seeking uterine sparing surgery for prolapse and a growing trend of gynecologists and urologists are managing uterine prolapse with vaginal mesh kit procedures. Our proposed randomized trial of uterine sparing, grafted vaginal apical suspension vs. traditional hysterectomy with native tissue suspension addresses the very important question of whether it is necessary to remove the uterus to treat uterine prolapse. This

proposed study recognizes the role of new devices and techniques that are changing our care of women with pelvic floor disorders. Our comprehensive outcome measures should allow us to answer whether these new uterine-sparing, apical vaginal procedures are reasonable alternatives to conventional vaginal hysterectomy and native tissue suspension. RELEVANCE: Our site's participation in the next cycle of the PFDN should allow successful network recruitment for surgical trials. Uterine prolapse is a very common pelvic floor disorder and we should determine the best vaginal surgical treatment for this condition. This proposed research study will answer whether uterine-sparing procedures are reasonable alternatives to hysterectomy for this condition.

Title: **Pelvic Floor Disorders Network Clinical Sites**
P.I.: **Lily A. Arya**
Institution: **University of Pennsylvania**
Grant No.: **HD069010-02**
Award: **$25,000**

The goal of this application is to competitively identify clinical sites to conduct clinical trials for female pelvic floor disorders. This application from the University of Pennsylvania with Lily Arya MD, MS (Epidemiology) as Principal Investigator demonstrates our research plan for a new treatment for urge urinary incontinence, myofascial physical therapy. This potentially effective and safe method will greatly enhance treatment choice and improve the quality of life of women with urge urinary incontinence. This application outlines our extensive experience with similar large multi-center clinical trials. We highlight our ability to recruit and maintain subjects in female pelvic floor disorder clinical trials, noting we have been one of the leading recruitment centers in the nation for similar trials. We have often been able to recruit a greater number of subjects than our original estimates. The facilities at the University of Pennsylvania are supportive and outstanding. Our existing research unit and personnel has continuously demonstrated highly successful management of large clinical trials with outstanding organization, attention to detail and compliance with Good Clinical Practice, federal regulations and local Institutional Review Boards. Dr. Arya is an active researcher in the field of health measurement for pelvic floor disorders and she has successfully conducted a number of clinical trials in women's health. Specifically, she and her team of co-investigators and staff have been actively involved in surgical and non-surgical trials for urinary incontinence. She will bring significant expertise regarding study design and health measurement research to the Pelvic Floor Disorders Network. She leads a team of co-investigators who have a track record of collaborative clinical and translational research. We feel that the combination of a high quality personnel, experience in the research area, ability to recruit, and outstanding management and organization will contribute to a high likelihood of successful completion of this and future trials of treatment methods of pelvic floor disorders. RELEVANCE: The University of Pennsylvania has the expertise, infrastructure and experience to be a significant contributor to the Pelvic Floor Disorders Network. The proposed study, to investigate the efficacy of a new treatment for urge urinary incontinance, will improve quality of life of women with urge incontinence and result in considerable savings of health care resources.

Title: **Pelvic Floor Disorders Network: Duke University Medical Center**
P.I.: **Anthony G. Visco**
Institution: **Duke University**
Grant No.: **HD041267-13**
Award: **$25,000**

Pelvic floor disorders research at Duke University Medical Center (DUMC) is sophisticated and comprehensive with committed investigators addressing issues of great importance to women. DUMC has a tradition of excellence in clinical care, training and research in pelvic floor disorders and includes one of the nation's first accredited fellowship programs in the field. DUMC

offers detailed evaluation and treatment in a high-volume, multidisciplinary setting that serves as a tertiary referral center for women across the southeast US. Each of the five Duke urogynecology investigators is fellowship-trained with expertise in both surgical and non-surgical management of urinary incontinence (Ul), pelvic organ prolapse (POP), fecal incontinence, and defecatory dysfunction. Last year, our Division cared for more than 1550 new patients and performed more than 400 surgical procedures for Ul and 270 for POP. Our patient population is 80% Caucasian, 15% African American, 2% Asian and 2% Hispanic, from both suburban and rural communities with stable care and follow-up patterns. DUMC is the hub of a multidisciplinary team of outstanding collaborative investigators in urogynecology, urology, colorectal surgery, gastroenterology, maternal-fetal medicine, physical therapy and epidemiology. DUMC offers a wide range of diagnostic resources: multi-channel urodynamic testing, video urodynamics, cystoscopy, defecography, pelvic MRI, endoanal ultrasound, and needle electromyography. During the current PFDN cycle, DUMC-initiated three active RCTs: 1. Anticholinergic vs Botox RCT (ABC, Dr. Visco, currently enrolling), Interstim vs Botox RCT (ROSETTA, Dr. Amundsen, full protocol), and a RCT evaluating transvaginal mesh for prolapse repair (Dr. Weidner, mini-protocol planned for fall of 2010. DUMC has consistently been a high recruitment site across a wide range of non-surgical and surgical studies with unparalleled retention rates. We have proven our ability to support and successfully complete large-scale, multi-centered investigations through our robust clinical practice and exceptional research infrastructure. Accordingly, Duke University Medical Center is well equipped and uniquely qualified to continue as a valuable and productive member of the Pelvic Floor Disorders Network. RELEVANCE: Female pelvic floor disorders represent a major public health burden given their high prevalence, impairment of quality of life, and substantial economic costs. As part of the Pelvic Floor Disorders Network, Duke University Medical Center is committed to actively participating in innovative clinical trials aimed at improving the evaluation and treatment of pelvic floor disorders through high-quality, high-impact clinical research.

Title: **Perioperative Pelvic Floor Rehab: A Randomized Trial**
P.I.: **Holly E. Richter**
Institution: **University of Alabama at Birmingham**
Grant No.: **HD041261-12**
Award: **$25,000**

The University of Alabama at Birmingham (UAB) is seeking to successfully compete in the third cycle of the NICHD sponsored Pelvic Floor Disorders Network. As a part of this important research infrastructure we have demonstrated our credible, productive, multidisciplinary clinical approach to the evaluation and treatment of women with pelvic floor disorders including urinary and fecal incontinence as well as pelvic organ prolapse. We have substantially contributed to the Network activities by participating at all levels of clinical trial design, implementation, recruitment, intervention implementation, retention and scientific reporting. We have reported outcomes and implication for care of these research initiatives at national and international scientific meetings and we are committed to continuing these activities. Through this application with its concept proposal, we wish to highlight our ability and commitment to continue these meaningful research activities. Current common treatment options for fecal incontinence (Fl) include behavioral therapy consisting of pelvic muscle exercises, diet and defecatory strategies and surgical approaches including anal sphincter repair, artificial bowel sphincter and as a last resort, colostomy. A significant proportion of women with Fl, however, do not gain benefit from behavioral therapy or sphincter repair yet do not wish to undergo colostomy. As the population of post-reproductive women continues to increase, it is imperative to study other treatment options that improve quality of life for this condition. An existing modality called sacral neuromodulation (SNM, Interstim®) has been FDA approved and utilized for the treatment of refractory urge incontinence. Two small randomized trials and several cohort studies have shown efficacy of sacral neuromodulation for the treatment of refractory Fl (although it is not yet FDA approved for this indication). We propose a randomized trial to credibly characterize the effect

of SNM on Fl episodes, symptom specific quality of life, effect on other pelvic floor symptoms, sexual function, predictors of response, adverse events, cost effectiveness and the role of biomarkers in optimal and suboptimal responses to this treatment. This information will allow us to more effectively individualize treatment for women with this condition. RELEVANCE: In order to improve on the care and individualized treatment for women with pelvic floor disorders, it is important that a credible research program exists that helps guide provider care. The Pelvic Floor Disorders Network (NICHD) performs such research and we are competing to continue to participate in this important initiative. As a part of this application, we propose a concept describing a randomized trial of sacral neuromodulation for the treatment of women with fecal incontinence refractory to current standard of care treatments. This exciting new treatment modality may help a cohort of women with diminished quality of life.

Title: **A Pharmacokinetic Evaluation of Levonorgestrel Implant and Antiretroviral Therapy**
P.I.: **Kimberly K. Scarsi**
Institution: **Northwestern University at Chicago**
Grant No.: **HD074462-01**
Award: **$150,734**

Family planning services, including hormone contraceptives, are critical for HIV-infected women, in whom prevention of unintended pregnancy not only decreases maternal and child mortality, but also reduces the risk of mother-to-child HIV transmission. Similarly, antiretroviral therapy (ART) is a lifesaving intervention tha improves the health and economic status of HIV-infected women throughout the world. Therefore, it is of significant public health importance to guide the appropriate use these essential medications. To this end, millions of HIV-infected women in low and middle income countries (LMIC) currently use or are gaining access to subdermal progestin-containing implants as a preferred method of long-acting reversible contraception. These implants are often combined with ART despite the lack of critically needed pharmacokinetic (PK) drug-interaction data to inform their safe and effective concomitant use. Highlighting this concern are several case reports of unintended pregnancy that occurred in patients with subdermal progestin-containing implants concurrently receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART, the most commonly used ART in LMICs. While NNRTIs are known to significantly decrease oral pill progestin concentrations, no data are available to inform healthcare providers of the impact of NNRTIs on progestin concentrations following release from subdermal implants. To fill this critical gap in knowledge, the overall aim of this proposal i to conduct a PK study to evaluate the combination of a levonorgestrel (LNG) implant and NNRTI (nevirapine or efavirenz)-based ART in HIV-infected Ugandan women. We hypothesize that lower LNG concentrations will be observed in patients on NNRTI-based ART and although the implant's efficacy may be retained initialy, this negative interaction will jeopardize implant effectiveness near the end of its intended duration of use (4 years). The specific aims of this project are (1) to characterize the PK of LNG released from a subdermal implant over one year in HIV-infected women with and without NNRTI-based ART and (2) to evaluate the potential for a bidirectional drug-interaction resulting from the long-term impact of chronic progestin exposure on antiretroviral concentrations. To achieve these aims, we will enroll 20 HIV-infected women into each of three study groups: a control group not receiving ART and two treatment arms consisting of patients receiving nevirapine- or efavirenz-based ART. Using sparse PK sampling strategies, LNG, nevirapine or efavirenz concentrations will be measured over one-year and compared between and within groups, as appropriate. The LNG data will also be used to develop a PK model that will predict LNG disposition over the following three years of intended use, allowing for identification of the safe duration of LNG implant use in women on NNRTI-based ART. At the conclusion of this project, the first evidence-based medical knowledge will be available to guide the safe and effective concomitant use of subdermal LNG implants and NRTIs, thereby improving management of reproductive health in millions of HIV-infected women worldwide.

Title: **Pittsburgh Pelvic Floor Research Program**
P.I.: **Halina M. Zyczynski**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **HD069006-02**
Award: **$25,000**

The purpose of this proposal is to demonstrate the capabilities of the University of Pittsburgh to participate as a clinical site in the NICHD-sponsored Pelvic Floor Disorders Network (PFDN). Our site has a longstanding track record of successful contribution to multicenter studies of urinary and fecal incontinence, and pelvic organ prolapse. We are particularly well suited to be a clinical site in the PFDN because of our volume, research infrastructure and track record, basic and translational experience and expertise. Access to large numbers of nulliparous women enables us to contribute uniquely to studies of the role of pregnancy and parturition in the etiology and prevention of pelvic floor disorders (PFDs). Magee-Womens Hospital (MWH) is the central resource for gynecologic specialty care for the 19 hospital University of Pittsburgh Health System serving a very large aging population. Our site brings expertise in urogynecology, physical therapy, geriatrics, urology, gastroenterology and mental health. We offer unique technical expertise in genomics, proteomics, tissue regenerative techniques, biochemical and biomechanical impact of meshes on the vagina and central neuronal control of bladder function. We propose to establish a comprehensive, scientifically rigorous clinical and translational research program within the PFDN for prospective comparative studies of mesh materials used in prolapse and incontinence procedures. The program will generate data of immediate clinical relevance as it will present scientifically sound, vendor independent evidence to guide surgeons' selection of specific graft materials and evidence-based practice guidelines for management of mesh complications. The 3 major components of the proposal are: 1) mesh specific infrastructure for implementation in PFDN clinical trials employing mesh inclusive of the development of a Mesh Morbidity Index and establishment of a Biospecimen Repository 2) the first RCT of meshes selected through rigorous analyses of biomechanical and biochemical properties and 3) translational studies on the cellular response to mesh materials and pathophysiology of mesh complications. The RCT will serve to pilot the database, compare clinical outcomes of meshes whilst providing specimens for translational studies.

Title: **RCT of Hypnotherapy vs. Tpolterodine for OAB: Voiding and Brain Activation Changes**
P.I.: **Rebecca Glenn Rogers**
Institution: **University of New Mexico Health Sciences Center**
Grant No.: **HD069025-02**
Award: **$25,000**

The University of New Mexico (UNM) proposes to join the Pelvic Floor Disorders Network (PFDN) to achieve the Network's primary goal of conducting rigorous, multi-center clinical trials to investigate the clinical and health aspects of pelvic floor disorders in women. Our site, in collaboration with other Network sites, aims to reduce the burden of pelvic floor disorders on women and their families. Through the design of innovative trials and participation in ongoing studies, the UNM PFDN site will make significant contributions to the Network. Dr. Rogers, Principal Investigator, and Dr. Komesu, Alternate Principal Investigator, have extensive experience in the design and conduct of multi-center randomized trials and proven leadership and productivity. The UNM PFDN site brings to the Network a busy clinical service with large numbers of under-represented Hispanic and Native American populations, as well as broad institutional support from the Department of Obstetrics and Gynecology and a recently funded Clinical and Translational Research Center. The concept proposal, based on preliminary data generated by our site and the work of others, is an innovative investigation comparing hypnotherapy to long-acting anticholinergic medicine for the treatment of overactive bladder (OAB). In addition to the hypnotherapy comparative-effectiveness trial, the concept proposal focuses

investigation into the underlying mechanisms of OAB on the brain, using functional magnetic resonance imaging (fMRI). This translational, comparative effectiveness clinical trial is an excellent example of cutting edge research that the UNM PFDN site will bring to the Network. Skilled investigators, a busy clinical practice, unique patient populations and broad institutional support make UNM a worthy new clinical site for the PFDN. RELEVANCE: Pelvic floor disorders are common and costly. Performance of rigorously designed, target randomized clinical trials that inform evidence-base health care practices for women with pelvic floor disorders is best done through collaboration with other clinical sites. The University of New Mexico is a highly productive clinical and research site and proposes to join the Pelvic Floor Disorders Network in order to meet the Network's goal of investigating innovative solutions to these common problems.

Title: **Unintended Birth, Fetal, and Infant Loss and Maternal Depressive Symptoms**
P.I.: **Pamela J. Surkan**
Institution: **Johns Hopkins University**
Grant No.: **HD069731-01A1**
Award: **$81,000**

Depression is the most prevalent mental health disorder and globally is two times more likely to occur in women. In rural areas of Bangladesh, women's autonomy in planning pregnancy and the likelihood of successful pregnancy remain uncertain, with stillbirth, perinatal and neonatal death occurring at over five-fold higher rates than in developed countries. These rates are likely to be higher for rural women with little access to medical care. Our aims are to study: 1) the relation of unintended pregnancy to maternal depressive symptoms in the third trimester of pregnancy and at six months postpartum; 2) the relation of unintended pregnancy and fetal and neonatal loss to postpartum maternal depressive symptoms; 3a) whether the relation of unintended pregnancy with postpartum maternal depressive symptoms differs by gender of the offspring; and 3b) whether the relation of fetal or neonatal loss with postpartum maternal depressive symptoms differs by gender of the offspring. Miscarriage, stillbirth, perinatal death, and neonatal death will be examined separately as risk factors. The proposed secondary analysis uses data from a population-based, randomized antenatal micronutrient supplementation trial conducted from 2001 to 2007 in northwestern rural Bangladesh among ~60,000 pregnant women. Women were enrolled in early gestation and followed through 6 months postpartum. Pregnancy outcomes and infant vital status were monitored weekly through 3 months of age. In the third trimester and at 6 months, symptoms of depression were elicited by maternal responses to questions about common depressive symptoms as well as about suicide. Statistical methods will include descriptive analyses and calculation of adjusted risk ratios to examine unintended pregnancy and fetal and neonatal death events as predictors of subsequent depressive symptoms. We will assess the effects of pregnancy intent from each parent as well as discordance between maternal and paternal pregnancy intentions on maternal depressive symptoms. Documentation of unintended pregnancy and loss of a fetus or infant as risk factors for depressive symptoms in a large South Asian population will help to show their extent and guide interventions relevant to a vulnerable period when maternal mental health is critical for the healthy development of her other children.

Title: **Uterine Leiomyoma Research Center Program**
P.I.: **Serdar E. Bulun**
Institution: **Northwestern University at Chicago**
Grant No.: **HD057877-04**
Award: **$250,000**

Uterine leiomyomata (fibroids) represent the most prevalent benign gynecologic disorder in the US. The cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Our multidisciplinary team has designed 3 well-integrated

projects focusing on Interactions between biologically critical hormonal pathways in uterine leiomyoma involving the transcription factors progesterone receptor (PR) and FOXO, the signaling pathway PI3K/AKT and the pro-fibrotic factor TGF-beta. Project I (Bulun) will be pursued to understand the mechanisms as to how antl-progestins such as RU486 reduce tumor size. We hypothesize that progesterone regulates a number of critical genes, that favors increased proliferation and decreased apoptosis of leiomyoma smooth muscle cells, whereas anti-progestins reverse this effect by enhancing apoptosis and decreasing proliferation. Project II (Kim/Chakravarti) will determine the role of the PI3K/AKT/F0X0 signaling pathway regulating leiomyoma cell growth and survival in response to progesterone. We hypothesize that progesterone Induces proliferation of leiomyoma cells through activation of the PI3K/AKT/F0X0 signaling pathway and that Inhibitors of the AKT pathway should override the proliferative effects of progesterone and promote apoptosis. Project III (Nowak) will define the mechanisms as to how antifibrotic drugs regulate leiomyoma growth. We hypothesize that the Increased proliferation exhibited by leiomyoma smooth muscle cells Is due to a major shift in the extracellular matrix environment caused by increased synthesis of new, monomeric collagen type I by these cells. We will determine whether antifibrotic drugs may be an effective new treatment for leiomyomas. These projects are supported by an Administrative Core (Bulun) and Tissue Procurement and Cell Culture Core (Kurita). Overall, as part of our long range goal, all projects investigate local hormonal signaling regulating apoptosis and proliferation as biologic endpoints and test existing and upcoming pharmaceutical compounds that target these pathways in uterine leiomyomata.

Title: **Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and Its Association with Incidence, Progression, and Recurrence of Pelvic Floor Disorders**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah**
Grant No.: **HD061787-04**
Award: **$66,667**

Pelvic floor disorders affect one in four American women. Few modifiable risk factors have been identified that might reduce the incidence or progression of pelvic floor disorders. Popular wisdom and scant clinical data suggest that strenuous activity causes or promotes pelvic floor disorders. Given the health benefits of activity, women should be encouraged to be maximally active unless there is scientific evidence to the contrary. Existing physical activity instruments are largely designed to assess cardiovascular exertion and are validated using activity diaries, accelerometers, and step counters. Such measures may not accurately measure activities that increase loading on the pelvic floor (such as lifting). After researching available technologies, we concluded that a tool to understand how physical activities impact abdominal pressure in the real world does not exist. Over the past 18 months, our interdisciplinary team of bioengineers, urogynecologists, electrical engineers, and exercise scientists developed and validated the performance of a prototype for an intravaginal abdominal pressure sensor that accurately measures pressure in the upper vagina, an easily accessible space that records pressures similar to the true intraabdominal pressure. In this proposal, we plan first to further develop an integrated system (the "WRAPS", Wireless Remote Abdominal Pressure System) to monitor intraabdominal pressure outside of the clinical setting. This system will consist of three key elements: an intravaginal pressure sensor with wireless data transmission capability, a small portable data monitoring and storage unit, and computer based data translation software for downloading and managing the pressure data. In a controlled exercise laboratory setting, we will then use intraabdominal pressure data generated by the WRAPS to determine the reproducibility of intraabdominal pressures measured during specific types of physical activity and will finalize development of a valid questionnaire that categorizes the magnitude of intraabdominal pressures during activities. Finally, in a real-world setting in which participants wear the intravaginal sensor during waking hours for four 1-week periods over the course of a year, we will characterize intraabdominal pressures

experienced by women of varying degrees of habitual physical activity and, using WRAPS data as the gold standard, determine whether activity can be appropriately categorized in terms of pelvic loading by means of self-administered questionnaires, the current standard. Obtaining future evidence about the impact of physical stressors on pelvic floor disorders relies on our ability to measure the risk factor in question. This innovative translational collaboration will remove a critical barrier to progress in understanding the etiology of pelvic floor disorders in women.

Title: **Xenograft Study on Growth Control of Human Uterine Leiomyomata**
P.I.: **Takeshi Kurita**
Institution: **Northwestern University at Chicago**
Grant No.: **HD064402-03**
Award: **$83,333**

The ultimate goal of this study is to elucidate the molecular mechanisms of uterine leiomyoma (UL) formation and growth, and identify potential targets for novel therapeutic and preventive treatments of this disease. UL is a benign tumor of the myometrium that affects millions of reproductive-age women. Surgical removal of the entire uterus (hysterectomy) is the primary treatment option, and management of UL puts an enormous burden on the healthcare system. Therefore, finding a new therapeutic treatment replacing surgery is of great interest to the public. Due to the absence of a proper research model system reflecting characteristics of the original tumors, the biological nature and the causes of UL are poorly understood. Although growth dependency of UL on ovarian steroids (172-estradiol and progesterone) is well established, the relative importance and function of 172-estradiol and progesterone are yet to be clarified. In spite of accumulating evidence for the essential role of progesterone in UL growth, no research model has clearly demonstrated a growth-promoting effect of progesterone on UL. To elucidate the function of ovarian steroids in UL, we have established a novel xenograft model in which tissue fragments of human leiomyoma were grafted beneath the renal capsule of immunodeficient mice. The size of the leiomyoma xenografts increased in response to 172-estradiol and progesterone as demonstrated by cell proliferation and accumulation of extra-cellular matrix. In contrast, xenograft growth induced by 172-estradiol and progesterone was blocked by the anti-progestin RU486, indicating the essential role of progesterone and progesterone receptor (PR) in leiomyoma tumor growth. Previously, 172-estradiol has been thought to be the primary stimulus for UL growth. Surprisingly, 172-estradiol by itself neither increased nor maintained tumor size. Likewise, progesterone alone did not affect UL growth in this model. Although not mitogenic, 172-estradiol was required for expression of PR, and was essential for progesterone to act on UL xenografts. Our study clearly demonstrates the pivotal role of progesterone in growth and maintenance of UL. The results of our xenograft model agree with clinical observations, yet radically change the paradigm of steroid hormone-regulated human UL growth by emphasizing the importance of progesterone instead of 172-estradiol. Using the novel xenograft model, we will elucidate the cellular and molecular mechanisms of human UL tumor growth controlled by 172-estradiol and progesterone.

National Institute on Drug Abuse

Title: **NIH Pain Consortium Centers of Excellence in Pain Education (CoEPEs)**
P.I.: **NIDA (coordinating center)**
Institution: **NIH Pain Consortium, funding 12 centers**
Grant No.: **1201100111U**
Award: **$200,000**

The NIH Pain Consortium has established 12 Centers of Excellence in Pain Education (CoEPEs), led by the National Institute on Drug Abuse, to develop and disseminate curriculum resources to improve medical, dental, nursing, and pharmacy education in the assessment, diagnosis,

and treatment of pain, while minimizing the abuse of opioid medications, an area that current training under-emphasizes. A wide variety of women's health issues will be addressed, including: Migraine and giant cell arteritis-related headaches; Hormonally-related headaches associated with menstruation, pregnancy, and menopause; Fibromyalgia and/or temporomandibular joint disorders; Stage IV endometriosis experiencing pelvic pain and dysmenhorrhea; Post-operative pain in an infant who underwent a laparotomy to remove an ovarian cyst; Female breast cancer patients and survivors experiencing pain related to or separate from cancer; Pelvic pain of unknown etiology; Musculoskeletal pain in a female who may be a victim of domestic abuse; End-of-life pain management scenario for a female patient with a 30 year history of systemic lupus erythematosus; Irritable bowel syndrome; Neuropathic dental pain, atypical odontalgia (phantom tooth pain), and burning mouth syndrome; and Vulvodynia and chronic fatigue syndrome.

Title: **Novel Assessment of Maternal Distress Tolerance Underlying Substance Use Relapse**
P.I.: **Carl W. Lejuez**
Institution: **University of Maryland, College Park**
Grant No.: **DA034176-01**
Award: **$228,000**

Women evidence worse substance use treatment outcomes than men (Greenfield et al., 2007), including higher rates of treatment dropout (Arfken et al., 2001; King & Canada, 2004; Sayre et al., 2002), lower treatment attendance (McCaul et al., 2001) and higher rates of post-treatment substance use relapse (Grella et al., 2006). Yet, substance abuse research often includes little attention to gender-specific factors relevant to particular vulnerabilities of female participants (Brady & Ashley, 2005; Greenfield et al., 2007). One factor especially relevant to risk of relapse for many female drug users is maternal stress; child care responsibilities and the associated stressors may significantly increase risk of substance use relapse, particularly during high-risk periods for relapse following substance abuse treatment. Further, although maternal factors have been a particular empirical and clinical focus regarding environmental risk factors for drug using women, but the large preponderance of this research is focused on the impact of maternal substance use on child outcomes, with little attention to drug use outcome for these women as an important target in its own right (cf., Pajulo et al., 2006). Accordingly, one promising factor that may help explain the maternal distress and substance use association when reintroduced to one's home environment following discharge from substance abuse treatment is maternal distress tolerance, or the ability to tolerate distress due to parenting issues. Indeed, one's ability to tolerate distress is associated with relapse following substance abuse treatment and length of abstinence attempts. However, despite its relevance to both substance use and parenting responses, little is known about the impact of low distress tolerance on substance using mothers. This may be due, at least in part, to the lack of distress tolerance assessment strategies that target directly the unique experience of maternal distress. To address the lack of research in this area, the following R21 attempts to provide an initial examination of maternal risk factors for substance use relapse, with a focus on the moderating role of distress tolerance. As a secondary aim, we explore a novel and ecologically valid measure of maternal distress tolerance to examine its utility over a standard distress tolerance task. Specifically, we will include 105 predominantly low-income, inner-city African American substance using mothers in their last week of residential drug use treatment that have a child in the critical age of 9 months to 4 years to examine the link between several indices of maternal distress and substance use outcomes with both general and maternal-specific measures of ability to tolerate distress as moderators of this relationship.

National Institute of Diabetes and Digestive and Kidney Diseases

Title: **Bedside to Bench—Role of Androgen and Estrogen Receptor Signaling in Pulmonary Arterial Hypertension**
P.I.: **Robert Danner**
Institution: **National Institute of Diabetes and Digestive and Kidney Diseases**
Award: **$80,000**

Idiopathic pulmonary arterial hypertension (IPAH), a subtype of plexogenic pulmonary arteriopathy (PAH), is a rare disorder associated with poor survival. Despite consistent epidemiological evidence demonstrating a 2 to 4 fold female predominance in IPAH, the underlying mechanisms for this imbalance are unclear. Endothelial dysfunction resulting from 1) genetic susceptibility, and 2) a triggering stimulus that initiates pulmonary vascular injury, the so-called two-hit hypothesis, appears to play a central role both in the pathogenesis and progression of PAH. Inflammation may drive this dysfunctional endothelial phenotype, propagating cycles of injury and repair in genetically susceptible patients with IPAH and patients with disease associated PAH (e.g. scleroderma, HIV, and sickle cell disease). Histologic specimens from patients with IPAH reveal the presence of inflammatory cells, including macrophages and T- and B-lymphocytes, within classic plexiform lesions that are the hallmark of PAH. Pulmonary artery endothelial cells (PAECs) in PAH orchestrate the recruitment of inflammatory cells as well as secreting pro-inflammatory and pro-coagulant cytokines into the circulation. Patients with IPAH have higher levels of circulating IL-1β, IL-6, P-selectin and E-selectin in comparison to healthy controls. Therefore, targeting PAEC inflammation may interrupt the cycles of injury/inflammation and repair that contribute to progressive increases in pulmonary vascular resistance in patients with PAH, and thereby delay or prevent right ventricular failure and death. Both estrogen and testosterone promote vasodilatation and affect vascular inflammation through binding to estrogen (ER) and androgen receptors (AR), respectively, members of the nuclear receptor (NR) family of transcription factors. However, the interaction between sex hormone signaling and IPAH-associated vascular injury/inflammation is not understood. Many NRs inhibit inflammation through a trans-repression mechanism that recruits co-repressor proteins to promoter NFκB and AP-1 binding sites in a tissue and target gene specific manner. Using an in silico bioinformatics approach, we found that the androgen receptor (AR) is relatively over-expressed in primary human endothelial cells compared to phagocytic leukocytes. Initial work in our laboratory using EA.hy926 cells, a human endothelial line, demonstrates that dihydrotestosterone (DHT) can suppress TNFα-induced VCAM1 mRNA expression, while spironolactone, a mixed mineralocorticoid receptor and AR antagonist currently used in PAH for advanced right heart failure, was found to inhibit NFκB signaling. We hypothesize that AR and ER differentially modulate endothelial inflammation in IPAH and this may in part explain the female predominance of this disease. Here, the effects of AR and ER signaling on endothelial dysfunction and inflammation will be investigated in cell culture models. Patients with PAH will be recruited to the NIH to investigate novel MRI-based methods to improve clinical phenotyping and as part of a pilot feasibility study on the effects of early spironolactone on endothelial inflammation in vivo. The Specific Aims include: 1.) Investigate the effects of AR and ER in endothelial cell culture systems that simulate key aspects of PAH pathophysiology using proinflammatory challenges (IL-1β, IL-6, IFNγ), targeted gene knockdown (eNOS, BMPR2) and dominant negative mutant protein expression (Smad proteins); 2.) Characterize the global transcriptomic response of naïve and dysfunctional PAECs (BMPR2 and/or eNOS silencing; Smad dominant negative mutant expression) to plasma from patients with PAH compared to matched controls using oligonucleotide microarrays; and 3.) Patients with PAH will be recruited to the NIH for a pilot study of early treatment with spironolactone to investigate its effects on endothelial dysfunction in vivo. In addition to standard clinical assessment (6-minute walk distance, echocardiography and right heart catheterization), plasma levels of inflammatory cytokines, neurohormonal markers and novel MRI-based techniques for assessing pulmonary artery endothelial function will be used to characterize treatment response. Using 6-minute walk distance as the gold standard

measurement of functional status, we will determine the sensitivity and specificity of MRI-based quantification of pulmonary artery endothelial function and MRI derived measurements of right ventricular (RV) structure and function for assessing disease progression.

Title: **Diabetes Prevention Program Outcomes Study**
P.I.: **Sarah E. Fowler**
Institution: **George Washington University**
Grant No.: **DK048489-19**
Award: **$1,050,000**

The George Washington University Biostatistics Center proposes to continue as the Coordinating Center for the Diabetes Prevention Program Outcomes Study (DPPOS). This application is companion to the Clinical Centers' application. The Diabetes Prevention Program (DPP), a multi-center controlled clinical trial in a multiracial population of overweight persons with impaired glucose tolerance, established the efficacy of a life-style intervention aimed at a modest degree of weight loss and increased moderate-intensity activity, and of metformin in decreasing the development of diabetes by 58 and 31%, respectively. The DPPOS, a 10-year follow-up, was funded in 2002 for a five-year period with the understanding that it would require refunding via competitive renewal. The overarching goal of DPPOS was to study whether the relatively shortterm benefits of delaying diabetes demonstrated in the DPP would translate into a more long-lasting impact that would reduce the public health burden of the diabetes epidemic. Specifically, DPPOS had the following major goals: 1) to determine the effects of DPP interventions on the long-term microvascular and cardiovascular disease (CVD) complications, atherosclerosis and CVD risk factors; 2) to examine the long-term effects and durability of prior DPP interventions on further diabetes development; and 3) to describe the incidence of long-term complications and their risk factors in new onset type 2 diabetes and IGT. To date, after 10 years of DPP/DPPOS, 93% of the DPPOS cohort attends annual follow-up visits. A durable effect of diabetes prevention associated with the life-style and metformin interventions has been demonstrated with 36 and 19% reductions in diabetes incidence, respectively, compared with the placebo group. Interim analyses also reveal significant reductions in CVD risk factors in the intervention groups, with decreased utilization of medications. The development of diabetes is associated with an increased frequency of retinopathy and microalbuminuria. The development of diabetes is associated with an increased frequency of retinopathy and microalbuminuria. This application is designed to support completing the second five-years of DPPOS focusing on complications that require more time to develop. RELEVANCE: The Diabetes Prevention Program (DPP) and first 5 years of the DPP Outcome Study (DPPOS) have demonstrated that a lifestyle intervention program aimed at weight loss, and metformin, prevent diabetes development over a 10 year period. Completion of DPPOS will examine the impact of diabetes prevention on long-term complications affecting the eye, kidney, nerves and heart, and remains critical to public health.

Title: **Glycated CD59 as a Novel Biomarker of Gestational Diabetes Mellitus**
P.I.: **Jose A. Halperin**
Institution: **Brigham and Women's Hospital**
Grant No.: **DK095429-01A1**
Award: **$200,000**

The goal of this proposal is to assess glycated CD59 in human serum as a pathogenically relevant early bio-marker for screening of gestational diabetes mellitus (GDM). This proposal is highly translational and addresses major Public Health priorities because 1) diabetes affects H 25 million Americans, 2) and GDM is a major source of adverse pregnancy outcomes including macrosomia and pre-eclampsia. The proposed work opens the possibility of using glyCD59 as a biomarker for GDM, an innovative departure from the use of OGTT, a cumbersome, costly

and time-consuming test with poor reproducibility and many times unwanted effects including nausea and vomiting. A simpler, easy to use, patient friendly marker that is also involved in the pathogenesis of diabetes and its complications may help fulfill an important clinical need in the widespread screening for GDM and prevention of associated adverse outcomes. The applicants have 1) discovered that human CD59 is inactivated by glycation, 2) provided evidence for a link between the complement system and the pathogenesis of the complications of diabetes, and 3) developed key reagents that allow quantification of glycated hCD59 in human fluids and tissues. Specifically, we have demonstrated that 1) glycated CD59 is present in target organs of diabetic complications, and 2) glyCD59 can be readily measured in normal urine and serum. Furthermore, our preliminary data show that glyCD59 is a) significantly increased (3-4 fold) in the serum of diabetic and pre-diabetics individuals, and b) seems to respond faster than HbA1c to changes in glycemic load within an individual All necessary tools and expertise to accomplish our aim are available in the laboratory of the applicant and expert collaborators, including monoclonal antibodies specific for glycated CD59 and assay calibrators, access to large and diverse population of pregnant women undergoing pre-natal care at BWH, and diagnostic tools, equipment and expertise to necessary to conduct all studies proposed in the application. Successful accomplishment of our aims would represent a major advancement in screening and early diagnosis of GDM.

Title: **Lifestyle Interventions in Overweight and Obese Pregnant Women**
P.I.: **Xavier Pi-Sunyer**
Institution: **St. Luke's Roosevelt Institute for Health Sciences**
Grant No.: **DK094463-02**
Award: **$100,000**

A randomized controlled trial is proposed to study the effect, in a cohort of racially and ethnically diverse group of overweight and obese pregnant women, of an Intensive Lifestyle Intervention (ILI) compared to Usual Care (UC) on gestational weight gain (GWG), infant fatness, and mothers' post-delivery weight retention. Women in the ILI arm will receive intensive counseling during pregnancy and group counseling after delivery regarding behavior, nutrition, and physical activity change. Visits to counselors will be weekly and additional telephone and internet contacts will occur. The mothers' will be assessed at 14 and 36 weeks of pregnancy and at 12 weeks and 52 weeks post-delivery. The measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (BodPod). The infants' measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (PeaPod) for fatness 12 weeks and 52 weeks. Mothers and children will have cardio-metabolic risk factors measured in plasma. Data will be collected regarding mothers' dietary intake and physical activity (questionnaires and accelerometry) to assist in counseling. Other data to be collected include questionnaires on quality of life, socio-economic status. Careful record will be kept of expenses in providing the ILI, so that cost analysis of the intervention can be calculated. The study is powered on the primary outcome, fatness of the infants at birth. We require 180 participants to attain appropriate power. We will enroll 210 so as to allow for some dropouts along the way. Each mother will be followed during pregnancy and for a year post delivery. Each infant will be followed for a year after birth. We have the ability o continue to follow these participants if further funding is forthcoming, as they are all local to or hospital's catchment area and our own physicians. If aims are achieved, namely that both children and mothers profit from the intervention, there should be a paradigm shift in how overweight pregnant women are treated. At present, there is a dearth of behavioral advice and intervention relating to GWG and physical activity provided to these women. Positive results from our study would provide evidence for ILI preventative intervention.

Title: **The Look AHEAD Continuation: Action for Health in Diabetes**
P.I.: **Rena R. Wing**
Institution: **Miriam Hospital**
Grant No.: **DK056992-14**
Award: **$100,000**

Look AHEAD is randomized clinical trial examining the long-term health effects of an intensive weight loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity, or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and non-fatal Ml and stroke and cardiovascular deaths) over a planed follow-up of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well—the sample of 5,145 was recruited on time; retention has been excellent and the intervention has been effective in producing initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific Aims are to retain the cohort over time, continue to complete annual in-person visits and semi-annual telephone interviews for outcome assessments and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular-related factors and complications, and cost-effectiveness of the intervention.

Title: **Molecular Basis of *E. coli* Adhesins in Bladder Disorders**
P.I.: **Scott J. Hultgren**
Institution: **Washington University**
Grant No.: **DK051406-15A1**
Award: **$200,000**

Over 15 million women suffer from urinary tract infections (UTI) annually in the U.S., ~85% of which are caused by uropathogenic *Escherichia coli* (UPEC). 20-40% of patients suffer from multiple and/or chronic recurrences and increasingly are left with few treatment options other than costly long-term antibiotic prophylaxis Indiscriminate use of antibiotics is leading to increased resistance to first-line empiric therapie such as trimethoprim-sulfamethoxazole and the undesirable use of fluoroquinolones for empiric treatment of UTI. Catheter-associated UTI (CAUTI) further exacerbates this problem. Consequently, multi-drug resistance is rising rapidly. Thus, there is a critical need for new therapeutics to better treat and prevent chronic recurrences. There are two bladder associated niches for UPEC during acute UTI: the bladder tissue and the luminal space/urine. FimH, the type 1 pilus adhesin mediates UPEC colonization and invasion of human and murine bladder epithelial cells (BECs). Murine models indicate that after invasion, UPEC can subvert innate expulsion mechanisms and escape into the cytoplasm where rapid bacterial replication results in the formation of intracellular bacterial communities (IBC) comprised of 104-105 bacteria. IBCs are transient and upon IBC maturation bacteria disperse from the biomass, filament, and spread to neighboring BECs, re-initiating the IBC cycle. This cycle potentiates the establishment of infection allowing the expansion of the bacterial population in a sequestered habitat protected from host immune and antibiotic clearance. Bacterial colonization of BECs, IBC formation, filamentation and biofilm formation on urinary catheters (also seen in mouse models) are all processes seen in human disease. Further, the fimH gene is under positive selection in UPEC clinical isolates consistent with its role in UTI. Murine models and human clinical studies show roles for the same specific cytokines and TLR4 signaling in UTI. In humans, UTI ranges from asymptomatic bacteriuria to acute self-limiting infection to chronic/recurrent

UTI. Murine models mimic these disease outcomes and reveal that the nature of host response dictates whether a UTI resolves or develops into long-lasting chronic/recurrent UTI. This grant proposal will use a panel of virulent clinical isolates including a multi-drug resistant strain that has spread globall, to focus on a direct experimental investigation of common but complex clinical problems associated with more severe UTI and/or recurrence. Aim 1 investigates mechanisms by which superinfection of UPEC leads to the development of chronic/recurrent infection. Aim 2 investigates catheterization, which may alter the pathogenesis and may trigger the recurrence of infection in patients with a history of UTI. Aim 3 investigates the efficacy of potent small molecular weight compounds called mannosides, which block FimH function, to treat and prevent UTI in the context of these complicating factors. The proposed experiments will elucidate how sequential infection and catheterization affect the course of UTI and aid in better clinical management and the development of new therapeutics for combating this prevalent infection.

Title: **Ovarian Hormone Suppression and Regulation of Adipogenesis in Women**
P.I.: **Wendy M. Kohrt**
Institution: **University of Colorado Denver**
Grant No.: **DK092718-02**
Award: **$191,250**

Estradiol (E2) deficiency triggers weight gain, and specifically abdominal fat gain, in women. The shift toward central adiposity after menopause likely contributes to increased risk for the metabolic syndrome and associated chronic diseases (i.e., type 2 diabetes, coronary artery disease, hypertension). The long-term aim is to understand the mechanisms by which E2 deficiency mediates increases in abdominal adiposity. The primary aim (PA1) of the R21 is to determine whether ovarian hormone suppression in premenopausal women, which is known to cause fat gain, triggers an increase in adipogenesis (i.e., increase in cell number) in abdominal adipose tissue. This will be assessed by measuring the changes in cell size distribution and the incorporation of deuterium (2H) into DNA of cells in the non-stromal (i.e., mature adipocyte) fraction. Secondary aims are to determine: SA2) effects of ovarian hormone suppression on mRNA expression of factors involved in adipogenesis (C/EBP1, PPAR3) and markers of macrophage infiltration (CD68, Emr-1) and inflammation (IL-6, TNF-1); and SA3) whether new adipocytes arise from non-resident bone marrow progenitor (BMP) cells using cell surface markers (Notch 4, Platelet-derived Growth Factor Receptor (PDGFR) 2, Integrin 15, CD36) that enable detection by flow cytometry. To achieve these aims, 24 premenopausal women will be studied before and after 30 and 60 days of ovarian hormone suppression via gonadotropin releasing hormone agonist therapy with add-back of placebo (GnRHAG+PL) or estradiol (GnRHAG+E2). Hypotheses are: H1a) GnRHAG+PL for 60 days will result in a larger increase in small adipocytes (< 40 5m) when compared with GnRHAG+E2. Because fat mass increases during GnRHAG+PL, an increase in the number of small adipocytes will be interpreted as an increase in adipogenesis and not as evidence of adipocyte atrophy; H1b) The incorporation of 2H in the non-stromal cell fraction DNA will be increased in response to GnRHAG+PL, as compared with GnRHAG+E2. Because the non-stromal fraction contains mature adipocytes, an increase in 2H-enriched DNA should reflect adipogenesis; H2) Ovarian hormone suppression will increase mRNA expression of factors associated with adipogenesis, macrophage infiltration, and inflammation (C/EBP1, PPAR3, CD68, Emr-1, IL-6, TNF-1) when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-back (GnRHAG+PL vs GnRHAG+E2); and H3) Ovarian hormone suppression will increase BMP-derived adipocytes when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-back (GnRHAG+PL vs GnRHAG+E2). To the best of our knowledge, this will be the first in vivo study of the role of E2 as a regulator of adipogenesis in humans. Because it is believed that adipocytes are programmed to achieve a certain volume of fat, an increase in adipocyte number would lead to a gain in fat mass that would be very difficult to reverse. Thus, identifying strategies that effectively prevent an increase in adipogenesis during ovarian hormone withdrawal would be of high clinical importance.

Title: **Urinary Incontinence Treatment Network: DCC**
P.I.: **Sharon L. Tennstedt**
Institution: **New England Research Institutes, Inc.**
Grant No.: **DK058229-12**
Award: **$100,000**

This proposal is submitted in response to RFA-DK-06-501 for continuation of the Urinary Incontinence Treatment Network (UITN) Data Coordinating Center (DCC) at New England Research Institutes, Inc. The DCC is responsible for the scientific management of the studies, including directing, training, and monitoring the performance of Clinical Centers in enrollment, data collection, and data management as well as for all data analysis, and reports to the DSMB. In Phase I and continuing to Phase II, NERI has provided several unique and innovative tools and capabilities, including a proprietary Web-based data management system, an automated patient randomization system, and an electronic repository for UDS tracings. The DCC is also responsible for network communications and meeting support and provides a secure study website and a public website. DCC scientists play a leadership role in all network activities, including protocol development, standing committees and work groups, manuscript development and presentations. Phase II will focus on conduct of the TOMUS trial as well as continuation of the observational follow-up studies for the SISTEr and BE-DRI studies (i.e., E-SISTEr and E-BE-DRI) of Phase I. Primary Aims of TOMUS are to compare objective and subjective cure rates for stress incontinence at 12 and 24 months between the retropubic and transobturator midurethral sling procedures. Performance of these procedures is increasing rapidly with limited data available on safety and efficacy. Therefore, this study will compare the efficacy and safety of the retropubic and transobturator (inside-out and outside-in) procedures in a 2-arm RCT; 588 women with stress Ul will be enrolled. Primary Aim of E-SISTEr is to compare long-term (60 mos.) effectiveness and durability of the Burch colposuspension and autologous fascial sling for treatment of stress Ul in a randomized cohort of 655 women. Primary Aim of E-BE-DRI is to examine long-term (26 mos.) durability of the addition of behavioral treatment to drug therapy for treatment of urge Ul in a randomized cohort of 307 women. The UITN is a multi-disciplinary, multi-center group of Investigators dedicated to high impact clinical research regarding the prevention, evaluation and management of Ul to improve the quality of life for adults. The UITN is conducting 3 studies of treatments for both stress and urge urinary incontinence.

Title: **Weight Management in Obese Pregnant Underserved African-American Women**
P.I.: **Samuel Klein**
Institution: **Washington University**
Grant No.: **DK094416-02**
Award: **$100,000**

Maternal obesity and inappropriate gestational weight gain (GWG) increase both maternal and neonatal morbidity and mortality. In addition, offspring of obese women are at increased risk for neurodevelopment delay, becoming obese, and developing metabolic diseases. Women who are socio-economically disadvantaged (SED), especially from African American (AA) populations, are particularly susceptible to adverse pregnancy-related outcomes because of their high prevalence rates of obesity. Therefore, successful weight management during pregnancy in SED, AA women has considerable public health implications. We have experience in testing lifestyle interventions among SED non-pregnant women that have been implemented and sustained within community organizations such as Parents As Teachers (PAT), a national home visiting program that provides parent-child education and services free-of-charge to high needs women, prenatally and post-partum, through up to 25 home visits per year until kindergarten. We propose to conduct a 24-month (6-month prenatal and 18-month post-partum) randomized, controlled trial in obese SED AA women to evaluate the ability of an innovative lifestyle intervention program (PAT-i-), delivered by PAT parent educators during prenatal and post-partum

home visits, to improve maternal and neonatal/infant weight, metabolic and health outcomes. An extensive programmatic evaluation will determine the applicability of the PAT+ intervention in real world settings by measuring programmatic reach, implementation, acceptability, and sustainability. If effective, PAT+ can be disseminated through this national organization, which currently reaches over 249,000 mothers and 319,000 children participating in 2,173 PAT programs across all 50 states.

National Institute of Environmental Health Sciences

Title: **Dioxin Exposure and the Invasive Pathogenesis of Endometriosis**
P.I.: **Kevin G. Osteen**
Institution: **Vanderbilt University Medical Center**
Grant No.: **ES014942-06**
Award: **$250,000**

Endometriosis, described as the ectopic growth of endometrial tissue, is a debilitating disease of reproductive age women. In North America, at least 5.5 million women are affected by endometriosis at any one time and estimates of the economic cost of treating this disease range from $1-20 billion annually in the United States alone. An emerging view is that a reduced endometrial responsiveness to progesterone (P4), a defect referred to as the "endometriosis phenotype," may play a significant role in development and/or progression of endometriosis. Relative to this question, we have explored whether exposure to TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin or dioxin) promotes development of the P4-resistant, endometrial phenotype. During our past funding period, we utilized adult human endometrial cell and tissue culture models, a chimeric model of experimental endometriosis in immunocompromised mice and a murine model of early life TCDD exposure to examine the impact of this toxicant. Using human cells, TCDD exposure was found to disrupt the anti-inflammatory action of P4, leading to cellular changes that potentiated the invasive behavior of endometrial tissues in our experimental endometriosis model. Our murine model of early life toxicant exposure revealed that TCDD-mediated defects in uterine P4 sensitivity can indeed arise from a developmental exposure. Perhaps more significant, our murine model also revealed that early life toxicant exposure leads to a heightened sensitivity to inflammation for multiple generations in the absence of additional toxicant exposure. Taken together our studies strongly suggest that disrupting the anti-inflammatory action(s) of P4 during endometrial maturation is the key mechanism by which TCDD-like toxicants alter reproductive function and impact a woman's risk of developing endometriosis. Thus, therapeutic interventions which target inflammatory signaling may have significant efficacy in blocking TCDD-mediated development of the P4 resistant endometrial phenotype associated with endometriosis. To validate this appoach we will utilize in vitro and in vivo studies designed to prevent the development and progression of the endometriosis phenotype as well as prevent the transmission of this phenotype to future generations. We propose three Specific Aims: 1): To evaluate the therapeutic potential(s) of resveratrol (RES) and PGE2 signaling inhibitors to reduce TCDD mediated loss of P4 responsiveness in human endometrial cells.. 2): To evaluate whether the anti-inflammatory effect(s) of RES and PGE2 signaling inhibitors alone or in combination will limit TCDD-mediated growth of experimental endometriosis in our humanized Rag2?(c) mouse model. 3): To evaluate the ability of RES and PGE2 signaling inhibitors to restore uterine progesterone sensitivity and reproductive function in a novel murine model of early life TCDD exposure that exhibits an adult endometriosis-like uterine phenotype.

Title: **Ex Vivo Female Reproductive Tract Integration in a 3D Microphysiologic System**
P.I.: **Teresa K. Woodruff**
Institution: **Northwestern University at Chicago**
Grant No.: **ES022920-01**
Award: **$300,000**

The female reproductive tract is responsible for producing endocrine hormones, developing mature, healthy gametes (oocytes) and providing the site for fertilization and an environment that supports fetal development. There are five main organs in the female reproductive tract-the ovary, fallopian tubes, uterus, cervix and vagina. Each organ is responsible for unique aspects of reproductive function, but act integrally to support overall endocrine health, fertility, and fetal development. The reproductive tract organs are assembled from multiple cell lineages to create individual follicles (that enclose and support oocytes), oviductal/fallopian tubes, uterine myometrium and endometrium, the cervix and the vagina. Traditionally, research of the female reproductive tract has relied on two-dimensional (2D) cultures of isolated primary cells or immortalized cell lines grown on plastic and independent of adjacent cells, tissue architecture, and functional context. Moving to a three-dimensional (3D) culture environment has allowed us to better understand the function and interaction of cells within individual organs and interrogate interactions between tract tissues in co-cultures (e.g., the follicle and the ovarian surface cells, or the uterine myometrium and endometrium) to measure responses to normal reproductive hormones, pathologic conditions (such as high levels of androgens) or exposure to endocrine disruptors. New biomaterials and 3D culture systems have now presented us with the exciting opportunity to create a complete in vitro reproductive tract whereby each of the cultured organs can be assembled into a linked perfusion culture system. Just as the biological function and responses of 2D monolayer cell cultures differ from those of 3D-cultured organoids, we predict that the biology of the reproductive organs when studied in an integrated series will more closely recapitulate the in vivo environment. In Aims 1 and 2, we propose to develop in vitro cultures of human reproductive tissues that phenocopy in vivo function in terms of hormone production and response to the physiologically relevant reproductive hormones follicle-stimulating hormone (FSH) and estrogen. We will use the 3DKUBE culture platform (KIYATEC), which not only permits control of perfusion to mimic tissue circulation, automated sampling for pharmacokinetic analyses, tissue imaging and in situ bioassays, but also will facilitate integration of the individal organ cultures into a functional in vitro female reproductive tract culture system in Aim 3. The successful development of an ex vivo female reproductive tract will give us the unique ability to interrogate normal hormonal responses of each organ in the context of the complete reproductive tract, as well as examine responses of the organs and system to agents that pose reproductive hazards. Toxicologic testing on female reproductive function and fertility is currently limited to animal studies. Our proposed Ex Vivo Female Reproductive Tract Integration In a 3D Microphysiologic System would permit earlier assessment of the effects of drugs, toxicants or vaccines on the human female reproductive system prior to exposure in clinical trials.

National Institute of General Medical Sciences

Title: **Pharmacogenetics of Phase II Drug Metabolizing Enzymes**
P.I.: **Richard M. Weinshilboum**
Institution: **Mayo Clinic**
Grant No.: **GM061388-13**
Award: **$237,958**

This proposal represents a request for continued funding of the Mayo Clinic Pharmacogenomics Research Network (PGRN) grant "Pharmacogenetics of Phase II Drug Metabolizing Enzymes". The Mayo PGRN is an integrated, multidisciplinary, pharmacogenomic research effort based on

a decades-long focus at Mayo on the pharmacogenetics of phase II (conjugating) drug metabolizing enzymes. The Mayo PGRN began by applying a "genotype-to-phenotype" research strategy that included, sequentially, gene resequencing, functional genomic, mechanistic and translational studies. During the present funding cycle, the Mayo PGRN has also incorporated the use of genome-wide techniques and pharmacogenomic model systems, with a special emphasis on functional mechanisms responsible for genetic effects on drug response. We have used that approach to study the pharmacogenomics of the endocrine therapy of breast cancer and selective serotonin reuptake inhibitor (SSRI) therapy of depression—research that grew out of the contribution of phase II enzymes to the biotransformation of the estrogens that play such an important role in breast cancer and biotransformation ofthe neurotransmitters that are central to the pathophysiology and treatment of depression. Recently, we have performed pharmacogenomic genome-wide association (GWA) studies of breast cancer, and we will soon perform similar studies of the SSRI therapy of depression. We propose to continue this genome-wide focus during the next funding cycle, with both clinical and model system GWA studies of the drug therapy of breast cancer and depression, always including replication as well as functional and mechanistic studies. We also propose two "Network Resources", one designed to provide access to "Next Generation" DNA sequencing for all PGRN Centers and the other focused on pharmacogenomic ontology. In summary, the studies in this application build on Mayo PGRN strengths in DNA sequencing and functional genomics—while incorporating genome-wide techniques—to provide insight into the role of inheritance in variation in the efficacy and side effects of drugs used to treat breast cancer and depression. RELEVANCE: Breast cancer is the most frequent cancer of women and depression is the most common major psychiatric illness. Drugs are available to treat both of these serious illnesses, but many patients fail to respond and some suffer serious adverse drug reactions. The Mayo Clinic PGRN will apply modern pharmacogenomic techniques to help make it possible to "individualize" the drug therapy of breast cancer and depression.

National Institute of General Medical Sciences & Indian Health Service

Title: **Oklahoma Native American Research Centers for Health (NARCH VI)**
P.I.: **Gloria Ann Grim**
Institution: **Cherokee Nation**
Grant No.: **GM092238-02**
Award: **$100,000**

The purposes of this project are: to encourage competitive research linked to reducing health disparities; to increase the capacity of the Tribes and University of Oklahoma to work in partnership to reduce distrust by the Native American communities and peoples toward research; and to develop a cadre of Native American scientists and health professionals engaged in biomedical, clinical and behavioral research that is competitive for NIH funding. The sixth Oklahoma Native American Research Center for Health (0NARCH6) continues the productive research and training partnership with the University of Oklahoma Health Sciences Center (OUHSC) by the Tribes, especially the Chickasaw, Creek, Choctaw and Cherokee Nations. Population served consists of 42,749 Chickasaws and 121,680 Cherokees, 49,714 Choctaws and 30,181 Creeks for a total of 244,324 in North East and South Central Oklahoma. The research will include 1) the impact of infections on maternal and child health in Native Americans, 2) research to develop better diagnostic and prognostic tests for rheumatic disease in Oklahoma tribal members, and to examine the potential roles of environmental triggers for autoimmunity focusing on vitamin D levels, tobacco smoke exposure (through serum cotinine levels) and abnormal immune responses to common viruses, 3) research to prevent excessive gestational weight gain in otherwise healthy but overweight Native American women and consequently decrease the proportion of women who gain in excess of the guidelines has the potential to decrease the risk and costs of obstetric complications associated with excessive weight gain, and 4) to develop methods

to understand attitudes, beliefs, and perceived barriers or motivators to organ/tissue donation among American Indians living off-reservation.

Title: **Research to Improve Preconception Health of Adolescent Women (NARCH VI)**
P.I.: **Sara Jumping Eagle**
Institution: **Oglala Lakota Oyate**
Grant No.: **GM087165-03**
Award: **$128,436**

The Oglala Sioux Tribe, in partnership with Stanford Research/University of South Dakota School of Medicine and the Oglala Lakota College, will be addressing priority health issues identified by the tribe and to support and expand the research capacity and infrastructure that will build on the research foundation that has been developed within the tribe over the past decade. Particular attention will be given to undertaking research to improve the preconception health of adolescent girls.

National Institute of Mental Health

Title: **Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia**
P.I.: **Deanna L. Kelly**
Institution: **University of Maryland, Baltimore**
Grant No.: **MH090071-02**
Award: **$189,455**

Risperidone is available generically and one of the most widely used antipsychotic medications; but is associated with elevated prolactin. This elevation is particularly pronounced in women and most recent studies show that the vast majority of women have elevated prolactin levels with approximately 50% also having the corresponding side effects of amenorrhea, oligomenorrhea or galactorrhea. Elevated prolactin may be associated with sexual dysfunction, decreased quality of life, medication nonadherence and decreases in bone mineral density over time. Lowering the dose or switching medications due to this side effect in stabilized patients is not a practical option in most cases. There is little evidence to guide treatment in this important area however dopamine agonists such as bromocriptine or amantadine may exacerbate symptoms, have lacking efficacy data and are associated with side effects. We have sizeable pilot data to suggest that a low dose of aripiprazole (10 mg/day), a dopamine partial agonist, added to Risperidone can improve symptomatic prolactin side effects. We will complete a double blind randomized 16-week control trial examining adjunct aripiprazole (10 mg/day with increase to 15 mg/day at 8 weeks if no response) vs. placebo in 70 women with symptomatic hyperprolactinemia and hypothesize it will be effective in the resolution of amenorrhea, oligomenorrhea and galactorrhea. We also hypothesize that aripiprazole will significantly improve quality of life, personal well-being and sexual function. And, we will examine improvements in positive, negative and depressive symptoms, sex hormone levels and measures of bone turnover. The significance and innovation of this application is high as this is a significant complaint and concern of women and very little evidence is available to guide treatment in women who are stabilized and doing well on antipsychotic treatments but develop these significant side effects. If funded, this important treatment research study of adjunct aripiprazole treatment will provide invaluable data and treatment options for thousands of women who suffer from schizophrenia and will help move the field towards better tailoring and personalizing antipsychotic treatment, particularly for women who suffer from these problems.

Title: **Course and Predictors of Depressive Relapse During IVF**
P.I.: **Lee S. Cohen**
Institution: **Massachusetts General Hospital**
Grant No.: **MH096006-01A1**
Award: **$248,607**

This revised proposal is an R21 application for the ORWH Funding Opportunity Announcement "Advancing Novel Science in Women's Health Research (ANSWHR)" (PAS-10-226). Major depressive disorder (MDD) is prevalent in women of reproductive age, and the course of MDD across infertility treatment and implications for clinical management have not previously received systematic study. At this time, clinicians do not have evidence-based treatment guidelines on which to rely in order to advise women with histories of MDD who plan in vitro fertilization (IVF) or other assisted reproductive procedures. The context of infertility treatment is an intriguing and clinically compelling setting for the stuy of the biological stress response, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and risk for major depression. The aims of the study are: 1) to delineate the clinical predictors of depressive relapse in women with histories of depression across a period of six months while they are undergoing IVF including: antidepressant continuation or discontinuation, previous course of depressive illness, duration of attempt to conceive, and partner support, 2) to describe the trajectory of depressive symptoms over the course of IVF cycles, and 3) to explore biological markers of the stress response, including those pertaining to HPA axis dysregulation and inflammation associated with depressive relapse and stress during IVF treatment. We will conduct a prospective naturalistic investigation in which participants (N=60) will each be followed longitudinally for six months, during which time they will proceed through at least one IVF cycle. Mood symptoms, antidepressant use, psychotherapy, perceived stress, partner support, use of gonadotropins and any hormonal interventions, and all infertility based treatments and interventions across each cycle will be tracked prospectively. The significance of the proposal is derived from: 1) its public health implications in light of the high prevalence rats of both infertility and major depression in women, 2) the lack of systematic data regarding risk of depressive relapse and predictors of relapse in women undergoing IVF, and 3) the need for systematic study of the biological sequelae of stress among women with histories of depression undergoing treatment for infertility.

Title: **The Influence of Estrogen on the Fear Extinction Network in Humans**
P.I.: **Mohammed R. Milad**
Institution: **Massachusetts General Hospital**
Grant No.: **MH097880-01**
Award: **$100,000**

The prevalence of anxiety disorders is twice as high in women. The reason for this eleveated prevalence is unclear, partly because most animal research has used only males, and most human research has not considered sex as a variable of interest. This proposal will begin to examine the neurobiological basis for these differences by first studying how natural fluctuations of estrogen in healthy women may influence the resting-state activity and the extinction-induced reactivity of the fear extinction network, including the amygdala, hippocampus, and the ventromedial prefrontal cortex (vmPFC). Additional experiments will involve exogenous manipulations of estrogen in naturally cycling women to see how these manipulations may interact with the functional activation of the fear extinction network. Healthy women will participate in a well-established fear conditioning and extinction protocol at different points of their menstrual cycle. Functional MRI and psychophysiological tools wil be employed to test two overall hypotheses: 1) Naturally elevated estrogen levels during the menstrual cycle will facilitate the resting-state activity and extinction-induced functional reactivity of the fear extinction network, and will be associated with enhanced extinction retention, and 2) Exogenous administration of estrogen to women will enhance extinction retention, which will be associated with enahnced resting-state activity and extinction-induced functional reactivity of this extinction circuitry

during extinction recall. Findings from his proposal may help develop sex-specific treatments for anxiety disorders, for example by using hormonal-based pharmacological adjuncts to facilitate the processes of safety learning during therapy.

Title: **Trajectories of Reward Sensitivity and Depression Across Adolescence**
P.I.: **Greg Hajcak**
Institution: **Stony Brook University, The State University of New York**
Grant No.: **MH097767-01**
Award: **$200,000**

There is increasing focus on changes in reward sensitivity that take place across adolescence; in particular, puberty appears to be a time characterized by increased sensitivity to rewards. At the same time, puberty is a time characterized by a significant increase in depressive symptoms, and depression is characterized by reductions in sensitivity to rewards. The current project examines reward sensitivity as a latent trait, capitalizing on a combination of EEG, functional neuroimaging (fMRI), behavioral, and self-report measures. Along the same lines, we consider multiple assessments of depressive symptoms (e.g., parent and child reports) so that depressive symptoms can also be modeled as a latent trait. The current proposal examines both reward sensitivity and depression in a large (N=300) sample of girls, ranging from 9 to 14 years of age; moreover, this sample will be examined two years after the initial visit, so that both cross-sectional and longitudinal relationships can be examined. In our pilot data, we have focused extensively on the feedback-related negativity (FRN), an electrocortical response observed at the scalp as an apparent negativity approximately 300 ms following feedback indicating monetary loss compared to gain. Our work suggests that the neural differentiation between gains and losses is being driven by a reward-related positive potential that is generated in the ventral striatum-part of the basal ganglia that has been implicated in reward-related neural circuits. We have found that the FRN relates to fMRI-based measures of striatal response to rewards, as well as behavioral metrics of reward sensitivity. Moreover, we have found that the FRN is reduced in both adults and adolescents who are more depressed-and have recently found that reduced reward-related brain activity can predict changes in depressive symptoms over the course of two years among adolescents. The current proposal extends this work into a much larger and longitudinal sample, and incorporates multiple measures of reward sensitivity, depressive symptoms, and puberty. We will assess: a) the relationship between multiple measures of reward sensitivity and depressive symptoms in a large sample that spans adolescence at two time points, separated by 2 years (Aim 1); b) normative developmental increases in both reward sensitivity and depressive symptoms, especially as a function of pubertal stage (Aim 2); c) prospective relations between reward sensitivity and depressive symptoms over time, and whether reward sensitivity at the first assessment can predict changes in depression two years later (Aim 3); finally, if pubertal changes predicts a stronger link between reward sensitivity and later depressive symptoms (Aim 3). A number of secondary aims are also evaluated (e.g., specificity to depressive symptoms and not anxious symptoms; utility of salivary testosterone as a marker of pubertal stage; role of stressful life events). The present study will contribute to the literature on the developmental neurobiology of reward, as well as the neurobiological changes related to individual differences in depression and risk for depression across adolescence.

Title: **Treatment of PTSD in Residents of Battered Women's Shelters**
P.I.: **Dawn M. Johnson**
Institution: **University of Akron**
Grant No.: **MH095767-01A1**
Award: **$300,000**

Intimate partner violence (IPV) is a pervasive social problem associated with high rates of post-traumatic stress disorder (PTSD). Moreover, PTSD is associated with considerable morbidity and a higher risk of re-abuse in victims of IPV. Domestic Violence Shelters provide an integral resource

for IPV victims in that they provide emergency shelter, support, and access to community resources that can aid in their establishing long-term safety for themselves and their children. However, PTSD symptoms can compromise battered women's ability to access and effectively use these vital personal and social resources, effectively establishing safety for themselves and their children. Despite the fact that annually 300,000 battered women and children access shelter services, and domestic violence shelters provide a prime time to initiate psychological treatment, virtually no research has systematically investigated the treatment of PTSD in residents of battered women's shelters. To address this gap in the literature, we have developed a shelter-based treatment for victims of IPV with PTSD, Helping to Overcome PTSD through Empowerment (HOPE). HOPE is a brief cognitive-behavioral treatment that that adopts an empowerment approach to treatment, emphasizing stabilization and safety, goals consistent with the theoretical and empirical literature on battere women and PTSD. HOPE is a novel treatment in that it adopts an empowerment approach to treating PTSD and emphasizes stabilization and safety; important needs of residents of battered women's shelters with PTSD. In this application we propose to expand upon our pilot work with HOPE and test the efficacy of HOPE relative to supportive therapy (i.e., Present Centered Therapy, PCT) in a sample of 186 female residents of battered women shelters with IPV-related PTSD. In an effort to facilitate future dissemination of HOPE, sessions will be delivered by community therapists and the study will be conducted in a range of shelter systems. Furthermore, the current proposal, unlike our pilot work, will compare HOPE to an attention matched control condition, have a longer follow-up period in order to determine whether positive findings are sustained over time, will assess the impact of HOPE on child abuse potential, will incorporate objective measures of stress responding (e.g., attentional biases and physiological reactivity to trauma cues), will explore novel mediators and moderators of treatment, and will include a cost-effectiveness analysis. Findings will be used to inform a future dissemination study of HOPE.

National Institute on Minority Health and Health Disparities

Title: **Scientific Conference R13**
P.I.: **Balwant Singh Ahluwalia**
Institution: **Howard University**
Grant No.: **MD006773-01S1**
Award: **$1,000**

The focus of this tissue oriented conference is to answer pivotal questions regarding the higher incidence and characteristics of uterine leiomyomas in African American Women (AAW). The conference will feature scientific presentations that address the current state of knowledge and identify emerging issues regarding leiomyomas in the AAW and serve as a catalyst for discussion during the final session on "New Course for Future Research and Directions". Newer, promising and innovative research that will continue to build upon and enhance our understanding of the basic pathophysiology of uterine leiomyoma will be discussed. Innovations in treatment modalities with an emphasis on impact to the female reproductive tract, reproductive potential and quality of life will be presented. The target audience includes researchers working in the fields of biomedicine, epidemiology basic, clinical and translational science, therapeutics, academic medicine, government, industry; physicians, nurses, other healthcare workers and the lay community. All participants will be invited to present posters and special area will be assigned for poster presentation. The Conference proceedings will be edited by the editorial committee to prepare for publication in a peer reviewed journal and the entire contents will be posted on the Howard University Web Site. Accreditation Statement: The activity will be planned and implemented with essential areas and policies of the Accreditation Council for Continuing Medical Education through the Howard University College of Medicine Credit Designation Statement. Howard University College of Medicine will designate this educational activity for a maximum of 8 credits AMA Category 1 Credits. Physicians will only claim credit commensurate with the extent of their participation in the activity.

National Institute of Neurological Disorders and Stroke

Title: **Brainstem Pain-Modulating Systems in Migraine-Related Photophobia**
P.I.: **Mary M. Heinricher**
Institution: **Oregon Health & Science University**
Grant No.: **NS082020-01**
Award: **$300,000**

Migraine is the most common neurological disorder, and affects over 10% of the population in any given year, with over half of these individuals reporting severe impairment. For many patients, a severe, even disabling, component of the migraine attack is photophobia, yet neuroscientists are just starting to investigate the underlying neurobiological mechanisms. The present application tests the overarching hypothesis that brainstem pain-modulating circuits, already implicated in migraine-related pain, also contribute to migraine-related photophobia. This hypothesis is based on the entirely unexpected observation that pain-modulating neurons in the rostral ventromedial medulla, the final output of an important brainstem pain-modulating system, develop photoresponsiveness in animal models of migraine headache, although they do not respond to light under normal conditions. In three Specific Aims using the nitroglycerin migraine model in the rat, we will document light-evoked activity in identified pain-modulating neurons and determine whether this is specific to migraine. We will also determine whether pain-modulating systems contribute to light aversion and light-induced pain enhancement. Finally, we will identify possible pathways through which light gains access to pain-modulating systems. The present proposal brings together electrophysiological and behavioral approaches to show how light engages pain-modulating systems to produce photophobia. These studies will provide insights into the neurobiological mechanisms of migraine-related photophobia, fundamental information critical for developing new migraine treatments.

Title: **Neuropathologic Abnormalities Define a Subgroup of Patients with CFS**
P.I.: **Benjamin Natelson**
Institution: **Beth Israel Medical Center**
Grant No.: **NS075653-02**
Award: **$66,509**

Chronic fatigue syndrome (CFS) is a debilitating multi-symptom disorder characterized by unexplained and prolonged fatigue, whose diagnosis is currently based on a relatively broad clinical case definition. Consequently, the pool of CFS patients included in clinical studies of the illness is greatly heterogeneous—a fact that might have impeded research progress to date. A major step forward in understanding the pathophysiology of CFS would involve reducing this heterogeneity by identifying one or more subgroups of patients with different pathophysiological causes of their illness, and then selecting one of these subgroups for inclusion into research studies. Over the past few years, we and others have provided substantial data supporting the existence of a subgroup of patients with a neurobiological cause for their illness, based on stratifying the sample according to the absence or presence of comorbid Axis I psychopathology (CFS-no psych or CFS-NP and CFS-psych or CFS-P, respectively). Compared to CFS-P patients, the CFS-NP patients had more cognitive dysfunction, a higher rate of abnormal cerebrospinal fluid (CSF) findings, lower regional cerebral blood flow (rCBF), and higher ventricular CSF lactate values. A further complication and limitation of these studies is that each had investigated only one brain-related variable, whose utility in separating CFS patients into subgroups was limited. The purpose of the present Exploratory/Developmental Research Grant (R21) proposal is to rigorously assess and confirm whether patients in the CFS-NP group have consistent abnormalities across several different neuropathological variables—an outcome that would be expected if this group, in fact, does have distinct neurobiological underpinnings. Specifically, in the same subjects, we will (a) assess cognitive function using objective neuropsychological testing; (b) conduct biochemical analysis of spinal fluid samples obtained by lumbar puncture; and (c) measure rCBF and

ventricular lactate using magnetic resonance imaging and spectroscopy, respectively, in CFS-P and CFS-NP patients. This will allow us to test the hypothesis that CFS-NP patients have more abnormalities in these outcome variables than CFS-P patients. Our second Aim will use the results from the first Aim in a cluster analysis to attempt objective, data-driven classification of the CFS subjects into subtypes, and then compare the resulting subgroups based on membership into CFS-NP or CFS-P groups. This aim will test the hypothesis that the results of the cluster analysis will identify a group with abnormalities across the multiple brain-based variables studied, and this group will be constituted of significantly more CFS-NP patients than in other groups.

Fogarty International Center for Advanced Study in the Health Sciences

Title: **AIDS International Training and Research Program**
P.I.: **Adaora A. Adimora**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **TW001039-14**
Award: **$25,000**

This is the second competitive renewal application for the UNC AIDS International Training and Research Program. We propose to continue to provide training in three countries: The Peoples Republic of China, Malawi and Cameroon. Investigators at UNC have worked in China since 1979, Malawi since 1989, and Cameroon since 1998. The UNC AITRP has embraced several guiding principles. First, we use training to build strong ties to key in-country organizations. Trainees with guaranteed "return jobs" in these organizations are preferentially selected. Second, our training opportunities build on funded research projects and bridge many of the strengths of UNC. Wherever possible we combine basic, clinical and epidemiological training and research in order to build critical mass. Third, we have used the Fogarty training to promote international research, working with many collaborators and funding agencies. Fourth, we have developed south-to-south and international collaborations to facilitate training and ongoing research opportunities. For example, University of the Witwatersrand is a training site for Malawi personnel, and we have developed a strong collaboration with the London School of Hygiene and Tropical Medicine for training of physicians from Malawi (a former British protectorate). Fifth, we have looked for opportunities for evolution and innovation. Such efforts have been particularly important in the development of a new Department of Public Health at the Malawi College of Medicine (which has received dedicated Fogarty support), extensive research ethics and IRB training in China, and rapid technology transfer in all three UNC AITRP countries. Sixth, we are committed to in-country leadership and ongoing mentorship after the trainee has completed our program.

Title: **Emory AIDS International Training and Research Program**
P.I.: **Carlos Del Rio**
Institution: **Emory University**
Grant No.: **TW001042-14**
Award: **$25,000**

Located in Atlanta, the Emory AIDS International Training and Research Program (AITRP) has established itself as an interdisciplinary training environment, that is producing highly qualified HIV/AIDS researchers. The collaborating countries of the Emory AITRP proposed for this application are Mexico, Georgia, Vietnam, Rwanda and Zambia. The specific aims of the research training program include: 1. To build academic capacity in partner countries through the support of in-country education and training. 2. To build HIV/AIDS research human resource capacity through the support of degree-seeking, long-term training. 3. To fill identified gaps in partner country research training capacity through the provision of specialized medium and

short-term training. 4. To build in-country capacity to conduct implementation science research that will allow our trainees to become involved in the evaluation of the impact of a variety of interventions that are currently occurring in our collaborating countries such as PEPFAR.

Title: **Fogarty Global Health Fellows Coordinating Center**
P.I.: **Charles Michael van der Horst**
Institution: **University of North Carolina at Chapel Hill**
Grant Nos.: **TW009340-01, TW009340-01S4**
Award: **$190,000**

The University of North Carolina, Johns Hopkins University, Morehouse School of Medicine, and Tulane University have formed a consortium, based on over 20 years of research and training collaboration, to launch the Fogarty Global Health Fellows Program (FGHF). This consortium brings together 17 primary research training sites in Africa (Ghana, Malawi, South Africa (2), Swaziland, Uganda (2), Zambia), Asia (Bangladesh, China (3), India, Thailand) and South America (Argentina, Brazil, Peru). Our proposal focuses on more advanced trainees, regional partnerships, multilayered mentoring. Each primary training site has a lengthy history of NIH and US government research funding, training of US and international research trainees, and on-the-ground faculty mentors, many of whom were trained through Fogarty International Center programs. Twelve of the proposed training sites are currently part of the Fogarty International Clinical Research Scholars & Fellows program. We will preferentially recruit advanced post-doctoral researchers from more than 50 T32 training grants at the affiliated institutions in all disciplines of health sciences, as well a early-stage post-doctoral researchers, and doctoral and health science students from Schools of Dentistry, Medicine, Nursing, Pharmacy, Public Health and Veterinary Medicine at our 4 universities and around the US. Trainees from the international sites will be "twinned" with US trainees through additional resources including other existing Fogarty training grants and the Gilead Foundation to build research capacity at the sites to which the consortium has long-standing commitment. The areas of research focus include a broad range of topics that are consistent with the NIH Fogarty 2008-2012 Strategic Plan, recognizing the growing importance of non-communicable diseases while continuing the commitment to infectious diseases. Trainee applications will be judged on the quality of the research proposal, their previous track record, and commitment to a global health academic research career. Trainees will be assigned a team of mentors, with at least one senior and one junior mentor, who will closely monitor the progress of the trainee and provide on-site supervision. Drawing on existing linkages between sites and training faculty, we will enhance regional partnerships in order to provide training and guidance for junior mentors. Trainees and their twins will have access to biostatistical and epidemiologic consultation from UNC and Tulane faculty for both data analyses and grant writing purposes as well as supplemental funding for their research from multiple small grant opportunities at UNC. FGHF leverages a unique set of resources, training faculty, and sites in order to directly respond to three of the four Fogarty Strategic 2008-2012 Goals: bridging the training gap, fostering sustainable research, and building strategic partnerships.

Title: **Global Health Fellows and Scholars Research Training**
P.I.: **Lee W. Riley**
Institution: **University of California, Berkeley**
Grant No.: **TW009338-01**
Award: **$40,000**

We propose to establish a Support Center (Consortium) involving University of California-Berkeley, Yale University, Stanford University and Florida International University to train postdoctoral fellows, PhD graduate students, and medical students for them to develop a long-term career in global health research. The main objective of the program is to generate a new and young cadre of global health researchers, educators, and professionals who will be

prepared to address the new challenges in global health that arise from our constantly changing planet, in particular, those challenges that emerge from the world's burgeoning human settlements known as slums that have developed in urban and rural communities of many low and middle-income countries (LMIC). Slum-specific factors associated with chronic, noncommunicable, as well as infectious diseases, environmental health hazards, risks specific to women and children, intentional and unintentional injuries, and mental disorders are poorly understood, and there are not many researchers dealing with these issues. These diseases comprise a large proportion of the world's health problems. Our training program will emphasize a multidisciplinary, problem-based approach using slum health as a platform to expose trainees to the new concepts, models, and approaches to global health research. The training will be conducted at US government-funded field research sites at 10 locations abroad, including Central and South America, Sub-Saharan Africa, South Asia, East Asia, and Eastern Europe, where the Consortium mentors have been conducting research for more than 3 years. The Consortium includes a large reservoir of postdoctoral fellows and upper division graduate and medical students who will be candidates for the training program. The Consortium has made a special effort to identify potential trainees from under-represented minority groups and it has thus partnered with Florida International University, the largest Hispanic-serving institution in the continental US, which also has a large pool of African-American students. Thus, this research training program will provide an opportunity to draw highly skilled researchers from diverse backgrounds from a wide spectrum of disciplines, who will use the knowledge gained from this program to develop their own research agenda to improve the lives of people who are exposed to a wide range of interacting health risks that engender new global health challenges.

Title: **Haiti AIDS Research Training: Models to Implementation**
P.I.: **Jean William Pape**
Institution: **GHESKIO Center**
Grant No.: **TW006896-09**
Award: **$25,000**

The goal of GHESKIO-Cornell ICOHRTA training program is to increase capacity in integrated clinical, operational, and health services research in support of Haiti's national scale-up of HIV and tuberculosis services. Haiti is the poorest country in the Western Hemisphere and has the highest rates of both HIV infection and tuberculosis. It is estimated that 3% of the adult population is HIV-infected and that the prevalence of tuberculosis is 402/100,000 population (100xUS rates). In response to this epidemic, the Haitian Ministry of Health asked GHESKIO to form a national HIV and TB Network, a collaboration of 32 public and private health care organizations across the country that is charged with "scaling-up" to provide a standardized package of HIV and tuberculosis services to 500,000 persons by 2014. The services include voluntary counseling and HIV testing, management of tuberculosis and sexually transmitted infections, prevention of mother to child HIV transmission, and comprehensive HIV care of children, adolescents, and adults. The Haitian Ministry of Health has asked GHESKIO (Haitian Study Group for the Study of Kaposi's Sarcoma and Opportunistic Infections) to lead this network through training, supervision, monitoring and evaluation, and through the conduct of operational and health services research. GHESKIO is an international research and training institution that has benefited from 25 years of uninterrupted NIH funding and research capacity building with Cornell University, and support from the Fogarty International Center. GHESKIO is recognized as a center of research excellence, and is a member of the NIH HIV Vaccine Trials Network (VTN), the AIDS Clinical Trials Group (ACTG) and a recipient of support from the United Nations Global Fund for AIDS, TB and Malaria and the President's Emergency Plan for AIDS relief (PEPFAR). In the current proposal, GHESKIO will continue as the primary training institution and extend research capacity to other organizations in Haiti that are participating in the GHESKIO HIV and Tuberculosis Network. The program will continue to emphasize medium- and long-term training in Haiti. Since its inception four years ago the ICOHRTA has provided training to 120

Haitian biomedical personnel, all of whom are working in Haiti, providing HIV/TB services and conducting operational and health services research. GHESKIO, in collaboration with Haitian and International partners, will develop training curricula in clinical, operational, and health services research methodology and in ethics, program management, and scientific writing. A Masters in Public Health Degree program, established with ICOHRTA support, will continue to be offered in Haiti by Quisqueya University, in partnership with GHESKIO and Cornell University.

Title: **Molecular Epidemiology of Drug Resistance and Population Genetic Structure of *Plasmodium falciparum* and *P. vivax* in Yunnan and Hainan, China**
P.I.: **Fangli Lu**
Institution: **Sun Yat-sen University**
Grant No.: **TW008151-04**
Award: **$50,000**

Malaria remains a serious public health problem in China. In the subtropical Yunnan Province and the tropical Hainan Island of China, malaria has been the most endemic with high transmission of both *Plasmodium falciparum* and *P. vivax*. However, most of the attention in terms of research and interventions have been focused in Africa and Southeast Asia, very few studies of malaria in China have been conducted. Because of extensive use, chloroquine (CQ) has now lost its efficacy due to the emergence of resistant strains in most parts of the world. Meanwhile, suspension of the use of CQ has resulted in reappearance of CQ sensitivity. However, there were differences in the evolution of CQ resistance between parasites from Yunnan and Hainan, the exact mechanism needs to be investigated. Sulfadoxine-pyrimethamine (SP) targets the dhfr and dhps genes of *P. falciparum*, and point mutations that confer resistance have been widely reported worldwide. Documenting the identity and extent of SP resistance is also critical for policy decisions regarding antimalarial drugs. In addition, *P. vivax* causes a large burden of morbidity in the world including China but traditionally has been understudied. Based on these, our long-term goal of this proposal is 1) to identify single-nucleotide polymorphism (SNP) and characterize the geographic distribution of genetic diversity, population structure, and haplotype variability at drug resistant loci of *P. falciparum* from Yunnan and Hainan, China, 2) to examine the geographic population structure, levels of genetic diversity of *P. vivax* using microsatellite and SNP, and 3) to yield valuable information for making more effective malaria control policies in China. In the past several years we have developed the molecular methods to study the genetics, population diversity, and evolution of malaria parasites, and have done some preliminary studies on malaria field isolates from Yunnan and Hainan using genetic markers, thus enabling us to study the molecular epidemiology of these important malaria parasites in this proposal. The specific aims are to: 1. Determine genetic polymorphisms associated with CQ resistance (CQR) in *P. falciparum* field isolates from Yunnan and Hainan provinces, China. 2. Determine the point mutation prevalence in the dhfr (pyrimethamine drug resistance) and dhps (sulfadoxine drug resistance) genes associated with SP resistance in *P. falciparum* field isolates from Yunnan and Hainan provinces, China. 3. Assess the changes of *P. vivax* genotypes using pvcsp, pvmsp1, pvmsp3-¿ genes, and microsatellite markers and determine the geographic structure and specific epidemiological characteristics of *P. vivax* transmission in Yunnan and Hainan, China.

Title: **Northern/Pacific Universities Global Health Research Training Consortium**
P.I.: **Joseph Raymond Zunt**
Institution: **University of Washington**
Grant No.: **TW009345-01**
Award: **$40,000**

This R25 proposal, the "Northern/Pacific Global Health Research Fellows Training Consortium" includes a consortium of four U.S. universities (the Universities of Hawaii, Michigan, Minnesota and Washington) and partnerships with universities and research institutions in six countries

(Kenya, Ghana, Uganda, Peru, China and Thailand). The Consortium will be housed within the Department of Global Health at the University of Washington. The four U.S. universities have each committed matching funds totaling $595,000 to support a second year of fellowship for the most productive fellows and additional fellows. The N/P Consortium will (1) implement an enhanced mentoring program emphasizing a manual of required, specific commitments and guidelines for mentors and mentees; bimonthly Internet-based research-in-progress sessions involving all Global Health Fellows and joint participation of mentors for the presenting trainee(s); (2) help in "globalizing" existing T32 research training programs, and strengthen and broaden the disciplines involved in our Consortium's global health research programs, by actively recruiting senior U.S. fellows from the 161 T32 research training grants of the N/P Consortium, and other trainees (e.g. senior Department of Global Health postdoctoral fellows of the UW Institute for Health Metrics and Evaluation), (3) promote entrepreneurial development of interdisciplinary, cross-institutional, sustainable research partnerships, particularly within neglected areas of global health, engaging comentors from the academic programs that house the T32 grants from which Global Health Research Fellows are recruited; (4) establish a "warranty" for the Global Health Research Fellows, beginning with a tried and proven expedited global research project trajectory during year one, progressing to presentation and then publication of research, a potential second year of fellowship funding for the most promising trainees, to assistance launching independent careers through further opportunities in new research programs as they develop, to ongoing mentoring of alumni in applications for new global health grants, such as Fogarty IRSDA K01 grants, ISGHA K02 grants, other K awards, including CTSA awards and Foundation awards, to creation of an alumni and mentor network involving posting of new publications, funding and job opportunities, and potential participation in cross-consortium Global Health Fellows reunions at global health conferences. This proposal would provide funding for a total of 12-15 trainees each year, depending on the number of second year trainee awards—for a total of 75 trainees. Including the Fulbright/Fogarty Fellows in Public Health (at least one each in Kenya, Ghana and Peru), who will receive the same orientation at NIH and mentoring by participants in this proposal, we anticipate at least 90 trainees over the five-year grant period.

Title: **Tobacco Control Network Among Women in Parana, Brazil**
P.I.: **Isabel C. Scarinci**
Institution: **University of Alabama at Birmingham**
Grant No.: **TW009272-01**
Award: **$100,000**

An understanding of women and their tobacco-related issues, as well as the need for the development of gender-relevant tobacco control efforts, have been highlighted as priorities in landmark guiding documents published in the past few years (e.g., WHO Framework Convention on Tobacco Control-WHO FCTC). Brazil is the second largest producer of tobacco in the world, and 95% of the tobacco is produced in the three Southern states (Paraná, Santa Catarina, and Rio Grande do Sul). Although, historically, tobacco use among women in developing countries, particularly Latin America, has been relatively low as compared to men, the smoking epidemic is rapidly spreading to women in developing countries, and these three Southern states have the highest prevalence of women smokers in the country. We have established a Network for Tobacco Control among Women in Paraná, Brazil with the purpose of establishing community and institutional capacity to promote gender-relevant tobacco control efforts among women through Community-Based Participatory Research (CBPR) and training. The goals of the network are to reduce tobacco use and exposure to environmental tobacco smoke (ETS) among women in Paraná, and to develop a cadre of well-trained researchers who will continue to address comprehensive tobacco control strategies at multiple levels. The network conducted an epidemiological survey on the prevalence and factors associated with tobacco use among women across the State of Paraná. Based on the results, the network identified four priorities: (1) to implement policy changes to decrease

ETS; (2) to understand the health/social issues of women in tobacco farming; (3) to develop and evaluate a comprehensive, culturally- and gender-relevant, school-based smoking prevention program; and (4) to improve access and delivery of smoking cessation programs through the public health system with a particular focus on "light smokers" as 74.8% of women smokers in our study reported smoking 10 or less cigarettes/day. The network is currently addressing the first three priorities, including support for legislation, which resulted in Paraná having the strongest indoor tobacco ban in the country. The overall goal of this renewal is three-fold: (1) to continue to sustain and strengthen the network; (2) to conduct a group randomized controlled trial to assess the efficacy of a theory-based, culturally- and gender-relevant Community Health Worker intervention for Brazilian women "light smokers" that will augment the smoking cessation programs offered through the public health system; and (3) to expand our current Career Development and Research Training Program to the other two major tobacco growing states in order to develop a cadre of well-trained researchers who will continue to develop and implement gender-relevant comprehensive tobacco control strategies at all levels.

Title: **University of California Global Health Institute Program for Fellows and Scholars**
P.I.: **Craig R. Cohen**
Institution: **University of California, San Francisco**
Grant Nos.: **TW009343-01, TW009343-01S1**
Award: **$190,000**

In response to RFA-TW-11-001, the University of California Global Health Institute (UCGHI), including UC San Francisco (UCSF), UC San Diego (UCSD), UC Los Angeles (UCLA) and UC Davis (UCD), along with a network consisting of 21 collaborating international institutions across 14 countries and 5 continents proposes the creation of the UCGHI Program for Fellows and Scholars (UCGHI-PFS). Our specific aims are: 1) To recruit a diverse group of trainees who are diverse in discipline and ethnicity, and who aspire to build successful academic research careers in global health focusing on interdisciplinary research; 2) To provide outstanding, interdisciplinary education and training in global health in collaboration with 230 faculty mentors from the Program, and 21 collaborating well established international institutions; 3) To provide each trainee with a rich and enduring mentored research experience that fosters scientific and career development in global health research; 4) To develop models of interdisciplinary, innovative global health research and training designed to improve health for populations around the world; and 5) To broaden and expand the global health faculty across the four UC campuses, UCGHI and international partner institutions, and strengthen existing global health networks between UCGHI and collaborating international institutions. UCGHI-PFS will recruit candidates from a pipeline of 57 T32 programs, representing 12 of the 15 NIH institutes participating in this RFA. In addition to these programs which annually support 160 predoctoral and 208 postdoctoral fellows, 20% of whom are under-represented minorities, we will recruit international trainees from 8 D43 training grants across al four campuses, affiliated schools and international partner institutions. For each trainee, 4 principal components include: i) an 11-month, hands-on research project on-site with one of our international collaborative partners; ii) a strong, interdisciplinary mentored research experience; iii) instruction in global health and related topics provided through on-site, and on-line courses; and iv) career development to help ensure that trainees attain their short-term career goals and succeed in transitioning to the next career stage. These four components are closely interlinked; a Leadership Group and campus Steering Committees will ensure they form a seamless, integrated program. Innovative aspects include a unified consortium that offers synergy by capitalizing upon the UCGHI's ten campuses, Centers of Expertise and faculty that regularly interact and collaborate; faculty mentors offering training across diverse disciplines (e.g., medicine, nursing, pharmacy, dentistry, public health, veterinary science, oceanography, agriculture, and biological and social sciences); training experiences on a wide range of diseases and problems of global health significance; an ability to leverage

common resources across the four participating UC campuses (e.g., UCGHI, CTSAs, CFARs and Research eXchange consortia); and an innovative mentoring initiative.

Title: **Vanderbilt University-CIDRZ AIDS International Training and Research Program**
P.I.: **Sten H. Vermund**
Institution: **Vanderbilt University Medical Center**
Grant No.: **TW001035-14**
Award: **$25,000**

The Vanderbilt University (VU) Center for Infectious Disease Research in Zambia (CIDRZ) AITRP, formerly the VU-University of Alabama at Birmingham AITRP, seeks renewal of its grant, now in its tenth year due to an NIH-initiated one-year extension. We contribute research training to both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care. The VU-CIDRZ training partnership with our international collaborators is designed to train foreign scientists and key research support staff to conduct independent research and training in their home countries, as well as perform at an internationally credible level in collaborations with local and foreign scientists. We now seek to renew our AITRP with a continued focus on Zambia (since 1998), Pakistan (since 1994), India (since 2000), China (since 2000), and our newest partnership in Mozambique (VU training partnership since 2006 and developmental AITRP engagement since 2007). We have completed our older training commitments in Mongolia, Jamaica, and Russia and will complete our training commitments for Bangladesh upon the graduation of a current doctoral training (anticipated in 2011). We have restricted our AITRP training partnerships to five focus cities in order not to dilute our impact to where we have funded overseas research and strong research training partners. At the same time, we have leveraged support in each of the five venues such that our AITRP resources will go much further than permitted by the grant's funding alone. We will continue to provide a diverse portfolio of long, medium, and short-term training options. To date 58 trainees have received graduate degrees, 97% of whom have returned to work in their home countries, 8 are currently in degree programs and over 2,000 have been trained through our in-country advanced short-courses. We believe VU remains an ideal university partner for this initiative for several significant reasons The migration of the training program to VU offers the opportunity for trainees to receive the absolute highest quality of graduate training and exposure to innovative HIV/AIDS/STD/TB related research, resources, and faculty mentors. The program is uniquely positioned within the infrastructure of the VU Institute for Global Health (VU IGH),directed by Dr. Vermund with its "center-without-walls" philosophy that nurtures noncompetitive partnerships among and within VU and with partner institutions around the globe. We feel that the innovative features of our renewal and our proven track record address the unmet needs in international AIDS training. RELEVANCE (Seeinstructions): The VU-CIDRZ training partnership with our international collaborators is designed to strengthen both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care in developing countries.

Title: **Vanderbilt-Emory-Cornell-Duke Consortium for Global Health Fellows (VECDor)**
P.I.: **Sten H. Vermund**
Institution: **Vanderbilt University Medical Center**
Grant No.: **TW009337-01**
Award: **$40,000**

The Vanderbilt-Emory-Cornell-Duke Consortium (VECDor) brings the substantial and complementary expertise of experienced institutions to the Fogarty Global Health Fellows Program. The Vanderbilt Institute for Global Health (VIGH) has served as the Fogarty International

Clinical Research Scholars and Fellows (FICRS-F) Program Support Center since 2007, working with 87 partner institutions to nurture 419 competitively chosen pre- and postdoctoral trainees from the US and from 27 low- and middle-income countries (LMICs). Topics have included infectious diseases, cancer, heart and lung disease, stroke, diabetes, nutrition, behavioral and mental health issues (including substance abuse), women's and children's health, ophthalmic disease, oral health, neurology, and animal-human health. VECDor's highly experienced global health mentors are already working together in the US and LMIC partner institutions, selected as diverse, well-funded research sites in Africa (Kenya, Zambia, Tanzania, Rwanda), Asia (India, China, Vietnam), Latin America (Brazil, Mexico), and the Caribbean (Haiti). Using a highly efficient support center that maximizes the direction of funds to research training, and leveraging multiple sources of financial and in-kind co-funding, we will link with more than 68 T32 and other NIH-funded training programs and with minority institution partners to select and deploy 80 to 100 US and LMIC trainees with outstanding promise for research careers. VECDor will implement a strategic mentoring and trainee support plan across the consortium, including a substantial preparation phase prior to field deployment and continuing after the research year is completed, to ensure the highest quality research publications and scientific meeting presentations, and maximum trainee success in obtaining research and career development grants. Research themes will address all topic and geographical areas of interest to trainees and NIH Institutes and Centers, emphasizing both communicable and non-communicable diseases. We will document the Program's impact through a long-term monitoring and evaluation (M&E) plan that tracks the career directions and outputs of all Fellows, using FIC's CareerTrac system, e.g., future employment, K grants, research grants, scientific presentations, and publications. We will further refine our existing web-based tools to share knowledge, foster local and global networking, and strengthen and sustain clinical research skills among global health fellows and alumni. We have brokered substantial institutional and site-based co-funding to leverage NIH resources. VECDor is built on the mutual respect of our US and global partners and our collective track record of research innovation and mentorship. Combining our extensive recent experience in research training program management, robust research funding bases in major diseases of global significance, renowned international research training partners and sites, and enhanced institutional co-funding commitments, VECDor will continue to nurture key members of the global health research workforce of the 21st century, as we have done within the incumbent FICRS-F program.

National Center for Complementary and Alternative Medicine

Title: **Brain-Centered Therapy vs. Medication for Urgency Urinary Incontinence—A Randomized Clinical Trial**
P.I.: **Loren Howard Ketai**
Institution: **University of New Mexico Health Sciences Center**
Grant No.: **AT007171-01A1**
Award: **$100,000**

Brain-Centered Therapy versus Medication for Urgency Urinary Incontinence RCT Project Summary/Abstract Urinary urgency incontinence, involuntary urine loss associated with a sudden, compelling desire to urinate, is a common and costly public health problem without cure. Urgency incontinence increases with age and its sufferers are primarily women. These women have severely compromised quality of life from the stigma and humiliation of urgency incontinence. They have attendant depression and loss of work productivity, income and independence. They must bear the burden of medication costs, despite medication's limited effectiveness. Due to unprecedented growth of the U.S. population older than 65, urgency incontinence will consume 86.2 billion dollars by 2020. Finding successful, durable treatment for this burgeoning public health problem is an unmet need. This project will evaluate hypnotherapy treatment to meet this need. This proposal will compare efficacy of hypnotherapy to pharmacotherapy in

urgency incontinence. Preliminary evidence supports pursuit of hypnotherapy in urgency incontinence treatment. Patients with functional disorders such as urgency incontinence respond differently to physiologic stimulus. This abnormal stress response, "hyper-vigilance," is associated with abnormal brain activation on functional brain imaging. Hypnotherapy offers the hope of modifying this abnormal response in urgency incontinence. A case series and our own pilot data support hypnotherapy's effectiveness in urgency incontinence. Therefore, the long term goal of this proposal is to shift focus of urgency incontinence treatment towards the brain and away from the peripheral nervous system, the target of pharmacotherapy. The objective of this application is to determine whether hypnotherapy can be more effective than current pharmacologic therapy of urgency incontinence. Its central hypothesis is that hypo-therapy modulates interactions between the brain and bladder, providing effective urgency incontinence treatment. This hypothesis will be tested pursuing 2 specific aims: 1) Determine whether a mind/body therapy (hypnotherapy) is a more effective and durable treatment of urgency urinary incontinence than a non-mind/body treatment (pharmacotherapy) 2) Determine whether hypnotherapy treatment of urgency urinary incontinence is associated with greater modification of limbic cortex activation and connectivity on functional MRI than that which occurs following pharmacotherapy. Urge incontinent women (N=152) will be randomized to medications or hypnotherapy and evaluated at months 2, 6 &12. Sixty women will undergo imaging before and after treatment. The rationale for the proposal is based on work which suggests that brain activation is abnormal in subjects with urgency incontinence, that urgency incontinence responds to hypnotherapy, and that the hypnotic state affects sites of abnormal brain activation. This proposal is significant because it seeks to treat urgency incontinence, a growing public health problem, with hypnotherapy, a mind/body intervention. This novel approach uses hypnotherapy to treat urgency incontinence and offers innovative use of brain imaging to elucidate hypnotherapy's mechanism of action and shifts the treatment paradigm from the bladder to the mind.

APPENDIX C

Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group

FY 2011

Charles A. Wells, Ph.D., *Chair*	ORWH/OD
Donald Blair, Ph.D.	NCI
Maureen Boyle, Ph.D.	OBSSR
Janine Clayton, M.D.	ORWH/OD
Becky Costello, Ph.D.	ODS
Basil Eldadah, M.D., Ph.D.	NIA
Simone Glynn, M.D., M.P.H.	NHLBI
Timothy Gondré-Lewis, Ph.D.	NIAID
Jenny Haliski	OCPL
Jack Harding, Ph.D.	NCRR
Kathy Jung, Ph.D.	NIAAA
Annette Kirshner, Ph.D.	NIEHS
Cheryl Kitt, Ph.D.	CSR
John Kusiak, Ph.D.	NIDCR
Catherine Laughlin, Ph.D.	NIAID
Cheryl L. McDonald, M.D.	NHLBI
Merill Mitler, Ph.D.	NINDS
Christopher Mullins, Ph.D.	NIDDK
Eun-Chung Park, Ph.D.	NIAID
Matthew Rudorfer, M.D.	NIMH
Xenia Tigno, Ph.D.	NINR
Yan Wang, M.D., Ph.D.	NINR

FY 2012

Susan E. Maier, Ph.D., *Chair*	ORWH/OD
Harvey J. Alter, M.D., M.A.C.P.	CC
Donald Blair, Ph.D.	NCI
Janine Clayton, M.D.	ORWH/OD
Basil Eldadah, M.D., Ph.D.	NIA
Timothy Gondré-Lewis, Ph.D.	NIAID
Jeanne Goshorn	NLM
Kathy Jung, Ph.D.	NIAAA
Annette Kirshner, Ph.D.	NIEHS
Cheryl Kitt, Ph.D.	CSR
John Kusiak, Ph.D.	NIDCR
Lynn Luethke, Ph.D.	CSR
Cheryl L. McDonald, M.D.	NHLBI
Christopher Mullins, Ph.D.	NIDDK
Eun-Chung Park, Ph.D. *(Alternate: Catherine Laughlin, Ph.D.)*	NIAID
Karen Peterson, Ph.D.	NIBIB
Matthew Rudorfer, M.D.	NIMH
Andrea Sawczuk, D.D.S., Ph.D. *(Alternate: François Boller, M.D.)*	NCATS
Xenia Tigno, Ph.D.	NINR
Yan Wang, M.D., Ph.D.	NIAMS
Vicky Holets Whittemore, Ph.D. *(Alternate: James Gnadt, Ph.D.)*	NINDS
Shimian Zou, Ph.D. *(Alternate: Simone Glynn, M.D., M.P.H.)*	NHLBI

APPENDIX D

Selected BIRCWH Scholar Publications, FY 2011–FY 2012

Duke University School of Medicine and North Carolina Central University

Scholars: Chad A. Grotegut, Janet K. Horton, Martha E. Payne, Darlene K. Taylor, Betty C. Tong, and Jennifer M. Wu

Paglia, M. J., **Grotegut, C. A.,** Johnson, L. N., Thames, B., & James, A. H. (2012). Body mass index and severe postpartum hemorrhage. *Gynecologic and Obstetric Investigation, 73*(1), 70–74.

Fortner, K. B., Fitzpatrick, C. B., **Grotegut, C. A.,** Swamy, G. K., Murtha, A. P., Heine, R. P., & Brown, H. L. (2012). Cervical dilation as a predictor of pregnancy outcome following emergency cerclage. *Journal of Maternal-Fetal Neonatal Medicine, 25*(10), 1884–1888.

Fitzpatrick, C. B., **Grotegut, C. A.,** Bishop, T. S., Canzoneri, B. J., Heine, R. P., & Swamy, G. K. (2012). Cervical ripening with foley balloon plus fixed versus incremental low-dose oxytocin: A randomized controlled trial. *Journal of Maternal-Fetal Neonatal Medicine, 25*(7), 1006–1010.

Beiswenger, T. R., Feng, L., Brown, H. L., Heine, R. P., Murtha, A. P., & **Grotegut, C. A.** (2012). The effect of cigarette smoke extract on trophoblast cell viability and migration: The role of adrenomedullin. *Reproductive Sciences, 19*(5), 526–533.

Fletcher, S., **Grotegut, C. A.,** & James, A. H. (2012). Lochia patterns among normal women: A systematic review. *Journal of Women's Health (Larchmt), 21*(12), 1290–1294.

Canzoneri, B. J., **Grotegut, C. A.,** Swamy, G. K., Brancazio, L. R., Sinclair, T., Heine, P. R., & Murtha, A. P. (2012). Maternal serum interleukin-6 levels predict impending funisitis in preterm premature rupture of membranes after completion of antibiotics. *Journal of Maternal-Fetal Neonatal Medicine, 25*(8), 1329–1332.

Grotegut, C. A., Feng, L., Mao, L., Heine, R. P., Murtha, A. P., & Rockman, H. A. (2011). ß-arrestin mediates oxytocin receptor signaling, which regulates uterine contractility and cellular migration. *American Journal of Physiology: Endocrinology and Metabolism, 300*(3), E468–E477.

Grotegut, C. A., Johnson, L. N., Fitzpatrick, C. B., Heine, R. P., Swamy, G. K., & Murtha, A. P. (2011). Bleeding per vaginam is associated with funisitis in women with preterm. *BJOG: An International Journal of Obstetrics and Gynecology, 118*(6), 735–740.

Grotegut, C. A., Paglia, M. J., Johnson, L. N., Thames, B., & James, A. H. (2011). Oxytocin exposure during labor among women with postpartum hemorrhage secondary to uterine atony. *American Journal of Obstetrics and Gynecology, 204*(1), 56e1–56e6.

Grotegut, C. A., Dulitzki, M., Gaughan, J. P., Achiron, R., Schiff, E., & Geifman-Holtzman, O. (2011). Transvaginal ultrasound of cervical length and its correlation to digital cervical examination, time to spontaneous labor and mode of delivery. *Archives of Gynecology and Obstetrics, 284*(4), 855–859.

Wu, Q., O'Daniel, J., **Horton, J.,** & Yin, F. F. (2012). Comparison of 3D conformal breast radiation treatment plans using the anisotropic analytical algorithm and pencil beam convolution algorithm. *Radiotherapy and Oncology, 103*(2), 172–77.

Palta, M., Yoo, S., Adamson, J. D., Prosnitz, L. R., & **Horton, J. K.** (2012). Preoperative single fraction partial breast radiotherapy for early-stage breast cancer. *International Journal of Radiation Oncology, Biology, Physics, 82*(1), 37–42.

Cuneo, K. C., Dash, R. C., Wilke, L. G., **Horton, J. K.,** Koontz, B. F. (2012). Risk of invasive breast cancer and ductal carcinoma in situ in women with atypical papillary lesions of the breast. *The Breast Journal, 18*(5), 475–78.

Horton, J. K., Gleason, J. F., Jr., Klepin, H. D., Isom, S., Fried, D. B., & Geiger, A. M. (2011). Age-related disparities in the use of radiotherapy for treatment of localized soft tissue sarcoma. *Cancer, 117*(17), 4033–40.

Shah, M. M., **Horton, J. K.,** Yoo, S., Hubbs, J. L., Demirci, S., Light, K. L., … Marks, L. B. (2011). A comparison of clinical and dosimetric outcomes in patients receiving partial breast irradiation with photon-only versus mixed photon/electron treatment plans. *Medical Dosimetry, 36*(4), 423–428.

Taylor, W. D., Benjamin, S., McQuoid, D. R., **Payne, M. E.,** Krishnan, R. R., MacFall, J. R., & Ashley-Koch, A. (2012). AGTR1 gene variation: Association with depression and frontotemporal morphology. *Psychiatry Research, 202*(2), 104–109.

Potter, G. G., McQuoid, D. R., **Payne, M. E.,** Taylor, W. D., & Steffens, D. C. (2012). Association of attentional shift and reversal learning to functional deficits in geriatric depression. *International Journal of Geriatric Psychiatry, 27*(11), 1172–1179.

Hayward, R. D., Taylor, W. D., Smoski, M. J., Steffens, D. C., & **Payne, M. E.** (2012). Association of five-factor model personality domains and facets with presence, onset, and treatment outcomes of major depression in older adults. *American Journal of Geriatric Psychiatry, 21*(1), 88–96.

Payne, M. E., Steck, S. E., George, R. R., & Steffens, D. C. (2012). Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. *Journal of the Academy of Nutrition and Dietetics, 112*(12), 2022–2027.

Hayward, R. D., Owen, A. D., Koenig, H. G., Steffens, D. C., & **Payne, M. E.** (2012). Longitudinal relationships of religion with posttreatment depression severity in older psychiatric patients: Evidence of direct and indirect effects. *Depression Research and Treatment, 2012*, 745970.

Hayward, R. D., Owen, A. D., Koenig, H. G., Steffens, D. C., & **Payne, M. E.** (2012). Religion and the presence and severity of depression in older adults. *American Journal of Geriatric Psychiatry, 20*(2), 188–192.

Burke, J., McQuoid, D. R., **Payne, M. E.,** Steffens, D. C., Krishnan, R. R., & Taylor, W. D. (2011). Amygdala volume in late-life depression: relationship with age of onset. *American Journal of Geriatric Psychiatry, 19*(9), 771–776.

Hayward, R. D., Owen, A. D., Koenig, H. G., Steffens, D. C., & **Payne, M. E.** (2011). Associations of religious behavior and experiences with extent of regional atrophy in the orbitofrontal cortex during older adulthood. *Religion, Brain & Behavior, 1*(2), 103–118.

Steffens, D. C., McQuoid, D. R., **Payne, M. E.,** & Potter, G. G. (2011). Change in hippocampal volume on magnetic resonance imaging and cognitive decline among older depressed and nondepressed subjects in the neurocognitive outcomes of depression in the elderly study. *American Journal of Geriatric Psychiatry, 19*(1), 4–12.

Taylor, W. D., Macfall, J. R., Boyd, B., **Payne, M. E.,** Sheline, Y. I., Krishnan, R. R., & Murali Doraiswamy, P. (2011). One-year change in anterior cingulate cortex white matter microstructure: Relationship with late-life depression outcomes. *American Journal of Geriatric Psychiatry, 19*(1), 43–52.

Chang, C. C., Yu, S. C., McQuoid, D. R., Messer, D. F., Taylor, W. D., Singh, K., …**Payne, M. E.** (2011). Reduction of dorsolateral prefrontal cortex gray matter in late-life depression. *Psychiatry Research, 193*(1), 1–6.

Owen, A. D., Hayward, R. D., Koenig, H. G., Steffens, D. C., & **Payne, M. E.** (2011). Religious factors and hippocampal atrophy in late life. *PLOS ONE, 6*(3), e17006.

Dai, G. P., Wu, M. H., **Taylor, D. K.,** Brennaman, M. K., Vinodgopal, K. (2012). Hybrid 3D graphene and aligned carbon nanofiber array architectures. *RSC Advances, 2*(24), 8965–8968.

Taylor, D. K., & Leppert, P. C. (2012). Treatment for uterine fibroids: Searching for effective drug therapies. *Drug Discovery Today: Therapeutic Strategies, 9*(1), e41–e49.

Taylor, D. K., Jayes, F. L., House, A. J., & Ochieng, M. A. (2011). Temperature-responsive biocompatible copolymers incorporating hyperbranched polyglycerols for adjustable functionality. *Journal of Functional Biomaterials, 2*(3), 173–194.

Berry, M. F., Onaitis, M. W., **Tong, B. C.,** Balderson, S. S., Harpole, D. H., & D'Amico, T. A. (2012). Feasibility of hybrid thoracoscopic lobectomy and en-bloc chest wall resection (dagger). *European Journal of Cardio-Thoracic Surgery, 41*(4), 888–892.

Tong, B. C., & Harpole, D. H. (2012). Molecular markers for incidence, prognosis, and response to therapy. *Surgical Oncology Clinics of North America, 21*(1), 161–175.

Ceppa, D. P., Kosinski, A. S., Berry, M. F., **Tong, B. C.,** Harpole, D. H., Mitchell, J. D., … Onaitis, M. W. (2012). Thoracoscopic lobectomy has increasing benefit in patients with poor pulmonary function: A Society of Thoracic Surgeons Database analysis. *Annals of Surgery, 256*(3), 487–493.

Tong, B. C., Huber, J. C., Ascheim, D. D., Puskas, J. D., Ferguson, T. B., Blackstone, E. H., & Smith, P. K. (2012). Weighting Composite Endpoints in Clinical Trials: Essential Evidence for the Heart Team. *Annals of Thoracic Surgery, 94*(6), 1908–1913.

D'Amico, T. A., **Tong, B. C.,** Berry, M. F., Burfeind, W. R., & Onaitis, M. W. (2011). Incorporating research into thoracic surgery practice. *Thoracic Surgery Clinics, 21*(3), 369–377.

Berry, M. F., Onaitis, M. W., **Tong, B. C.,** Harpole, D. H., & D'Amico, T. A. (2011). A model for morbidity after lung resection in octogenarians. *European Journal of Cardio-Thoracic Surgery, 39*(6), 989–994.

Ceppa, D. P., Welsby, I. J., Wang, T. Y., Onaitis, M. W., **Tong, B. C.,** Harpole, D. H., … Berry, M. F. (2011). Perioperative management of patients on clopidogrel (Plavix) undergoing major lung resection. *Annals of Thoracic Surgery, 92*(6), 1971–1976.

Levin, P. J., Visco, A. G., Shah, S. H., Fulton, R. G., & **Wu, J. M.** (2012). Characterizing the phenotype of advanced pelvic organ prolapse. *Female Pelvic Medicine & Reconstructive Surgery, 18*(5), 299–302.

Wu, J. M., Visco, A. G., Grass, E. A., Craig, D. M., Fulton, R. G., Haynes, C., …Shah, S. H. (2012). Comprehensive analysis of LAMC1 genetic variants in advanced pelvic organ prolapse. *American Journal of Obstetrics and Gynecology, 206*(5), 447 e441–e446.

Behera, M. A., Likes, C. E., 3rd, Judd, J. P., Barnett, J. C., Havrilesky, L. J., & **Wu, J. M.** (2012). Cost analysis of abdominal, laparoscopic, and robotic-assisted myomectomies. *Journal of Minimally Invasive Gynecology, 19*(1), 52–57.

Levin, P. J., **Wu, J. M.,** Siddiqui, N. Y., & Amundsen, C. L. (2012). Does obesity impact the success of an InterStim test phase for the treatment of refractory urge urinary incontinence in female patients? *Female Pelvic Medicine & Reconstructive Surgery, 18*(4), 243–246.

Kawasaki, A., **Wu, J. M.,** Amundsen, C. L., Weidner, A. C., Judd, J. P., Balk, E. M., & Siddiqui, N. Y. (2012). Do urodynamic parameters predict persistent postoperative stress incontinence after midurethral sling? A systematic review. *International Urogynecology Journal, 23*(7), 813–822.

Levin, P. J., **Wu, J. M.,** Kawasaki, A., Weidner, A. C., & Amundsen, C. L. (2012). The efficacy of posterior tibial nerve stimulation for the treatment of overactive bladder in women: A systematic review. *International Urogynecology Journal, 23*(11), 1591–1597.

Jonsson Funk, M., Siddiqui, N. Y., Kawasaki, A., & **Wu, J. M.** (2012). Long-term outcomes after stress urinary incontinence surgery. *Obstetrics and Gynecology, 120*(1), 83–90.

Wu, J. M., Visco, A. G., Grass, E. A., Craig, D. M., Fulton, R. G., Haynes, C., … Shah, S. H. (2012). Matrix metalloproteinase-9 genetic polymorphisms and the risk for advanced pelvic organ prolapse. *Obstetrics and Gynecology, 120*(3), 587–593.

Schaffer, J., Nager, C. W., Xiang, F., Borello-France, D., Bradley, C. S., **Wu, J. M.,** … Richter, H. E. (2012). Predictors of success and satisfaction of nonsurgical therapy for stress urinary incontinence. *Obstetrics and Gynecology, 120*(1), 91–97.

Siddiqui, N. Y., Fulton, R. G., Kuchibhatla, M., & **Wu, J. M.** (2012). Sexual function after vaginal versus nonvaginal prolapse surgery. *Female Pelvic Medicine & Reconstructive Surgery, 18*(4), 239–242.

Jonsson Funk, M., Levin, P. J., **Wu, J. M.** (2012). Trends in the surgical management of stress urinary incontinence. *Obstetrics and Gynecology, 119*(4), 845–851.

Wechter, M. E., Stewart, E. A., Myers, E. R., Kho, R. M., & **Wu, J. M.** (2011). Leiomyoma-related hospitalization and surgery: prevalence and predicted growth based on population trends. *American Journal of Obstetrics and Gynecology, 205*(5), 492 e491–e495.

Wu, J. M., Fulton, R. G., Amundsen, C. L., Knight, S. K., & Kuppermann, M. (2011). Patient preferences for different severities of and treatments for overactive bladder. *Female Pelvic Medicine & Reconstructive Surgery, 17*(4), 184–189.

Wu, J. M., Kawasaki, A., Hundley, A. F., Dieter, A. A., Myers, E. R., & Sung, V. W. (2011). Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. *American Journal of Obstetrics and Gynecology, 205*(3), 230 e231–e235.

Bradley, S. L., Weidner, A. C., Siddiqui, N. Y., Gandhi, M. P., & **Wu, J. M.** (2011). Shifts in national rates of inpatient prolapse surgery emphasize current coding inadequacies. *Female Pelvic Medicine & Reconstructive Surgery, 17*(4), 204–208.

Wu, J. M., Gandhi, M. P., Shah, A. D., Shah, J. Y., Fulton, R. G., & Weidner, A. C. (2011). Trends in inpatient urinary incontinence surgery in the USA, 1998–2007. *International Urogynecology Journal, 22*(11), 1437–1443.

Harvard University

Scholars: Suzy D. Bianco, Karen H. Costenbader, Altan Ercan, John C. Gill, Laura M. Holsen, Tamarra James-Todd, Elizabeth A. Lawson, Hernan D. Kopcow, Jun S. Liu, Margaret E. McLaughlin-Drubin, Aditi R. Saxena, and Elaine W. Yu

Bianco, S. D. C., Vandepas, L., Medina, M. C., Gereben, B., Mukherjee, A., Kuohung, W., … Kaiser, U. B. (2011). KISS1R intracellular trafficking and degradation: effect of the Arg386Pro disease-associated mutation. *Endocrinology, 152*(4), 1616–1626.

Demas, K. L., Keenan, B. T., Solomon, D. H., Yazdany, J., & **Costenbader, K. H.** (2010). Osteoporosis and cardiovascular disease care in systemic lupus erythematosus according to new quality indicators. *Seminars in Arthritis and Rheumatism, 40*(3), 193–200.

Ercan, A., Cui, J., Hazen, M. M., Batliwalla, F., Royle, L., Rudd, P. M., & Nigrovic, P. A. (2012). Hypogalactosylation of serum N-glycans fails to predict clinical response to methotrexate and TNF inhibition in rheumatoid arthritis. *Arthritis Research & Therapy, 14*(2), R43.

Ercan, A., Hazen, M. M., Tory, H., Henderson, L., Dedeoglu, F., Fuhlbrigge, R. C., … Nigrovic, P. A. (2012). Multiple juvenile idiopathic arthritis subtypes demonstrate pro-inflammatory IgG glycosylation patterns. *Arthritis & Rheumatism, 64*(9), 3025–3033.

Gill, J. C., Navarro, V., Kwong, C., Noel, S., Martin, C., Xu, S., … Kaiser, U. B. (2012). Increased neurokinin B (Tac2) expression in the mouse arcuate nucleus is an early marker of pubertal onset with differential sensitivity to sex steroid–negative feedback than Kiss1. *Endocrinology, 153*(10), 4883–4893.

Holsen, L. M., Lee, J.-H., Spaeth, S. B., Ogden, L. A., Klibanski, A., Whitfield-Gabrieli, S., … Goldstein, J. M. (2012). Brain hypoactivation, autonomic nervous system dysregulation, and gonadal hormones in depression: A preliminary study. *Neuroscience Letters, 524*, 57–61.

Holsen, L. M., Savage, C. R., Martin, L. E., Bruce, A. S., Lepping, R. J., Ko, E., … Goldstein, J. M. (2012). Importance of reward and prefrontal circuitry in hunger and satiety: Prader-Willi syndrome vs. simple obesity. *International Journal of Obesity, 36*, 638–647.

Honea, R. A., **Holsen, L. M.,** Lepping, R. J., Perea, R., Butler, M. G., Brooks, W. M., & Savage, C. R. (2012). The neuroanatomy of genetic subtype differences in Prader-Willi syndrome. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 159B*, 243–253.

Holsen, L. M., Spaeth, S. B., Lee, J.-H., Ogden, L. A., Klibanski, A., Whitfield-Gabrieli, S., & Goldstein, J. M. (2011). Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. *Journal of Affective Disorders, 131*, 379–387.

Holsen, L. M., Lawson, E. A., Blum, J., Ko, E., Makris, N., Fazeli, P., … Goldstein, J. M. (2012). Food motivation circuitry hypoactivation related to hedonic and non-hedonic aspects of hunger and satiety in women with active and weight-restored anorexia nervosa. *Journal of Psychiatry and Neuroscience, 37*(5), 322–332.

Lawson, E. A., Holsen, L. M., Santin, M., Meenaghan, E., Eddy, K. T., Becker AE, … Klibanski, A. (2012). Oxytocin secretion is associated with severity of disordered eating psychopathology and insular cortex hypoactivation in anorexia nervosa. *Journal of Clinical Endocrinology & Metabolism, 97*(10), E1898–E1908.

Lawson, E. A., Miller, K. K., Blum, J. I., Meenaghan, E., Misra, M., Eddy, K. T., … Klibanski, A. (2012). Leptin levels are associated with decreased depressive symptoms in women across the weight spectrum, independent of body fat. *Clinical Endocrinology, 76*(4), 520–525.

James-Todd, T., Senie, R., & Terry, M. B. (2012). Racial/ethnic differences in hormonally-active hair product use: A plausible risk factor for health disparities. *Journal of Immigrant and Minority Health, 14*(3), 506–511.

James-Todd, T., Stahlhut, R., Meeker, J. D., Powell, S. G., Hauser, R., Huang, T., & Rich-Edwards, J. (2012). Urinary phthalate metabolite concentrations and diabetes among women in the National Health and Nutrition Examination Survey (NHANES) 2001–2008. *Environmental Health Perspectives, 120*(9), 1307–1313.

Cerdeira, A. S., **Kopcow, H. D.,** & Karumanchi, S. A. (2012). Regulatory T cells in preeclampsia: Some answers, more questions? *American Journal of Pathology, 181*(6), 1900–1902.

Liu, J. S., Schubert, C. R., Fu, X., Fourniol, F. J., Jaiswal, J. K., Houdusse, A., … Walsh, C. A., (2012). Molecular Basis for specific regulation of neuronal kinesin-3 motors by doublecortin family proteins. *Molecular Cell, 47*(5), 707–721.

McLaughlin-Drubin, M. E., Meyers, J., & Munger, K. (2012). Cancer associated human papillomaviruses. *Current Opinion in Virology, 2*(4), 459–466.

Herfs, M., Yamamoto, Y., Laury, A., Wang, X., Nucci, M. R., **McLaughlin-Drubin, M. E.,** … Crum, C. P. (2012). A discrete population of squamocolumnar junction cells implicated in the pathogenesis of cervical cancer. *Proceedings of the National Academy of Sciences, 109*(26), 10516–10521.

Levitt, J. M., **McLaughlin-Drubin, M. E.,** Münger, K., & Georgakoudi, I. (2011). Automated biochemical, morphological, and organizational assessment of precancerous changes from endogenous two-photon fluorescence images. *PLOS ONE, 6*(9), e24765.

McLaughlin-Drubin, M. E., Crum, C. P., & Münger K. (2011). Human papillomavirus E7 oncoprotein induces KDM6A and KDM6B histone demethylase expression and causes epigenetic reprogramming. *Proceedings of the National Academy of Sciences, 108*(5), 2130–2135.

Saxena, A. R., Seely, E. W., & Goldfine, A. B. (2012). Cardiovascular risk factors and menstrual cycle phase in premenopausal women. *Journal of Endocrinological Investigation, 35*, 715–719.

Saxena, A. R., & Seely, E. W. (2012). Luteinizing hormone correlates with adrenal function in postmenopausal women. Menopause: *The Journal of the North American Menopause Society, 19*, 1280–1283.

Saxena, A. R., & Seely, E. W. (2012). Smoking cessation and associated risk of metabolic syndrome in women. *Women's Health, 8*, 367–369.

Yu, E. W., & Finkelstein, J. S. (2012). Bone density screening intervals for osteoporosis: One size does not fit all. *Journal of the American Medical Association, 307*(24), 2591–2592.

Desai, G., Avinash, K., Uppot, R., **Yu, E. W.,** & Sahani, D. (2012). Impact of iterative reconstruction (ASiR) on image quality and radiation dose in multidetector CT of obese adults. *European Radiology, 22*(8), 1631–1640.

Spatz, J. M., Fields, E. E., **Yu, E. W.,** Divieti-Pajevic, P., Bouxsein, M. L., Sibonga, J. D., & Smith, S. M. (2012). Serum sclerostin increases in healthy adult men bedrest subjects. *Journal of Clinical Endocrinology and Metabolism, 97*(9), E1736–1740.

Yu, E. W., Kumbhani, R., Siwila-Sackman, E., & Leder, B. Z. (2011). Acute decline in serum sclerostin in response to PTH infusion in healthy men. *Journal of Clinical Endocrinology and Metabolism, 96*(11), E1848–E1851.

Yu, E. W., Thomas, B. J., Brown, K., & Finkelstein, J. S. (2011). Simulated increases in body fat and errors in bone density measurements by DXA and QCT. *Journal of Bone and Mineral Research, 27*(1), 119–124.

Mayo Clinic

Scholars: Jamie N. Bakkum-Gamez, Julie A. Fields, Limor Raz, and Wolfgang Singer

Alhilli, M. M., Long, H. J., Podratz, K. C., & **Bakkum-Gamez, J. N.** (2012). Aromatase inhibitors in the treatment of recurrent ovarian granulosa cell tumors: Brief report and review of the literature. *Journal of Obstetrics & Gynaecology Research, 38*(1), 340–344.

Bakkum-Gamez, J. N., Kalogera, E., Keeney, G. L., Mariani, A., Podratz, K. C., & Dowdy, S. C. (2012). Conservative management of atypical hyperplasia and grade I endometrial carcinoma: Review of the literature and presentation of a series. *Journal of Gynecologic Surgery, 28*(4), 262–269.

Bakkum-Gamez, J. N., Chien, J., Clayton, A. C., Halling, K. C., Cliby, W. A., Dowdy, S. C., … Shridhar, V. (2012). Development of biomarkers in endometrial cancer and its precursor lesions. *Journal of Women's Health, 21*(10), 1004.

Dowdy, S. C., Borah, B. J., **Bakkum-Gamez, J. N.,** Kumar, S., Weaver, A. L., McGree, M. E., … Podratz, K. C. (2012). Factors predictive of postoperative morbidity and cost in patients with endometrial cancer. *Obstetrics & Gynecology, 120*(6), 1419–1427.

Alhilli, M. M., Dowdy, S. C., Weaver, A. L., St. Sauver, J. L., Keeney, G. L., Mariani, A., … **Bakkum-Gamez, J. N.** (2012). Incidence and factors associated with synchronous ovarian and endometrial cancer: A population-based case-control study. *Gynecologic Oncology, 125*(1), 109–113.

Bakkum-Gamez, J. N., Langstraat, C. L., Martin, J. R., Lemens, M. A., Weaver, A. L., Allensworth, S., … Podratz, K. C. (2012). Incidence of and risk factors for postoperative ileus in women undergoing primary staging and debulking for epithelial ovarian carcinoma. *Gynecologic Oncology, 125*(3), 614–620.

Barney, B. M., Petersen, I. A., Dowdy, S. C., **Bakkum-Gamez, J. N.,** & Haddock, M. G. (2012). Long-term outcomes with intraoperative radiotherapy as a component of treatment for locally advanced or recurrent uterine sarcoma. *International Journal of Radiation Oncology, Biology, Physics, 83*(1), 191–197.

Dowdy, S. C., Borah, B. J., **Bakkum-Gamez, J. N.,** Weaver, A. L., McGree, M. E., Haas, L. R., … Podratz, K. C. (2012). Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. *Gynecologic Oncology, 127*(1), 5–10.

Kumar, S., Medeiros, F., Dowdy, S. C., Keeney, G. L., **Bakkum-Gamez, J. N.,** Podratz, K. C., … Mariani, A. (2012). A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer. *Gynecologic Oncology, 127*(3), 525–531.

Kalogera, E., Dowdy, S. C., Mariani, A., Aletti, G., **Bakkum-Gamez, J. N.,** & Cliby, W. A. (2012). Utility of closed suction pelvic drains at time of large bowel resection for ovarian cancer. *Gynecologic Oncology, 126*(3), 391–396.

Fields, J. A., Ferman, T. J., Boeve, B. F., & Smith, G. E. (2011). Neuropsychological assessment of patients with dementing illness. *Nature Reviews Neurology, 7*(12), 677–687.

Raz, L., Jayachandran, M., Tosakulwong, N., Lesnick, T. G., Dowling, M. N., Wharton, W., … Kantarci, K. (2012). White matter hyperintensities area associated with surrogate markers of cerebrovascular risk. *The FASEB Journal, 26*.

Singer, W., Klein, C., McKeon, A., & Low, P. (2012). Autoimmune autonomic ganglionopathy associated with voltage-gated potassium channel antibodies. *Neurology, 78*.

Parsaik, A., Allison, T. G., **Singer, W.,** Sletten, D. M., Joyner, M. J., Benarroch, E. E., … Sandroni, P. (2012). Deconditioning in patients with orthostatic intolerance. *Neurology, 79*(14), 1435–1439.

Singer, W., Klein, C. J., & Dyck, P. J. (2012). Gait imbalance, urinary urgency, and mild cognitive dysfunction: A case of adult polyglucosan body disease. In P. J. Dyck, et al., (Eds.), *Companion to Peripheral neuropathy: Illustrated cases and new developments* (pp. 135–138). Philadelphia, PA: Saunders.

Kimpinski, K., Figueroa, J. J., **Singer, W.,** Sletten, D. M., Iodice, V., Sandroni, P., … Low, P. A. (2012). A prospective, 1-year follow-up study of postural tachycardia syndrome. *Mayo Clinic Proceedings, 87*(8), 746–752.

Singer, W., Yung, I, O., Wollmann, R., Kelly, T., & Keegan, B. M. (2011). A middle-aged woman with nausea, weight loss, and orthostatic hypotension. *Neurology, 77*(5), 489–495.

Figueroa, J. J., Bosch, E. P., Dogan, A., Dyck, P. J. B., **Singer, W.,** & Klein, C. J. (2011). Nerve amyloid-like IGM protein composition by mass spectrophotometry. *Journal of the Peripheral Nervous System, 16*(3), S38.

Medical University of South Carolina

Scholars: Mona Buhusi, Matthew W. Feltenstein, Crystal V. Flynn Longmire, Constance Guille, Karen J. Hartwell, Margaret M. Moran-Santa Maria, Carmela M. Reichel, and Natasha M. Ruth

Fortress, A. M., **Buhusi, M.,** Helke, K. L., & Granholm, A. C. (2011). Cholinergic degeneration and alterations in the TrkA and p75NTR balance as a result of po-NGF injection into aged rats. *Journal of Aging Research, 2011*, 460543.

Buffalari, D. M., Baldwin, C. K., **Feltenstein, M. W.,** & See, R. E. (2012). Corticotrophin releasing factor (CRF) induced reinstatement of cocaine seeking in male and female rats. *Physiology & Behavior, 105*(2), 209–214.

Feltenstein, M. W., Ghee, S. M., & See, R. E. (2012). Nicotine self-administration and reinstatement of nicotine-seeking in male and female rats. *Drug and Alcohol Dependence, 121*(3), 240–246.

Feltenstein, M. W., Henderson, A. R., & See, R. E. (2011). Enhancement of cue-induced reinstatement of cocaine-seeking in rats by yohimbine: Sex differences and the role of the estrous cycle. *Psychopharmacology, 216*(1), 53–62.

Flynn Longmire, C. V., & Knight, B. G. (2011). Confirmatory factor analyses of the Zarit Burden Interview with Black and White dementia caregivers. *The Gerontologist, 51*(4), 453–462.

Guille, C., & Sen, S. (2012). Prescription drug use and self-prescription among training physicians. *Archives of Internal Medicine, 172*(4), 371–372.

Gray, K. M., Carpenter, M. J., Baker, N. L., **Hartwell, K. J.,** Lewis, A. L., Hiott, D. W., … Upadhyaya, H. P. (2011). Bupropion SR and contingency management for adolescent smoking cessation. *Journal of Substance Abuse Treatment, 40*(1), 77–86.

Hartwell, K. J., Johnson, K. A., Li, X., Myrick, H., LeMatty, T., George, M. S., & Brady, K. T. (2011). Neural correlates of craving and resisting craving for tobacco in nicotine dependent smokers. *Addiction Biology, 16*(4), 654–666.

Prisciandaro, J. J., McRae-Clark, A. L., **Moran-Santa Maria, M. M., Hartwell, K. J.,** & Brady, K. T. (2011). Psychoticism and neuroticism predict cocaine dependence and future cocaine use via different mechanisms. *Drug and Alcohol Dependence, 116*(1–3), 80–85.

Desantis, S. M., Baker, N. L., Back, S. E., Spratt, E., Ciolino, J. D., **Moran-Santa Maria, M. M.,** … Brady, K. T. (2011). Gender differences in the effect of early life trauma on hypothalamic-pituitary-adrenal axis functioning. *Depression and Anxiety, 28*(5), 383–392.

Reichel, C. M., & See, R. E. (2012). Chronic N-acetylcysteine after cocaine self-administration produces enduring reductions in drug-seeking. *Neuropsychopharmacology Reviews, 37*, 298.

Schwendt, M., **Reichel, C. M.,** & See, R. E. (2012). Extinction-dependent alterations in corticostriatal metabotropic glutamate receptor 2/3 and 7 following chronic methamphetamine self-administration in rats. *PLOS ONE, 7*, e3429.

Reichel, C. M., Ramsey, L. A., Schwendt, M., McGinty, J. F., & See, R. E. (2012). Methamphetamine-induced changes in the object recognition memory circuit. *Neuropharmacology, 62*, 1119–1126.

Reichel, C. M., & See, R. E. (2011). Chronic modafinil effects on drug-seeking following methamphetamine self-administration in rats. *The International Journal of Neuropsychopharmacology, 15*(7), 919–929.

Reichel, C. M., Moussawi, K., Do, P. H., Kalivas, P. W., & See, R. E. (2011). Chronic N-acetylcysteine during abstinence or extinction following cocaine self-administration produces enduring reductions in drug-seeking. *Journal of Pharmacology and Experimental Therapeutics, 337*(2), 487–493.

Reichel, C. M., Schwendt, M., McGinty, J. F., Olive, M. F., & See, R. E. (2011). Loss of object recognition memory produced by extended access to methamphetamine self-administration is reversed by positive allosteric modulation of metabotropic glutamate receptor 5. *Neuropsychopharmacology, 36*(4), 782–792.

Ruth, N. M., & Passo, M. H. (2012). Juvenile idiopathic arthritis: Management and therapeutic options. *Therapeutic Advances in Musculoskeletal Disease, 4*(2), 99–110.

Gilkeson, G., James, J., Kamen, D., Knackstedt, T., Maggi, D., Meyer, A., & **Ruth, N.** (2011). The United States to Africa lupus prevalence gradient revisited. *Lupus, 20*(10), 1095–1103.

Michigan State University

Scholars: Sue C. Grady, Anne K. Hughes, Daniel Velez-Ortiz, Dinesh Vyas, and April M. Zeoli

McLafferty, S., Widener, M., Chakrabarti, R., & **Grady, S. C.** (2012). Ethnic density and immigrant health inequalities: Bangladeshi immigrant women in New York City in the 1990s. *Annals of the Association of American Geographers, Special Issue on Health Geography, 102*(5), 893–903.

Tyler, C. P., **Grady, S. C.,** Griogorescu, V., Luke, B., Todem, D., & Paneth, N. (2012). Impact of state fetal death reporting requirements on racial disparities in early neonatal and fetal mortality rates. *Public Health Reports, 127,* 507–515.

Demante, P., Messina, J., Shortridge, A., & **Grady, S. C.** (2012). Measuring geographic access to health care: Raster and network-based methods. *International Journal Health Geographics, 11,* 15.

Grady, S. C., & Darden, J. T. (2012). Spatial methods to study local racial residential segregation and infant health in Detroit, Michigan. *Annals of the Association of American Geographers, Special Issue on Health Geography, 102*(5), 922–931.

Sing, A., Syal, M., Korkmaz, S., & **Grady, S. C.** (2011). Life cycle cost analysis of occupant well-being and productivity in LEED® offices based on indoor environmental quality (IEQ) improvements. *Journal of Infrastructure Systems, 17*(2).

Zeoli, A., Pizarros, J., **Grady, S.,** & Melde, C. (2012). Homicide as infectious disease: Using public health methods to investigate the diffusion of homicide. *Justice Quarterly,* 1–24. doi:10.1080/07418825.2012.732100

Rivera, E., **Zeoli, A. M.,** & Sullivan, C. (2012). Abused mothers' safety concerns and court mediators' custody recommendations. *Journal of Family Violence, 27*(4), 321–332.

Rivera, E., Sullivan, C., & **Zeoli, A. M.** (2012). Secondary victimization of abused mothers by family court mediators. *Feminist Criminology, 7*(3), 234–252.

Kubiak, S., Essenmacher, L., Hanna, J., & **Zeoli, A.** (2011). Co-occurring serious mental illness and substance use disorders within a county-wide system: Who interfaces with the jail and who does not? *Journal of Offender Rehabilitation, 50*(1), 1–17.

Kubiak, S., **Zeoli, A. M.,** Hanna, J., & Essenmacher, L. (2011). Longitudinal analysis of transitions between jail and community based treatment for individuals with co-occurring disorders. *Psychiatric Services, 62*(6), 679–681.

Zeoli, A. M., Norris, A., & Brenner, H. (2011). Mandatory, preferred or discretionary: How the classification of domestic violence warrantless arrest laws impacts their estimated effects on intimate partner homicide. *Evaluation Review, 35*(2), 129–152.

Zeoli, A. M., Norris, A., & Brenner, H. (2011). A summary and analysis of warrantless arrest statutes for domestic violence in the United States. *Journal of Interpersonal Violence, 26*(14), 2811–2833.

Park, J., & **Hughes, A. K.** (2012). Looking at alternatives: Non-pharmacological treatments for chronic pain in community-dwelling older adults. *Journal of the American Geriatrics Society, 60,* 555–568.

Hughes, A. K., & Admiraal, K. (2012). A systematic review of HIV/AIDS knowledge measures. *Research on Social Work Practice, 22,* 313–322.

Hughes, A. K., Harold, R. D., & Boyer, J. (2011). Awareness of LGBT aging issues among aging services network providers. *Journal of Gerontological Social Work, 54,* 659–677.

Hughes, A. K. (2011). HIV knowledge and attitudes among providers in aging: A national survey. *AIDS Patient Care and STDs, 25,* 539–545.

Hughes, A. K., Velez-Ortiz, D., & Horner, P. S. (2012). Academic, professional, and community outcomes of a faculty-mentored BASW research experience. *Journal of Baccalaureate Social Work, 17,* 133–147.

Hughes, A. K., Horner, P. S., & **Velez-Ortiz, D.** (2012). Being the diversity hire: Negotiating identity in an academic job search. *Journal of Social Work Education, 48,* 595–612.

Vyas, D. (Ed.). (2012). *Comprehensive textbook of surgery.* New Delhi, India: Jaypee Brothers Medical Publishing.

Vyas, D. L. S., Chaturvedi, M. E., Basson, M., Vyas, A., Mohankumar, P. S., & Huang, X. (2012). Novel theranostic nanoparticle use for efficient administration of Doxorubicin in breast cancer cell [Abstract]. *Journal of Women's Health (Larchmt), 21*(10), 1008.

Vyas, D., & Vyas, A. (2012). Time to detoxify medical literature from guideline overdose. *World Journal of Gastroenterology, 18*(26), 3331–3335.

Northwestern University

Scholars: Kelly G. Baron, Maria O. Cardenas, Colleen M. Fitzgerald, Monique Hinchcliff, Jami Josefson, and Brian T. Layden

Baron, K. G., Corden, M., Jin, L., & Mohr, D. C. (2011). Impact of psychotherapy on insomnia symptoms in patients with depression and multiple sclerosis. *Journal of Behavioral Medicine, 34,* 92–101.

Baron, K. G., Reid, K. J., Kern, A. S., & Zee, P. (2011). Role of sleep timing and caloric intake and BMI. *Obesity, 19,* 1374–1381.

Yalamanchi, S. K., Sam, S., **Cardenas, M. O.,** Holaday, L. W., Urbanek, M., & Dunaif, A. (2012). Association of fibrillin-3 and transcription factor-7-like 2 gene variants with metabolic phenotypes in PCOS. *Obesity, 20,* 1273–1278.

Fitzgerald, C. M., & Mallinson, T. (2012). The association between pelvic girdle pain and pelvic floor muscle function in pregnancy. *International Urogynecology Journal, 23,* 893–898.

Fitzgerald, C. M., Santos, L. R., & Mallinson, T. (2012). The association between pelvic girdle pain and urinary incontinence among pregnant women in the second trimester. *International Journal of Gynecology & Obstetrics, 117,* 248–250.

Neville, C. E., **Fitzgerald, C. M.,** Mallinson, T., Badillo, S. A., & Hynes, C. A. (2012). A preliminary report of musculoskeletal dysfunction in female chronic pelvic pain: A blinded study of examination findings. *Journal of Bodywork Movement Therapy, 16,* 50–56.

Fitzgerald, C. M., Neville, C. E., Mallinson, T., Badillo, S. A., Hynes, C. K., & Tu, F. F. (2011). Pelvic floor muscle examination in female chronic pelvic pain. *Journal of Reproductive Medicine, 56,* 117–122.

Clinton, S. C., George, S. E., Mehnert, M., **Fitzgerald, C. M.,** & Chimes, G. P. (2011). Pelvic floor pain: Physical therapy versus injections. *Physical Medicine & Rehabilitation, 3,* 762–770.

Fitzgerald, C. M., Plastaras, C., & Mallinson, T. (2011). A retrospective study on the efficacy of pubic symphysis corticosteroid injections in the treatment of pubic symphysis pain. *Pain Medicine, 12,* 1831–1835.

Hinchcliff, M., Huang, C. C., Ishida, W., Fang, F., Lee, J., Jafari, N., … Varga, J. (2012). Imatinib mesylate causes genome-wide transcriptional changes in systemic sclerosis fibroblasts in vitro. *Clinical and Experimental Rheumatology, 30,* S86–S96.

Hinchcliff, M., Desai, C. S., Varga, J., & Shah, S. J. (2012). Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. *Clinical and Experimental Rheumatology, 30,* S30–S37.

Hinchcliff, M., Just, E., Podlusky, S., Varga, J., Chang, R. W., & Kibbe, W. A. (2012). Text data extraction for a prospective, research-focused data mart: Implementation and validation. *BMC Medical Informatics and Decision Making, 12,* 106.

Wei, J., Melichian, D., Komura, K., **Hinchcliff, M.,** Lam, A. P., Lafyatis, R., … Varga, J. (2011). Canonical Wnt signaling induces skin fibrosis and subcutaneous lipoatrophy: A novel model for scleroderma? *Arthritis & Rheumatism, 63,* 1707–1717.

Hinchcliff, M., Fischer, A., Schiopu, E., Steen, V. D., & PHAROS Investigators. (2011). Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Baseline characteristics and description of study population. *Journal of Rheumatology, 38,* 2172–2179.

Josefson, J. (2012). Metabolic programming of obesity in utero: Is there sufficient evidence to explain increased obesity rates? *Journal of Developmental Origins of Health and Disease, 3,* 70–72.

Layden, B. T., Durai, V., Newman, M. V., Marinelarena, A. M., Ahn, C. W., Feng, G., … Lowe, W. L., Jr. (2010). Regulation of pancreatic islet gene expression in mouse islets by pregnancy. *Journal of Endocrinology, 207,* 265–279.

Oregon Health & Science University

Scholars: Rebecca Block, Beth D. Darnall, Karen B. Eden, Nancy E. Glass, Paco S. Herson, Sonnet S. Jonker, Erin S. LeBlanc, Christopher S. Lee, Carrie M. Nielson, Tania Pejovic, Howard K. Song, Philippe Thuillier, and Wendy W. Wu

Zebrack, B. J., **Block, R.,** Hayes-Lattin, B., Embry, L., Aguilar, C., Meeske, K. A., … Cole, S. (2013). Psychosocial service use and unmet need among recently diagnosed adolescent and young adult cancer patients. *Cancer, 119*(1), 201–214.

Darnall, B. D., & Li, H. (2012). Home-based self-delivered mirror therapy for phantom pain: A pilot study. *Journal of Rehabilitation Medicine, 44*(3), 254–260.

Darnall, B. D., Stacey, B. R., & Chou, R. (2012). Medical and psychological risks and consequences of long-term opioid therapy in women. *Pain Medicine, 13*(9), 1181–1211.

Darnall, B. D., & Sazie, E. (2012). Pain characteristics and pain catastrophizing in incarcerated women with chronic pain. *Journal of Health Care for the Poor and Underserved, 23*(2), 543–556.

Schatman, M. E., & **Darnall, B.** (2012). The resurrection of the ethics forum in pain medicine: An introduction. *Pain Medicine, 14*(4), 453–454.

Darnall, B. D., & Stacey, B. R. (2012). Sex differences in long-term opioid use: Cautionary notes for prescribing in women. *Archives of Internal Medicine, 172*(5), 431–432.

Darnall, B. & Li, H. (2011). Hysterectomy and predictors for opioid prescription in a chronic pain clinic sample. *Pain Medicine, 12*(2), 196–203.

Eden, K. B., Denman, M. A., Emeis, C. L., McDonagh, M. S., Fu, R., Janik, R. K., … Guise, J. M. (2012). Trial of labor and vaginal delivery rates in women with a prior cesarean. *Journal of Obstetric, Gynecologic, and Neonatal Nursing.* Advance online publication. doi:10.111 1/j.1552-6909.2012.01388

Stacey, D., Bennett, C. L., Barry, M. J., Col, N. F., **Eden, K. B.,** Holmes-Rovner, M., … Thomson, R. (2011). Decision aids for people facing health treatment or screening decisions. *Cochrane Database of Systematic Reviews* (10), CD001431.

Cheng, Y. W., **Eden, K. B.,** Marshall, N., Pereira, L., Caughey, A. B., & Guise, J. M. (2011). Delivery after prior cesarean: Maternal morbidity and mortality. *Clinics in Perinatology, 38*(2), 297–309.

Sharma, P. S., **Eden, K. B.,** Guise, J. M., Jimison, H. B., & Dolan, J. G. (2011). Subjective risk vs. objective risk can lead to different post-cesarean birth decisions based on multiattribute modeling. *Journal of Clinical Epidemiology, 64*(1), 67–78.

Yragui, N. L., Mankowski, E. S., Perrin, N. A., & **Glass, N. E.** (2012). Dimensions of support among abused women in the workplace. *American Journal of Community Psychology, 49*(1–2), 31–42.

Tappis, H., Biermann, E., **Glass, N.,** Tileva, M., & Doocy, S. (2012). Domestic violence among Iraqi refugees in Syria. *Health Care for Women International, 33*(3), 285–297.

Rollins, C., **Glass, N. E.,** Perrin, N. A., Billhardt, K. A., Clough, A., Barnes, J., … Bloom, T. L. (2012). Housing instability is as strong a predictor of poor health outcomes as level of danger in an abusive relationship: findings from the SHARE Study. *Journal of Interpersonal Violence, 27*(4), 623–643.

Samuel, L. J., Tudor, C., Weinstein, M., Moss, H., & **Glass, N.** (2011). Employers' perceptions of intimate partner violence among a diverse workforce. *Safety and Health at Work, 2*(3), 250–259.

Rybarczyk, M., Tosha, M., Mbika, B., Bulonza, P., Ramazani, P., Zahiga, I., … **Glass, N.** (2011). Evaluation of medical supplies essential for the care of survivors of sex- and gender-based violence in post-conflict Eastern Democratic Republic of Congo. *Medicine, Conflict and Survival, 27*(2), 91–110.

Mankowski, E. S., Galvez, G., & **Glass, N.** (2011). Interdisciplinary linkage of community psychology and cross-cultural psychology: History, values, and an illustrative research and action project on intimate partner violence. *American Journal of Community Psychology, 47*(1–2), 127–143.

Perrin, N. A., Yragui, N. L., Hanson, G. C., & **Glass, N.** (2011). Patterns of workplace supervisor support desired by abused women. *Journal of Interpersonal Violence, 26*(11), 2264–2284.

Ssengooba, F., Atuyambe, L., Kiwanuka, S. N., Puvanachandra, P., **Glass, N.,** & Hyder, A. A. (2011). Research translation to inform national health policies: Learning from multiple perspectives in Uganda. *BMC International Health and Human Rights, 11*(Suppl 1), S13.

Hutchens, M. P., Fujiyoshi, T., Komers, R., **Herson, P. S.,** Anderson, S., Ren, X., … Offner, H. (2012). Estrogen protects renal endothelial barrier function from ischemia-reperfusion in vitro and in vivo Myelin specific cells infiltrate MCAO lesions and exacerbate stroke severity. *American journal of physiology: Renal physiology, 303*(3), F377–F385.

Ren, X., Akiyoshi, K., Dziennis, S., Vandenbark, A. A., Herson, P. S., Hurn, P. D., & Offner, H. (2011). Regulatory B cells limit CNS inflammation and neurologic deficits in murine experimental stroke. *The Journal of Neuroscience, 31*(23), 8556–8563.

Cheng, J., Uchida, M., Zhang, W., Grafe, M. R., **Herson, P. S.,** & Hurn, P. D. (2011). Role of salt-induced kinase 1 in androgen neuroprotection against cerebral ischemia. *Journal of Cerebral Blood Flow & Metabolism, 31*(1), 339–350.

Kelley, M. H., Kuroiwa, M., Taguchi, N., & **Herson, P. S.** (2011). Sex difference in sensitivity to allopregnanolone neuroprotection in mice correlates with effect on spontaneous inhibitory post synaptic currents, *Neuropharmacology, 61*(4), 724–729.

Jia, J., Verma, S., Nakayama, S., Quillinan, N., Grafe, M. R., Hurn, P. D., & **Herson, P. S.** (2011). Sex differences in neuroprotection provided by inhibition of TRPM2 channels following experimental stroke. *Journal of Cerebral Blood Flow & Metabolism, 31*(11), 2160–2168.

Jonker, S. S., Scholz, T. D., & Segar, J. L. (2011). The effect of adrenalectomy on the cardiac response to subacute fetal anemia. *Canadian Journal of Physiology and Pharmacology, 89*(2), 79–88.

Thornburg, K., **Jonker, S.,** O'Tierney, P., Chattergoon, N., Louey, S., Faber, J., & Giraud, G. (2011). Regulation of the cardiomyocyte population in the developing heart. *Progress in Biophysics and Molecular Biology, 106*(1), 289–299.

Jonker, S. S., Scholz, T. D., & Segar, J. L. (2011). Transfusion effects on cardiomyocyte growth and proliferation in fetal sheep after chronic anemia. *Pediatric Research, 69*(6), 485–490.

LeBlanc, E. S., Rizzo, J. H., Pedula, K. L., Ensrud, K. E., Cauley, J., Hochberg, M., … Hillier T. A.; Study of Osteoporotic Fractures. (2012). Associations between 25-hydroxyvitamin D and weight gain in elderly women. *Journal of Women's Health 21*(10), 1066–1073.

Tang, J. Y., Fu, T., **LeBlanc, E.,** Manson, J. E., Feldman, D., Linos, E., … Stefanick, M. L. (2011). Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: Post hoc analyses of the women's health initiative randomized controlled trial. *Journal of Clinical Oncology, 29*(22), 3078–3084.

LeBlanc, E. S., O'Connor, E., Whitlock, E. P., Patnode, C. D., & Kapka, T. (2011). Effectiveness of primary care-relevant treatments for obesity in adults: A systematic evidence review for the U.S. Preventive Services Task Force. *Annals of Internal Medicine, 155*(7), 434–447.

LeBlanc, E. S., Wang, P. Y., Lee, C. G., Barrett-Connor, E., Cauley, J. A., Hoffman, A. R., … Orwoll, E. S. (2011). Higher testosterone levels are associated with less loss of lean body mass in older men. *Journal of Clinical Endocrinology & Metabolism, 96*(12), 3855–3863.

LeBlanc, E. S., Hillier, T. A., Pedula, K. L., Rizzo, J. H., Cawthon, P. M., Fink, H. A., … Browner, W. S. (2011). Hip fracture and increased short-term but not long-term mortality in healthy older women. *Archives of Internal Medicine, 171*(20), 1831–1837.

Nielson, C. M., Marshall, L. M., Adams, A. L., **LeBlanc, E. S.,** Cawthon, P. M., Ensrud, K, … Orwoll, E. S. (2011). BMI and fracture risk in older men: the osteoporotic fractures in men study (MrOS). *Journal of Bone and Mineral Research, 26*(3), 496–502.

Nielson, C. M., Srikanth, P., & Orwoll, E. S. (2012). Obesity and fracture in men and women: An epidemiologic perspective. *Journal of Bone and Mineral Research, 27*(1), 1–10.

Nielson, C. M., Zmuda, J. M., Carlos, A. S., Wagoner, W. J., Larson, E. A., Orwoll, E. S., & Klein, R. F. (2012). Rare coding variants in ALPL are associated with low serum alkaline phosphatase and low bone mineral density. *Journal of Bone and Mineral Research, 27*(1), 83–103.

Abalos, A. T., Eggers, R., Hogan, M., **Nielson, C. M.,** Giuliano, A. R., Harris, R. B., & Thompson, P. A. (2011). Design and validation of a multiplex specific primer-directed polymerase chain

reaction assay for killer-cell immunoglobulin-like receptor genetic profiling. *Tissue Antigens, 77*(2), 143–148.

Lee, C. G., Boyko, E. J., **Nielson, C. M.,** Stefanick, M. L., Bauer, D. C., Hoffman, A. R., (2011). Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *Journal of the American Geriatrics Society, 59*(2), 233–240.

Buck, H. G., **Lee, C. S.,** Moser, D. K., Albert, N. M., Lennie, T., Bentley, B., … Riegel, B. (2012). Relationship between self-care and health-related quality of life in older adults with moderate to advanced heart failure. *Journal of Cardiovascular Nursing, 27*(1), 8–15.

Lee, C. S., Moser, D. K., Lennie, T. A., Tkacs, N. C., Margulies, K. B., & Riegel, B. (2011). Biomarkers of myocardial stress and systemic inflammation in patients who engage in heart failure self-care management. *Journal of Cardiovascular Nursing, 26*(4), 321–328.

Lee, C. S., Moser, D. K., Lennie, T. A., & Riegel, B. (2011). Event-free survival in adults with heart failure who engage in self-care management. *Heart Lung: The Journal of Critical Care, 40*(1), 12–20.

Riegel, B., **Lee, C. S.,** Albert, N., Lennie, T., Chung, M., Song, E. K., … Moser, D. K. (2011). From novice to expert: Confidence and activity status determine heart failure self-care performance. *Nursing Research, 60*(2), 132–138.

MacDonald, K., **Lee, C. S.,** Chen, H. C., Ko, M. L., Fidel, G. E., Brie, H., … Abraham, I. (2011). Gender-specific, multi-level determinants of outcomes of antihypertensive treatment: A sub-analysis of the Belgian PREVIEW study. *Journal of Human Hypertension, 25*(6), 372–382.

Abraham, I., MacDonald, K., Hermans, C., Aerts, A., **Lee, C.,** Brié, H., & Vancayzeele, S. (2011). Real-world effectiveness of valsartan on hypertension and total cardiovascular risk: Review and implications of a translational research program. *Vascular Health and Risk Management, 7*, 209–235.

Wysham, W. Z., Mhawech-Fauceglia, P., Li, H., Hays, L., Syriac, S., Skrepnik, T., … **Pejovic, T.** (2012). BRCAness profile of sporadic ovarian cancer predicts disease recurrence. *PLOS ONE, 7*(1), e30042.

Mhawech-Fauceglia, P., Afkhami, M., & **Pejovic, T.** (2012). MET/HGF signaling pathway in ovarian carcinoma: Clinical implications and future direction. *Pathology Research International, 2012, 2012,* 960327.

Mhawech-Fauceglia, P., Wang, D., Samrao, D., Menesses, T., Godoy, H., Ough, F., … **Pejovic, T.** (2012). The role of hypoxic-inducible factor (HIF1alpha) and aldolaseC protein in endometrial carcinogenesis: A retrospective study of 279 patients. *BMJ Open, 2*(4), Pii: e001450.

Pejovic, T., & Nezhat, F. (2011). Missing link: Inflammation and ovarian cancer. *The Lancet Oncology,* 12(9), 833–834.

Hutchens, M., **Song, H.,** & Ibsen, L. (2012). Extracorporeal membrane oxygenation for ARDS in adults. *The New England Journal of Medicine, 366*(6), 575–576.

Ariyachaipanich, A., Mudd, J. O., Gelow, J., & **Song, H. K.** (2012). Long-term systemic right ventricular support in transposition and dextrocardia. *Journal of Thoracic and Cardiovascular Surgery, 144*(4), e108–e110.

Mao, P., Meshul, C. K., **Thuillier, P.,** Goldberg, N. R., & Reddy, P. H. (2012). CART peptide is a potential endogenous antioxidant and preferentially localized in mitochondria. *PLOS ONE, 7*(1), e29343.

Stapleton, C. M., Mashek, D. G., Wang, S., Nagle, C. A., Cline, G. W., **Thuillier, P.,** … Coleman, R. A. (2011). Lysophosphatidic acid activates peroxisome proliferator activated receptor-gamma in CHO cells that over-express glycerol 3-phosphate acyltransferase-1. *PLOS ONE, 6*(4), e18932.

Ballesteros-Merino, C., Lin, M., **Wu, W. W.,** Ferrandiz-Huertas, C., Cabanero, M. J., Watanabe, M., … Lujan, R. (2012). Developmental profile of SK2 channel expression and function in CA1 neurons. *Hippocampus, 22*(6), 1467–1480.

Krause, A., Xu, Y., Ross, S., **Wu, W.,** Joh, J., & Worgall, S. (2011). Absence of vaccine-enhanced RSV disease and changes in pulmonary dendritic cells with adenovirus-based RSV vaccine. *Virology Journal, 8*, 375.

Lioy, D. T., **Wu, W. W.,** & Bissonnette, J. M. (2011). Autonomic dysfunction with mutations in the gene that encodes methyl-CpG-binding protein 2: Insights into Rett syndrome. *Autonomic Neuroscience, 161*(1–2), 55–62.

Wu, W. W., Adelman, J. P., & Maylie, J. (2011). Ovarian hormone deficiency reduces intrinsic excitability and abolishes acute estrogen sensitivity in hippocampal CA1 pyramidal neurons. *The Journal of neuroscience, 31*(7), 2638–2648.

Cai, L. Q., Cai, J., **Wu, W.,** & Zhu, Y. S. (2011). 17alpha-Estradiol and genistein inhibit high fat diet induced prostate gene expression and prostate growth in the rat. *Journal of Urology, 186*(4), 1489–1496.

Pennsylvania State University

Scholars: Ping Du, Steriani Elavsky, Michelle L. Frisco, Daphne C. Hernandez, Amy D. Marshall, Jennifer S. McCall-Hosenfeld, and Nazia Raja-Khan

Du, P., Camacho, F., Zurlo, J., & Lengerich, E. J. (2011). Human immunodeficiency virus testing behaviors among U.S. adults: The roles of individual factors, legislative status, and public health resources. *Sexually Transmitted Diseases, 38*(9), 858–864.

Elavsky, S., Molenaar, P., Gold, C. H., Williams, N. I., & Aronson, K. R. (2012). Daily physical activity and menopausal hot flashes: Applying a novel within-person approach to demonstrate individual differences. *Maturitas, 71*(3), 287–93.

Moore, D. J., Gonzales, J. U., Tucker, S. H., **Elavsky, S.,** & Proctor, D. N. (2012). Exercise-induced vasodilation is associated with menopause stage in healthy middle-aged women. *Applied Physiology, Nutrition, and Metabolism, 37*(3), 418–424.

Hyde, A. L., **Elavsky, S.,** Doerksen, S. E., Conroy, D. E. (2012). Habit strength moderates the strength of within-person relations between weekly self-reported and objectively-assessed physical activity. *Psychology of Sport and Exercise, 13*(5), 558–591.

Conroy, D. E., **Elavsky, S.,** Hyde, A. L., & Doerksen, S. E. (2011). The dynamic nature of physical activity intentions: A within-person perspective on intention-behavior coupling. *Journal of Sport & Exercise Psychology, 33*(6), 807.

Vallance, J. K., Murray, T. C., Johnson, S. T., & **Elavsky, S.** (2011). Understanding physical activity intentions and behavior in postmenopausal women: An application of the theory of planned behavior. *International Journal of Behavioral Medicine, 18*(2), 139–149.

Frisco, M. L., Weden, M. M., Lippert, A. M., & Burnett, K. D. (2012). The multidimensional relationship between early adult body weight and women's childbearing experiences. *Social Science & Medicine, 74*(11), 1703–1711.

Van Hook, J., Baker, E., Altman, C. E., & **Frisco, M.** (2011). Canaries in a coalmine: Immigration and overweight among Mexican-origin children in the U.S. and Mexico. *Social Science & Medicine. 74*(2), 125–134.

Martin, M. A., **Frisco, M. L.,** Nau, C., & Burnett, K. (2011). Social stratification and adolescent overweight in the United States: How income and educational resources matter across families and schools. *Social Science & Medicine, 74*(4), 597–606.

Hernandez, D. C. (2012). Soda consumption among food insecure households with children: A call to restructure food assistance policy. *Journal of Applied Research on Children: Informing Policy for Children at Risk, 3*(1), Article 16.

Hernandez, D. C., Francis, L. A., & Doyle, E. A. (2011). National School Lunch Program and gender differences in low-income children's BMI trajectories. *Archives of Pediatric and Adolescent Medicine, 165*(4), 346–353.

Jennings-Kelsall, V., Aloia, L. S., Solomon, D. H., **Marshall, A. D.,** & Leifker, F. R. (2012). Stressors experienced by women within marine corps families: A qualitative study of discourse within an online forum. *Military Psychology, 24*(4), 363–381.

Marshall, A. D., Robinson, L. R., & Azar, S. T. (2011). Cognitive and emotional contributors to intimate partner violence perpetration following trauma. *Journal of Traumatic Stress, 24*(5), 586–590.

Marshall, A. D., Jones, D. E., & Feinberg, M. E. (2011). Enduring vulnerabilities, relationship attributions, and couple conflict: An integrative model of the occurrence and frequency of intimate partner violence. *Journal of Family Psychology, 25*(5), 709.

Marshall, A. D., Panuzio, J., Makin-Byrd, K. N., Taft, C. T., & Holtzworth-Munroe, A. (2011). A multilevel examination of interpartner intimate partner violence and psychological aggression reporting concordance. *Behavior Therapy, 42*(3), 364–377.

Marshall, A. D., Sippel, L. M., & Belleau, E. L. (2011). Negatively biased emotion perception in depression as a contributing factor to psychological aggression perpetration: A preliminary study. *The Journal of Psychology, 145*(6), 521–535.

Sippel, L. M., & **Marshall, A. D.** (2011). Posttraumatic stress disorder symptoms, intimate partner violence perpetration, and the mediating role of shame processing bias. *Journal of Anxiety Disorders, 25*(7), 903–910.

Walling, S. M., Meehan, J. C., **Marshall, A. D.,** Holtzworth-Munroe, A., & Taft, C. T. (2011). The relationship of intimate partner aggression to head injury, executive functioning, and intelligence. *Journal of Marital and Family Therapy, 38*(3), 471–485.

McCall-Hosenfeld, J. S., Weisman, C. S., Camacho, F., Hillemeier, M. M., & Chuang, C. H. (2012). Multilevel analysis of the determinants of receipt of clinical preventive services among reproductive-age women. *Women's Health Issues, 22*(3), e243–e251.

Chuang, C. H., Hwang, S. W., **McCall-Hosenfeld, J. S.,** Rosenwasser, L., Hillemeier, M. M., & Weisman, C. S. (2012). Primary care physicians' perceptions of barriers to preventive reproductive health care in rural communities. *Perspectives on Sexual and Reproductive Health, 44*(2), 78–83.

Kraschnewski, J. L., **McCall-Hosenfeld, J. S.,** & Weisman, C. S. (2012). Prospective association between body mass index and receipt of preventive services: Results from the Central Pennsylvania Women's Health Study (CePAWHS). *Preventive Medicine, 54*(5), 302–305.

McCall-Hosenfeld, J. S., Weisman, C. S., & Weisman, J. M. H. C. (2011). Receipt of preventive counseling among reproductive-aged women in rural and urban communities. *Rural and Remote Health, 11*(1), 1617.

Hillemeier, M. M., Weisman, C. S., Chuang, C., Downs, D. S., **McCall-Hosenfeld, J.,** & Camacho, F. (2011). Transition to overweight or obesity among women of reproductive age. *Journal of Women's Health, 20*(5), 703–710.

Mattocks, K. M., Nikolajski, C., Haskell, S., Brandt, C., **McCall-Hosenfeld, J.,** Yano, E., Pham, T., & Borrero, S. (2011). Women veterans' reproductive health preferences and experiences: A focus group analysis. *Women's Health Issues, 21*(2), 124–129.

Raja-Khan, N., Shuja, S. A., Kunselman, A. R., Hogeman, C. S., Demers, L. M., Gnatuk, C. L., & Legro, R. S. (2011). Brachial artery conductance during reactive hyperemia is increased in women with polycystic ovary syndrome. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 155*(1), 49–53.

Pauli, J. M., **Raja-Khan, N.,** Wu, X., & Legro, R. S. (2011). Current perspectives of insulin resistance and polycystic ovary syndrome. *Diabetic Medicine, 28*(12), 1445–1454.

Raja-Khan, N., Kunselman, A. R., Hogeman, C. S., Stetter, C. M., Demers, L. M., & Legro, R. S. (2011). Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: A double-blind, randomized, placebo-controlled trial. *Fertility and Sterility, 95*(5), 1849–1852.

Raja-Khan, N., Stener-Victorin, E., Wu, X., & Legro, R. S. (2011). The physiological basis of complementary and alternative medicines for polycystic ovary syndrome. *American Journal of Physiology-Endocrinology and Metabolism, 301*(1), E1–E10.

Tulane University

Scholars: Tanika N. Kelly, Lovie F. Lewis Rodgers, Jennifer McGee, Lisa A. Molix, Minolfa C. Prieto, Tina K. Thethi, and Andrea Zsombok

Khan, N., Abbas, A. M., Whang, N., Balart, L. A., Bazzano, L. A., & **Kelly, T. N.** (2012). Incidence of liver toxicity in inflammatory bowel disease patients treated with methotrexate: A meta-analysis of clinical trials. *Inflammatory Bowel Diseases, 18,* 359–367.

He, J., Gu, D., **Kelly, T. N.,** Hixson, J. E., Rao, D. C., Jaquish, C. E., … Whelton, P. K. (2011). Genetic variants in the renin-angiotensin-aldosterone system and blood pressure responses to potassium intake: The GenSalt Study. *Journal of Hypertension, 29,* 1719–1730.

Montasser, M. E., Gu, D., Chen, J., Shimmin, L. C., Gu, C. C., **Kelly, T. N.,** … Hixson, J. E. (2011). Interactions of genetic variants with physical activity are associated with blood pressure in Chinese: The GenSalt study. *American Journal of Hypertension, 24,* 1035–1040.

Kato, N., Takeuchi, F., Tabara, Y., **Kelly, T. N.,** Go, M. J., Sim, X., … He, J. (2011). Meta-analysis of genome-wide association studies identifies five novel loci associated with blood pressure in East Asians. *Nature Genetics, 43,* 531–538.

Lewis Rodgers, L. F., Holt, E. W., & Krousel-Wood, M. A. (2012). Gender disparities in blood pressure control among older adults: Findings from CoSMO. *Journal of Investigative Medicine, 60,* 404.

Rapp, K. I., **Lewis Rodgers, L. F.,** Leon, K., & Roberts, A. (2011). Optimizing patient care in asthma during pregnancy. *U.S. Pharmacist, 36*(7), 30–34.

McGee, J., Mave, V., Yau, C. L., Killackey, M., Paramesh, A., Buell, J. F., … Zhang, R. (2012). Cytomegalovirus disease in African-American kidney transplant patients. *Transplant Infectious Disease, 14*(6), 604–610.

McGee, J., Jackson, N. R., & Slakey, D. P. (2012). Disability and kidney transplantation in the United States. *Clinical Transplantation, 26*(3), 377–381.

Malazai, A. J., Worku, D. G., **McGee, J.,** Van Meter, K., & Slakey, D. P. (2011). The history of hyperbaric oxygen therapy and kidney transplant surgery. *Undersea and Hyperbaric Medicine, 38*(4), 247–255.

Worku, D., Laluf, S., **McGee, J.,** Goswami, M., Van Meter, K., & Slakey, D. P. (2011). P-selectin expression in cold preserved kidneys in University of Wisconsin and histidine-tryptophan-ketoglutarate solutions. *Journal of Surgical Research, 169*(1), 125–131.

McGee, J., Magnus, J. H., Zhang, R., Florman, S. S., Hamm, L. L., Islam, T. M., … Slakey, D. P. (2011). Race and gender are not independent risk factors of allograft loss after kidney transplantation. *American Journal of Surgery, 201*(4), 463–467.

Molix, L. & Nichols, C. P. (2012). The importance of perspective taking and respect for dignity in understanding radicalization. *Analyses of Social Issues and Public Policy, 12*, 320–323.

Schlegel, R. J., Manning, M. A., **Molix, L. A.,** Talley, A. E., & Bettencourt, B. A. (2012). Predictors of depressive symptoms among breast cancer patients during the first year post diagnosis. *Psychology and Health, 27*, 277–293.

Talley, A. E., Kocum, L., Schlegel, R. J., **Molix, L.,** & Bettencourt, B. A. (2012). Social roles, basic need satisfaction, and psychological health: The central role of competence. *Personality and Social Psychology Bulletin, 38*, 155–173.

Prieto, M. C., Das, S., Somanna, N. K., Harrison-Bernard, L. M., Navar, L. G., & Pandey, K. N. (2012). Disruption of Npr1 gene differentially regulates the juxtaglomerular and distal tubular renin levels in null mutant mice. *International Journal of Physiology, Pathophysiology & Pharmacology, 4*(3), 128–139.

Gonzalez, A. A., Liu, L., Lara, L. S., Seth, D. M., Navar, L. G., & **Prieto, M. C.** (2011). Angiotensin II stimulates renin in the collecting duct cells via protein kinase C and independent of ENAC and mineralocorticoid receptor. *Hypertension, 57*, 594–599.

Navar, L. G., **Prieto, M. C.,** Sato, R., & Kobori, H. (2011). Intrarenal angiotensin II and its contribution to the genesis of chronic hypertension. *Current Opinion in Pharmacology, 11*, 180–186.

Navar, L. G., Kobori, H., **Prieto, M. C.,** & Gonzalez-Villalobos, R. A. (2011). Intratubular renin-angiotensin system in hypertension. *Hypertension, 57*(3), 355–362.

Gonzalez, A. A., Lara, L. S., Seth, D. M. & **Prieto, M. C.** (2011). The soluble form of the prorenin receptor [S(PRR)] is augmented in the collecting ducts and in the urine of angiotensin II(ang ii)-dependent rats. *Hypertension, 57*, 859–864.

Thethi, T. K., Sigel, A., Shanker, J., McDuffie, R., Ali, S., Banka, A… . Fonseca, V. (2011). Polymorphisms of the endocannabinoid system in obese African-American women. *Journal of Investigative Medicine, 59*(2), 510.

Thethi, T., Rajapurkar, M., Walker, P., McDuffie, R., Goff, D. C., Probstfield, J., … Fonseca, V. (2011). Predictors of duloxetine versus other treatments among veterans with diabetic peripheral neuropathic pain: A retrospective study. *Pain Practice, 12*(5), 366–373.

Kandil, E., Khalek, M. A., **Thethi, T.,** Abd Elmageed, Z., Khan, A., & Jaffe, B. M. (2011). Thyroid storm in a patient with fulminant hepatic failure. *Laryngoscope, 121*(1), 164–166.

Thethi, T., Rajapurkar, M., Walker, P., McDuffie, R., Goff, D. C., Probstfield, J., … Fonseca, V. (2011). Urinary catalytic iron and oxidative stress in patients with type 2 diabetes without microalbuminuria—A sub-study in the ACCORD Trial. *Clinical Chemistry, 57*(2), 341–344.

Thethi, T. K., Parsha, K., Rajapurkar, M., Mukhopadhyay, B., Shah, S., Yau, C. L., … Fonseca, V. (2011). Urinary catalytic iron in obesity. *Clinical Chemistry, 57*(2), 272–278.

Lara, L. S., Satou, R., Bourgeois, C. R. T., Gonzalez, A. A., **Zsombok, A.,** Prieto, M. C., & Navar, G. L. (2012). The sodium-activated sodium channel (Na-sensor) is expressed in the rat kidney thick ascending limb and collecting duct cells and is upregulated during high salt intake. *American Journal of Physiology: Renal Physiology, 303*(1), F105–F109.

Gao, H., Miyata, K., Bhaskaran, M. D., Derbenev, A. V., & **Zsombok, A.** (2012). TRPV1-dependent regulation of liver-related neurons in the paraventricular nucleus of the hypothalamus diminished in type 1 diabetic mouse. *Diabetes, 61*(6), 1381–1390.

Kamiyama, M., **Zsombok, A.,** & Kobori, H. (2012). Urinary angiotensinogen as a novel biomarker of intrarenal renin-angiotensin system activation in experimental type 1 diabetes. *Journal of Pharmacological Sciences, 119*(4), 314–323.

Zsombok, A., Bhaskaran, M. D., Gao, H., Derbenev, A. V., & Smith, B. N. (2011). Functional plasticity of central TRPV1 receptors in brainstem dorsal vagal complex circuits of streptozotocin-treated hyperglycemic mice. *The Journal of Neuroscience, 31*(39), 14024–14031.

Zsombok, A., Gao, H., Miyata, K., Issa, A. T., & Derbenev, A. V. (2011). Immunohistochemical localization of transient receptor potential vanilloid type 1 and insulin receptor substrate 2 and their co-localization with liver-related neurons in the hypothalamus and brainstem. *Brain Research, 1398,* 30–39.

University of California, Davis

Scholars: Ester C. Apesoa-Varano, Blaine A. Christiansen, Lorena Garcia, Sumathi Sankaran-Walters, Rebecca J. Schmidt, Kimber L. Stanhope, and Barton Wise

Hinton, L., **Apesoa-Varano, E. C.,** Barker, J., Aguilar-Gaxiola, S., & Untuzer, J. (2012). Falling through the cracks: Gaps in depression care among older Mexican Origin and White non-Hispanic men in primary care. *International Journal of Geriatric Psychiatry, 27*(12), 1283–1290.

Apesoa-Varano, E. C., Barker J. C., & Hinton L. (2012). Mexican-American Families and Dementia: An Exploration of "Work" in Response to Dementia-Related Aggressive Behavior. In J. L. Angel, F. Torres-Gil, & K. Markides (Eds.), *Aging, Health and Longevity in the Mexican-American Population* (pp. 277–292). New York, NY: Springer.

Apesoa-Varano, E. C., Barker, J. C., & Hinton, L. (2011). Curing and caring: The work of primary care physicians with dementia patients. *Qualitative Health Research, 21*(11), pp. 1469–1483.

Symons, J. E., Entwistle, R. C., Arens, A. M., Garcia, T. C., **Christiansen, B. A.,** Fyhrie, D. P., & Stover, S. M. (2012). Mechanical and morphologic properties of trabecular bone from horses with a bone fragility syndrome. *American Journal of Veterinary Research, 73*(11), 1742–1751.

Christiansen, B. A., Anderson, M. J., Lee, C. A., Williams, J. C., Yik, J. H., & Haudenschild, D. R. (2012). Musculoskeletal changes following non-invasive knee injury using a novel mouse model of post-traumatic osteoarthritis. *Osteoarthritis and Cartilage, 20*(7), 773–782.

Christiansen, B. A., Kopperdahl, D. L., Kiel, D. P., Keaveny, T. M., & Bouxsein, M. L. (2011). Mechanical contributions of the cortical and trabecular compartments contribute to differences in age-related changes in vertebral body strength in men and women assessed by QCT-based finite element analysis. *Journal of Bone and Mineral Research, 26*(5), 974–983.

Christiansen, B. A., & Bouxsein, M. L. (2011). Methods in bone biology in animals: Imaging. In G. Duque, & K. Watanabe (Eds.), *Osteoporosis Research* (pp. 45–56). New York, NY: Springer.

Samelson, E. J., **Christiansen, B. A.,** Demissie, S., Broe, K. E., Louie-Gao, Q., Cupples, L. A., … Bouxsein, M. L. (2011). QCT measures of bone strength at the thoracic and lumbar spine: The Framingham study. *Journal of Bone and Mineral Research, 27*(3), 654–663.

Samelson, E. J., **Christiansen, B. A.,** Demissie, S., Broe, K. E., Meng, C. A., Yu, W., … Bouxsein, M. L. (2011). Reliability of vertebral fracture assessment using multidetector CT lateral scout views: The Framingham osteoporosis study. *Osteoporosis International, 22*(4), 1123–1131.

Garcia, L., Gold, E. B., Wang, L., Yang, X., Mao, M., & Schwartz, A. (2012). Obesity, pre-diabetes and diabetes by acculturation level among U.S. Mexican-American women and men. *Ethnicity & Disease, 22,* 58–64.

Qi, L., Nassir, R., Kosoy, R., **Garcia, L.,** Curb, J. D., Tinker, L., … Seldin, M. F. (2012). Relationship between diabetes risk and admixture in post-menopausal African-American and Hispanic-American women. *Diabetologica, 55*(5), 1329–1337.

Nassir, R., Qi, L., **Garcia, L.,** Robbins, J., & Seldin, M. F. (2012). Relationship between gallbladder removal and gallstone removal in African-American and Hispanic post-menopausal women. *American Journal of Gastroenterology, 107*(6), 932–940.

Kosoy, R., Qi, L., Nassir, R., **Garcia, L.,** Allison, M., Shigeta, R., … Seldin, M. F. (2012). Relationship between hypertension and admixture in post-menopausal African-American and Hispanic American women. *Journal of Human Hypertension, 26*(6), 365–373.

McTigue, K. M., Chang, Y. F., Eaton, C., **Garcia, L.,** Johnson, K. C., Lewis, C. E., … Kuller, L. H. (2012). Severe obesity, heart disease, and death among White, African-American and Hispanic postmenopausal women. *Obesity.* Advance online publication. doi:10.1002/oby.20224

Kroenke, C. H., Michael, Y., Tindle, H., Gage, E., Chlebowski, R., **Garcia, L.,** … Caan, B. J. (2012). Social networks, social support, stage at breast cancer diagnosis, and mortality after diagnosis. *Breast Cancer Research and Treatment, 133*(1), 375–385.

Nassir, R., Qi, L., Kosoy, R., **Garcia, L.,** Allison, M., Ochs-Balcom, H. M., … Seldin, M. F. (2011). Relationship between adiposity and admixture in African American and Hispanic-American Women. *International Journal of Obesity, 36,* 304–313.

Martin, K., & **Garcia, L.** (2011). Unintended pregnancy and intimate partner violence (IPV) before and during pregnancy among Latina women in Los Angeles, California. *Journal of Interpersonal Violence, 26*(6), 1157–1175.

Dang, A. T., Cotton, S., **Sankaran-Walters, S.,** Li, C. S., Lee, C. Y., Dandekar, S., … George, M. D. (2012). Evidence of an increased pathogenic footprint in the lingual microbiome of HIV-1 infected patients with high viremia. *BMC Microbiology, 12,* 153.

Sankaran-Walters, S. (2012). Real-time PCR in clinical diagnostic settings [Editorial]. *Journal of Medical Microbiology & Diagnosis, 1,* e106.

Sankaran-Walters, S., Ransibrahmanakul, K., Grishina, I., Hung, J., Martinez, E., Prindiville, T., & Dandekar, S. (2011). Epstein-Barr virus replication linked to B cell proliferation in inflamed areas of colonic mucosa of patients with inflammatory bowel disease. *Journal of Clinical Virology, 50*(1), 31–36.

Zaragoza, M. M., **Sankaran-Walters, S.,** Canfield, D. R., Hung, J. K., Martinez, E., Ouellette, A. J., & Dandekar, S. (2011). Persistence of gut mucosal innate immune defenses by enteric alpha-defensin expression in the Simian immunodeficiency virus model of AIDS. *Journal of Immunology, 186*(3), 1589–1597.

Mitchell, M. M., Woods, R., Chi, L.-H., **Schmidt, R. J.,** Pessah, I. N., Kostyniak, P. J., & LaSalle, J. M. (2012). Levels of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorder. *Environmental and Molecular Mutagenesis, 53*(8), 589–598.

Schmidt, R. J., Tancredi, D. J., Ozonoff, S., Hansen, R. L., Hartiala, J., Allayee, H., … Hertz-Picciotto, I. (2012). Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. *American Journal of Clinical Nutrition, 96*(1), 80–89.

Chen, L., Bell, E. M., Browne, M. L., Druschel, C. M., Romitti, P. A., **Schmidt, R. J.,** & Burns, T. L., (2012). National Birth Defects Prevention Study. Maternal caffeine consumption and risk of congenital limb deficiencies. *Birth Defects Research. Part A, Clinical and Molecular Teratology, 94*(12), 1003–1043.

Schmidt, R. J., Hansen, R. L., Hartiala, J., Allayee, H., Schmidt, L., Tancredi, D. J., … Hertz-Picciotto, I. (2011). Prenatal vitamins, functional one-carbon metabolism gene variants, and risk for autism in the CHARGE Study. *Epidemiology, 22*(4), 476–485.

Cox, C. L., **Stanhope, K. L.,** Schwarz, J. M., Graham, J. L., Hatcher, B., Griffen, S. C., … Havel, P. J. (2012). Consumption of fructose—but not glucose—sweetened beverages for 10 weeks increases circulating concentrations of uric acid, retinol binding protein-4, and gamma-glutamyl transferase activity in overweight/obese humans. *Nutrition & Metabolism (London), 9*(1), 68.

Cox, C. L., **Stanhope, K. L.,** Schwarz, J. M., Graham, J. L., Hatcher, B., Griffen, S. C., … Keim, N. L. (2012). Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women. *European Journal of Clinical Nutrition, 66*(2), 201–208.

Butler, A. A., Tam, C. S., **Stanhope, K. L.,** Wolfe, B. M., Ali, M. R., O'Keeffe, M., … Havel, P. J. (2012). Low circulating adropin concentrations with obesity and aging correlate with risk factors for metabolic disease and increase after gastric bypass surgery in humans. *Journal of Clinical Endocrinology & Metabolism, 97*(10), 3783–3791.

Stanhope, K. L. (2012). Role of fructose-containing sugars in the epidemics of obesity and metabolic syndrome. *Annual Review of Medicine, 63,* 329–343.

Cummings, B. P., Bettaieb, A., Graham, J. L., **Stanhope, K. L.,** Kowala, M., Haj, F. G., … Havel, P. J. (2012). Vertical sleeve gastrectomy improves glucose and lipid metabolism and delays diabetes onset in UCD-T2DM rats. *Endocrinology, 153*(8), 3620–3632.

Cox, C. L., **Stanhope, K. L.,** Schwarz, J. M., Graham, J. L., Hatcher, B., Griffen, S. C., … Havel, P. J. (2011). Circulating concentrations of monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and soluble leukocyte adhesion molecule-1 in overweight/obese men and women consuming fructose- or glucose-sweetened beverages for 10 weeks. *Journal of Clinical Endocrinology & Metabolism, 96*(12), E2034–E2038.

Stanhope, K. L., Bremer, A. A., Medici, V., Nakajima, K., Ito, Y., Nakano, T., & Havel, P. J. (2011). Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. *Journal of Clinical Endocrinology & Metabolism, 96*(10), E1596–E605.

Cummings, B. P., Bettaieb, A., Graham, J. L., **Stanhope, K. L,** Dill, R., Morton, G. J., … Havel, P. J. (2011). Subcutaneous administration of leptin normalizes fasting plasma glucose in obese type 2 diabetic UCD-T2DM rats. *Proceedings of the National Academy of Sciences, 108*(35), 14670–14675.

Wise, B., Peloquin, C., Choi, H., Lane, N. E., & Zhang, Y. (2012). Impact of age, gender, obesity, and steroid use on quinolone-associated tendon disorders. *American Journal of Medicine, 125*(12), 1228.e23–1228.e28.

Wise, B., Yang, M., Niu, J., Lane, N. E., Harvey, W., Felson, D. T., … Zhang, Y. (2012). Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African-Americans. *Arthritis Care & Research, 64*(6), 847–852.

Wise, B., Felson, D. T., Clancy, M., Niu, J., Neogi, T., Lane, N., … Zhang, Y. Q. (2011). Consistency of knee pain and risk of knee replacement: The Multicenter Osteoarthritis Study. *The Journal of Rheumatology, 38,* 1390–1395.

University of California, San Francisco

Scholars: Lyndsay A. Avalos, Laura Fejerman, A. Jo Chien, Wendy B. Katzman, Susan M. Meffert, Julie A. Schmittdiel, and Julia R. Steinberg

Roberts, S. C. M., **Avalos, L. A.,** Sinkford, D., & Foster, D. G. (2012). Alcohol, tobacco and drug use as reasons for abortion. *Alcohol and Alcoholism, 47*(6), 640–648.

Avalos, L. A., & Mulia, N. (2012). Formal and informal substance use treatment utilization and alcohol abstinence over seven years: Is the relationship different for blacks and whites? *Drug and Alcohol Dependence, 121*(1–2), 73–80.

Avalos, L. A., Galindo, C., & Li, D. K. (2012). A systematic review to calculate background miscarriage rates using life table analysis. *Birth Defects Research Part B: Developmental and Reproductive Toxicology, 94*(6), 417–423.

Avalos, L. A., Kaskutas, L. A., Block, G., Abrams, B., & Li, D.-K. (2011). Does lack of multinutrient supplementation during early pregnancy increase vulnerability to alcohol-related preterm or small-for-gestational-age birth? *Maternal and Child Health Journal, 15*(8), 1324–1332.

Fejerman, L., Chen, G. K., Eng, C., Huntsman, S., Hu, D., Williams, A., … Ziv, E. (2012). Admixture mapping identifies a locus on 6q25 associated with breast cancer risk in U.S. Latinas. *Human Molecular Genetics, 21*(8), 1907–1917.

Via, M., Gignoux, C. R., Roth, L. A., **Fejerman, L.,** Galanter, J., Choudhry, S., … Martínez-Cruzado, J. C. (2011). History shaped the geographic distribution of genomic admixture on the island of Puerto Rico. *PLOS ONE, 6*(1), e16513.

Rugo, H. S., **Jo Chien, A.,** Franco, S. X., Stopeck, A. T., Glencer, A., Lahiri, S., … Dickler, M. N. (2012). A phase II study of lapatinib and bevacizumab as treatment for HER2-overexpressing metastatic breast cancer. *Breast Cancer Research and Treatment, 134*(1), 13–20.

Letourneau, J. M., Ebbel, E. E., Katz, P. P., Katz, A., Ai, W. Z., **Chien, A. J.,** … Rosen, M. P. (2012). Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer, 118*(6), 1710–1717.

Katzman, W., Cawthon, P., Hicks, G. E., Vittinghoff, E., Shepherd, J., Cauley, J. A., … Kado, D. M. (2012). Association of spinal muscle composition and prevalence of hyperkyphosis in healthy community-dwelling older men and women. *Journal of Gerontology. Series A, Biological Sciences and Medical Sciences, 67*(2), 191–195.

Knight, S., Luft, J., Nakagawa, S., & **Katzman, W. B.** (2012). Comparisons of pelvic floor muscle performance, anxiety, quality of life and life stress in women with dry overactive bladder compared with asymptomatic women. *BJU International, 109*(11), 1685–1689.

Pastore, L., & **Katzman, W. B.** (2012). Recognizing myofascial pelvic pain in the woman with chronic pelvic pain. *Journal of Obstetric, Gynecologic, & Neonatal Nursing.* Advance online publication. doi:10:1111/j.1552-6909.2012.01404.x

Katzman, W. B., Vittinghoff, E., & Kado, D. M. (2011). Age-related hyperkyphosis, independent of spinal osteoporosis, is associated with impaired mobility in older community-dwelling women. *Osteoporosis International, 22*(1), 85–90.

Katzman, W. B., Vittinghoff, E., Ensrud, K., Black, D. M., & Kado, D. M. (2011). Increasing kyphosis predicts worsening mobility in older community-dwelling women: A prospective cohort study. *Journal of the American Geriatrics Society, 59*(1), 96–100.

Meffert, S. M., Abdo, A. O., Alla, O. A., Elmakki, Y. O., Omer, A. A., Yousif, S., … Marmar, C. R. (2011). Sudanese refugees in Cairo, Egypt: A randomized controlled trial of interpersonal psychotherapy for trauma, depression and interpersonal violence. *Psychological Trauma: Theory, Research, Practice, and Policy.* doi:10.1037/a0023540

Katon, W., Russo, J., Lin, E., **Schmittdiel, J.,** Ciechanowski, P., Ludman, E., … Von Korff, M. (2012). Cost-effectiveness of a multicondition collaborative care intervention: A randomized controlled trial. *Archives of General Psychiatry, 69*(5), 506–514.

Heisler, M., Hofer, T. P., **Schmittdiel, J. A.,** Selby, J. V., Klamerus, M. L., Bosworth, H., … Kerr, E. A. (2012). Improving blood pressure control through a clinical pharmacist outreach program in

patients with diabetes mellitus in 2 high-performing health systems: The adherence and intensification of medications cluster randomized, controlled pragmatic trial. *Circulation, 125*(23), 2863–2872.

Selby, J. V., **Schmittdiel, J. A.,** Fireman, B., Jaffe, M., Ransom, L. J., Dyer, W., … Hsu, J. (2012). Improving treatment intensification to reduce cardiovascular disease risk: A cluster randomized trial. *BMC Health Services Research, 12*(1), 183.

Daugherty, S. L., Masoudi, F. A., Ellis, J. L., Ho, P. M., **Schmittdiel, J.,** Tavel, H. M., … Magid, D. J. (2011). Age dependent gender differences in hypertension management. *Journal of Hypertension, 29*(5), 1005–1011.

Schmittdiel, J., Karter, A., Dyer, W., Parker, M., Uratsu, C., Chan, J., & Duru, O. K. (2011). The comparative effectiveness of mail order pharmacy vs. local pharmacy use on LDL-C control in new statin users. *Journal of General Internal Medicine, 26*(12), 1396–1402.

Schmittdiel, J., Selby, J. V., Swain, B., Daugherty, S. L., Leong, T. K., Ho, M., … Bibbins-Domingo, K. (2011). Missed opportunities in cardiovascular disease prevention? Low rates of hypertension recognition for women at medicine and obstetrics-gynecology clinics. *Hypertension, 57*(4), 717–722.

Steinberg, J. R., & Finer, L. B. (2012). Coleman, Coyle, Shuping, and Rue make false statements and draw erroneous conclusions in analyses of abortion and mental health using the National Comorbidity Survey. *Journal of Psychiatric Research, 46*(3), 407–408.

Russo, N. F., & **Steinberg, J. R.** (2012). Contraception and abortion: Critical tools for achieving reproductive justice. In J. Chrisler (Ed.), *Reproductive Justice: A Global Concern* (pp. 145–172). Santa Barbara, CA: Praeger.

Steinberg, J. R., Trussell, J., Hall, K. S., & Guthrie, K. (2012). Fatal flaws in a recent meta-analysis on abortion and mental health. *Contraception, 86*(5), 430–437.

Norris, A., Bessett, D., **Steinberg, J. R.,** Kavanaugh, M., De Zordo, S., & Becker, D. (2011). Abortion stigma: A reconceptualization of constituents, causes, and consequences. *Women's Health Issues, 21*(3 Suppl), S49–S54.

Steinberg, J. R., Becker, D., & Henderson, J. T. (2011). Does the outcome of a first pregnancy predict depression, suicidal ideation, or lower self-esteem? Data from the National Comorbidity Survey. *The American Journal of Orthopsychiatry, 81*(2), 193–201.

Steinberg, J. R. & Finer, L. B. (2011). Examining the association of abortion history and current mental health: A reanalysis of the National Comorbidity Survey using a common-risk-factors model. *Social Science and Medicine, 72*(1), 72–82.

Steinberg, J. R. (2011). Later abortions and mental health: Psychological experiences of women having later abortions—A critical review of research. *Women's Health Issues, 21*(3Suppl), S44–S48.

Rubin, L. & **Steinberg, J. R.** (2011). Self-objectification and pregnancy: Are body functionality dimensions protective? *Sex Roles, 65*(7–8), 606–618.

University of Cincinnati

Scholars: Jennifer B. Hillman, Susanna M. Hofmann, Beena D. Kamath-Rayne, Jennifer L. Reed, and Glendon M. Zinser

Hillman, J. B., Dorn, L. D., Loucks, T. L., & Berga, S. L. (2012). Obesity and the hypothalamic-pituitary-adrenal axis in adolescent girls. *Metabolism, 61*(3), 341–348.

Hillman, J. B., Miller, R. J., & Inge, T. H. (2011). Menstrual concerns and intrauterine contraception among adolescent bariatric surgery patients. *Journal of Women's Health, 20*(4), 533–538.

Yi, C. X., Al-Massadi, O., Donelan, E., Lehti, M., Weber, J., Ress, C., … **Hofmann, S. M.** (2012). Exercise protects against high-fat diet-induced hypothalamic inflammation. *Physiology & Behavior, 106*(4), 485–490.

Yi, C. X., Tschöp, M. H., Woods, S. C., **Hofmann, S. M.** (2012). High-fat-diet exposure induces IgG accumulation in hypothalamic microglia. *Disease Models & Mechanisms, 5*(5), 686–690.

Habegger, K. M., Grant, E., Pfluger, P. T., Perez-Tilve, D., Daugherty, A., Bruemmer, D., … **Hofmann, S. M.** (2011). Gherlin receptor deficiency does not affect diet-induced atherosclerosis in low-density lipoprotein receptor-null mice. *Frontiers in Endocrinology, 2,* 67.

Kamath-Rayne, B. D., DeFranco, E. A., & Marcotte, M. (2012). Antenatal steroids for treatment of fetal lung immaturity after 34 weeks of gestation. *Obstetrics & Gynecology, 119*(5), 909–916.

Huppert, J. S., **Reed, J. L.,** Munafo, J. K., Ekstrand, R., Gillespie, G., Holland, C., & Britto, M. T. (2012). Improving notification of sexually transmitted infections: A quality improvement project and planned experiment. *Pediatrics, 130*(2), e2011–e3326.

Wagh, P. K., **Zinser, G. M.,** Gray, J. K., Shrestha, A., & Waltz, S. E. (2012). Conditional deletion of β-catenin in mammary epithelial cells of Ron receptor, Mst1r, overexpressing mice alters mammary tumorigenesis. *Endocrinology, 153*(6), 2735–2746.

Ching, S., Kashinkunti , S., Niehaus, M. D., **Zinser, G. M.** (2011). Mammary adipocytes bioactivate 25-hydroxyvitamin D_3 and signal via vitamin D_3 receptor, modulating mammary epithelial cell growth. *Journal of Cellular Biochemistry, 112*(11), 3393–3405.

University of Colorado, Denver

Scholars: Carrie E. McCurdy, Irene E. Schauer, and Hong Wang

Barbour, L. A., **McCurdy, C. E.,** Hernandez, T. L., & Friedman, J. E. (2011). Chronically increased S6K1 is associated with impaired IRS1 signaling in skeletal muscle of GDM women with impaired glucose tolerance postpartum. *Journal of Clinical Endocrinology & Metabolism, 96*(5), 1431–1441.

Schenk, S., **McCurdy, C. E.,** Philp, A., Chen, M. Z., Holliday, M. J., Bandyopadhyay, G. K., … Olefsky, J. M. (2011). Sirt1 enhances skeletal muscle insulin sensitivity in mice during caloric restriction. *The Journal of Clinical Investigation, 121*(11), 4281–4288.

Pereira, R. I., Snell-Bergeon, J. K., Erickson, C., **Schauer, I. E.,** Bergman, B. C., Rewers, M., & Maahs, D. M. (2012). Adiponectin dysregulation and insulin resistance in type 1 diabetes. *Journal of Clinical Endocrinology & Metabolism, 97*(4), E642–647.

Bergman, B. C., Howard, D., **Schauer, I. E.,** Maahs, D. M., Snell-Bergeon, J. K., Eckel, R. H., … Rewers, M. (2012). Features of hepatic and skeletal muscle insulin resistance unique to type 1 diabetes. *Journal of Clinical Endocrinology & Metabolism, 97*(5), 1663–1672.

Lobo, I. E., Loeb, D. F., Ghushchyan, V., **Schauer, I. E.,** & Huebschmann, A. G. (2012). Missed opportunities for providing low-fat dietary advice to people with diabetes. *Preventing Chronic Disease, 9,* E161.

Maahs, D. M., Nadeau, K., Snell-Bergeon, J. K., **Schauer, I.,** Bergman, B., West, N. A., … Dabelea, D. (2011). Association of insulin sensitivity to lipids across the lifespan in people with Type 1 diabetes. *Diabetic Medicine, 28*(2), 148–155.

Schauer, I. E., Snell-Bergeon, J. K., Bergman, B. C., Maahs, D. M., Kretowski, A., Eckel, R. H., & Rewers, M. (2011). Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: The CACTI study. *Diabetes, 60*(1), 306–314.

Wang, H., & Eckel, R. H. (2012). Lipoprotein lipase in the brain and nervous system. *Annual Review of Nutrition, 32,* 147–160.

Wang, H., Astarita, G., Taussig, M. D., Bharadwaj, K. G., DiPatrizio, N. V., Nave, K. A., … Eckel, R. H. (2011). Deficiency of lipoprotein lipase in neurons modifies the regulation of energy balance and leads to obesity. *Cell Metabolism, 13*(1), 105–113.

University of Illinois at Chicago

Scholars: Joanna E. Burdette, Patricia E. Hershberger, Hyunyoung Jeong, Michelle A. Kominiarek, Leah H. Rubin, Julienne N. Rutherford, and Thasarat S. Vajaranant

Toh, M. F., & **Burdette, J. E.** (2011). Identifying botanical mechanisms of action. *Fitoterapia, 82,* 67–70.

King, S. M., Hilliard, T. S., Wu, L. Y., Jaffe, R. C., Fazleabas, A. T., & **Burdette, J. E.** (2011). The impact of ovulation on fallopian tube epithelial cells: Evaluating three hypotheses connecting ovulation and serous ovarian cancer. *Endocrine-Related Cancer, 18,* 627–642.

Hershberger, P. E., Gallo, A. M., Kavanaugh, K., Olshansky, E., Schwartz, A., & Tur-Kaspa, I. (2012). The decision-making process of genetically at-risk couples considering preimplantation genetic diagnosis: Initial findings from a grounded theory study. *Social Science & Medicine, 74*(10), 1536–1543.

Hershberger, P. E., Kavanaugh, K., Hamilton, R., Klock, S. C., Merry, L., Olshansky, E., & Pierce, P. F. (2011). Development of an informational web site for recruiting research participants: Process, implementation, and evaluation. *CIN: Computers, Informatics, Nursing, 29*(10), 544–551.

Hershberger, P. E., Schoenfeld, C., & Tur-Kaspa, I. (2011). Unraveling preimplantation genetic diagnosis for high-risk couples: Implications for nurses at the front line of care. *Nursing for Women's Health, 15*(1), 36–45.

Koh, K. H., Yang, K., Choi, S. Y., Jung, J. W., Kim, K. P. Zhang, W., & **Jeong, H.** (2012). Estradiol induces cytochrome P450 2B6 expression at high concentrations: Implication in estrogen-mediated gene regulation in pregnancy. *Biochemical Pharmacology, 84*(1), 93–103.

Koh, K. H., Xie, H., Yu, A. M., & **Jeong, H.** (2011). Altered cytochrome P450 expression in mice during pregnancy. *Drug Metabolism and Disposition, 39*(2), 165–169.

Choi, S. Y., Fischer, L., Yang, K., Chung, H., & **Jeong, H.** (2011). Isoform-specific regulation of cytochrome P450 expression and activity by estradiol in female rats. *Biochemical Pharmacology, 81*(6), 777–778.

Cavallari, L. H., **Jeong, H.,** & Bress, A. (2011). Role of cytochrome P450 genotype in the steps toward personalized drug therapy. *Pharmacogenomics and Personalized Medicine, 4,* 123–136.

Landy, H. J., Laughon, K., Bailit, J., **Kominiarek, M. A.,** Gonzalez-Quintero, V. H., Ramirez, M, … Zhang, J. (2011). Characteristics associated with severe perineal and cervical lacerations during vaginal delivery. *Obstetrics & Gynecology, 117,* 627–635.

Hoffman, M. K., Bailit, J. L., Branch, D. W., Burkman, R. T., VanVeldhuisen, P., Lu, L., **Kominiarek, M. A.,** … Zhang, J. (2011). A comparison of obstetrical maneuvers for the acute management of shoulder dystocia. *Obstetrics & Gynecology, 117,* 1272–1278.

Kominiarek, M. A., Zhang, J., VanVeldhuisen, P., Troendle, J., Beaver, J., & Hibbard, J. U. (2011). Contemporary labor patterns: The impact of maternal body mass index. *American Journal of Obstetrics & Gynecology, 205*(3), 244.e1–244.e8.

Shapiro, N., **Kominiarek, M. A.,** Nutescu, E. A., Chevalier, A. B., & Hibbard, J. U. (2011). Low molecular weight heparin in high-risk pregnancy: Dosing and monitoring approaches based on a single center observational study. *Pharmacotherapy, 31*, 678–685.

Kominiarek, M. A., Zork, N., Pierce, S., & Zollinger, T. (2011). Perinatal outcome in the liveborn infant with prenatally diagnosed omphalocele. *American Journal of Perinatology, 28*, 627–633.

Kominiarek, M. A. (2011). Preparing for and managing a pregnancy after bariatric surgery. *Seminars in Perinatology, 35*, 356–361.

Maki, P. M., **Rubin, L. H.,** Cohen, M., Golub, E. T., Greenblatt, R. M., Young, M., Schwartz, R. M., … Cook, J. A. (2012). Depressive symptoms are increased in the early perimenopausal stage in ethnically diverse HIV+ and HIV- women. *Menopause, 19*(11), 1215–1223.

Miller, L. J., McGlynn, A., Suberlak, K. **Rubin, L. H.,** Miller, M., & Pirec, P. (2012). Now what? Effects of on-site assessment on treatment entry after perinatal depression screening. *Journal of Women's Health, 21*(10), 1046–1052.

Bishop, J. R., **Rubin, L. H.,** Reilly, J. L., Akroush, M., Pavuluri, M., & Sweeney, J. A. (2012). Risperidone-associated prolactin elevation and markers of bone turnover during acute treatment. *Therapeutic Advances in Psychopharmacology, 2*(3), 95–102.

Rubin, L. H., Carter, C. S., Drogos, L., Jamadar, R., Pournajafi-Nazarloo, H. P., Sweeney, J. A., & Maki, P. M. (2011). Sex-specific associations between peripheral oxytocin and emotion perception in schizophrenia. *Schizophrenia Research, 130*, 266–270.

Clancy, K. H. B., Hinde, K., & **Rutherford, J. N.** (Eds.). (2012). *Building babies: Primate development in proximate and ultimate perspective*. New York, NY: Springer.

deMartelly, V., Hurley, P., Lawrence, M., Redmond, D. E., & **Rutherford, J. N.** (2012). Comparison of fresh to fixed weights of the vervet monkey (Chlorocebus sabaeus) placenta and its relation to gestational age. *Journal of Medical Primatology, 41*(2), 158–162.

Abrams, E. T. & **Rutherford, J. N.** (2012). Is postpartum hemorrhage a legacy of our evolutionary past? In: L. Keith & C. Jones (Eds.), *Textbook of Postpartum Hemorrhage* (2nd ed.) (pp. 55–63). London, UK: Sapiens.

Rutherford, J. N. (2012). Toward a nonhuman primate model of fetal programming: Phenotypic plasticity of the common marmoset fetoplacental complex. *Placenta, 33*(S2), e35–e39.

Abrams , E. T., & **Rutherford, J. N.** (2011). Framing postpartum hemorrhage as a consequence of human placental biology: An evolutionary and comparative perspective. *American Anthropologist, 113*(3), 417–430.

Vajaranant, T. S., Wu, S., Torres, M., & Varma, R. (2012). The changing face of primary open-angle glaucoma in the United States: Demographic and geographic changes from 2011 to 2050. *American Journal of Ophthalmology, 154*(2), 303–314.

Vajaranant, T. S., & Pasquale, L. R. (2012). Estrogen deficiency accelerates aging of the optic nerve. *Menopause, 19*(8), 942–947.

Vajaranant, T. S., Anderson, R. J., Zelkha, R., Zhang, C., Wilensky, J. T., Edward, D. P., & Shahidi, M. (2011). The relationship between macular cell layer thickness and visual function in different stages of glaucoma. *Eye, 25*(5), 612–618.

University of Kansas Medical Center

Scholars: Christie A. Befort, Kelly Bosak, Sarah L. Kieweg, Jennifer R. Klemp, Clifford W. Mason, and Harsh B. Pathak

Befort, C. A., Klemp J. R., Austin H. L., Perri M. G., Schmitz K. H., Sullivan D. K., & Fabian C. J. (2012). Outcomes of a weight loss intervention among rural breast cancer survivors. *Breast Cancer Research and Treatment, 132*(2), 631–639.

Befort, C. A., Nazir, N., & Perri, M. (2012). Prevalence of obesity among adults from rural and urban areas of the United States: Findings from NHANES (2005–2008). *Journal of Rural Health, 28*(4), 392–397.

Davis, A. M., Bennett, K. J., **Befort, C.,** & Nollen, N. (2011). Obesity and related health behaviors among urban and rural children in the United States: Data from the National Health and Nutrition Examination Survey 2003–2004 and 2005–2006. *Journal of Pediatric Psychology, 36*(6), 669–676.

Befort, C. A., & Klemp, J. R. (2011). Sequelae of breast cancer and the influence of menopausal status at diagnosis among rural breast cancer survivors. *Journal of Women's Health, 20*(9), 1307–1313.

Befort, C. A., Austin, H., & Klemp, J. R. (2011). Weight control needs and experiences among rural breast cancer survivors. *Psycho-Oncology, 20*(10), 1069–1075.

Bosak, K., Pozehl, B., & Yates, B. (2012). Challenges of applying a comprehensive model of intervention fidelity. *Western Journal of Nursing Research, 34*(4), 504–519.

Bosak, K. (2012). Managing metabolic syndrome in women. The Nurse Practitioner, 37(8), 14–21.

Osaka, I., Hills, J. M., **Kieweg, S. L.,** Shinogle, H. E., Moore, D. S., & Hefty, P. S. (2012). An automated image-based method for rapid analysis of Chlamydia infection as a tool for screening antichlamydial agents. *Antimicrobial Agents and Chemotherapy, 56*(8), 4184–4188.

Hu, B., & **Kieweg, S. L.** (2012). The effect of surface tension on the gravity-driven thin film flow of Newtonian and power-law fluids. *Computers & Fluids, 64*, 83–90.

Park, J. G., Ye, Q., Singh, V., **Kieweg, S. L.,** Misra, A., & Spencer, P. (2012). Synthesis and evaluation of novel dental monomer with branched aromatic carboxylic acid group. *Journal of Biomedical Research Part B: Applied Biomaterials.* Advance online publication. doi:10.1002/jbm.b.31987

Singh, V., Misra, A., Marangos, O., Park, J. G., Ye, Q., **Kieweg, S. L.,** & Spencer, P. (2011). Fatigue life prediction of dentin-adhesive interface using micromechanical stress analysis. *Dental Materials, 27*(9), 187–195.

Befort, C., Austin, H., **Klemp, J.,** Fabian, C., Sullivan, D. K., Schmitz, K., & Perri, M. G. (2012). Delivering behavioral weight management to rural breast cancer survivors. *Annals of Behavioral Medicine, 41*(Suppl), s257.

Klemp, J. R., & Kim, S. S. (2012). Fertility preservation in young women with breast cancer. *Journal of Assisted Reproduction and Genetics, 29*(6), 469–472.

Befort, C. A., **Klemp J. R.,** Austin H. L., Perri M. G., Schmitz K. H., Sullivan D. K., & Fabian C. J. (2012). Outcomes of a weight loss intervention among rural breast cancer survivors. *Breast Cancer Research and Treatment, 132*(2), 631–639.

Kim, S. S., **Klemp, J. R.,** & Fabian, C. J. (2011). Breast cancer and fertility preservation. *Fertility and Sterility, 95*(5), 1535–1543.

Klemp, J. R., Frazier, L. M., Glennon, C., Trunececk, J. & Irwin, M. (2011). Improving cancer survivorship care: Oncology nurses' educational needs and preferred methods of learning. *Journal of Cancer Education, 26*(2), 234–242.

Befort, C. A. & **Klemp, J. R.** (2011). Sequelae of breast cancer and the influence of menopausal status at diagnosis among rural breast cancer survivors. *Journal of Women's Health, 20*(9), 1307–1313.

Befort, C. A., Austin, H., & **Klemp, J. R.** (2011). Weight control needs and experiences among rural breast cancer survivors. *Psycho-Oncology, 20*(10), 1069–1075.

Mason, C. W., Buhimschi, I. A., Buhimschi, C., Dong, Y., Weiner, C. P., & Swaan, P. W. (2011). ABC placental transporter expression as a function of pregnancy condition. *Drug Metabolism and Disposition, 39,* 1000–1007.

Ratushny, V., **Pathak, H. B.,** Beeharry, N., Tikhmyanova, N., Xiao, F., Li, T., … Golemis, E. A. (2012). Dual inhibition of SRC and Aurora kinases induces postmitotic attachment defects and cell death. *Oncogene, 31*(10), 1217–1227.

Sasaroli, D., Gimotty, P. A., **Pathak, H. B.,** Hammond, R., Kougioumtzidou, E., Katsaros, D., … Coukos, G. (2011). Novel surface targets and serum biomarkers from the ovarian cancer vasculature. *Cancer Biology & Therapy, 12*(3), 169–180.

University of Maryland, Baltimore

Scholars: Dawn E. Alley, Jessica P. Brown, Sharon M. Gordon, Gregory E. Hicks, Kristen M. Hurley, Laundette P. Jones, Niharika Khanna, Julie A. Markham, Jessica A. Mong, Gail B. Rattinger, Michelle D. Shardell, J. Kathleen Tracy, and Peixin Yang

Alley, D., Lloyd, J., Shaffer, T., & Stuart, B. (2012). Changes in the association between body mass index and Medicare costs, 1997–2006. *Archives of Internal Medicine, 172*(3), 277–278.

Hicks, G. E., Shardell, M., Alley, D. E., Miller, R. R., Bandinelli, S., Guralnik, J., … Ferrucci, L. (2012). Absolute strength and loss of strength as predictors of mobility decline in older adults: The InCHIANTI study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 67*(1), 66–73.

Shardell, M., Alley, D. E., Miller, R. R., **Hicks, G. E.,** & Magaziner, J. (2012). Comparing reports from hip-fracture patients and their proxies: Implications on evaluating sex differences in disability and depressive symptoms. *Journal of Aging and Health, 24*(3), 367–383.

Shardell, M., D'Adamo, C., **Alley, D. E.,** Miller, R. R., **Hicks, G. E.,** Milaneschi, Y., … Ferrucci, L. (2012). Serum 25-hydroxyvitamin D, transitions between frailty states, and mortality in older adults: The Invecchiare in Chianti Study. *Journal of the American Geriatrics Society, 60*(2), 256–264.

Shardell, M. D., Alley, D. E., Hicks, G. E., El-Kamary, S. S., Miller, R. R., Semba, R. D., & Ferrucci, L. (2011). Low-serum carotenoid concentrations and carotenoid interactions predict mortality in U.S. adults: The third national health and nutrition examination survey. *Nutrition Research (New York, N.Y.), 31*(3), 178–189.

Alley, D. E., Hicks, G. E., Shardell, M., Hawkes, W., Miller, R., Craik, R. L., … Magaziner, J. (2011). Meaningful improvement in gait speed in hip fracture recovery. *Journal of the American Geriatrics Society, 59*(9), 1650–1657.

Hicks, G. E., Benvenuti, F., Fiaschi, V., Lombardi, B., Segenni, L., Stuart, M., … Macchi, C. (2012). Adherence to a community-based exercise program is a strong predictor of improved back pain status in older adults: An observational study. *The Clinical Journal of Pain, 28*(3), 195–203.

Katzman, W., Cawthon, P., **Hicks, G. E.,** Vittinghoff, E., Shepherd, J., Cauley, J. A., … Kado, D. M. (2012). Association of spinal muscle composition and prevalence of hyperkyphosis in healthy community-dwelling older men and women. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 67*(2), 191–195.

Sabol, V. K., Resnick, B., Galik, E., Gruber-Baldini, A. L., Morton, P. G., & **Hicks, G. E.** (2011). Exploring the factors that influence functional performance among nursing home residents. *Journal of Aging and Health, 23*(1), 112–134.

Sions, J. M., & **Hicks, G. E.** (2011). Fear-avoidance beliefs are associated with disability in older American adults with low back pain. *Physical Therapy, 91*(4), 525–534.

D'Adamo, C. R., Miller, R. R., **Hicks, G. E.,** Orwig, D. L., Hochberg, M. C., Semba, R. D., … Shardell, M. D. (2011). Serum vitamin E concentrations and recovery of physical function during the year after hip fracture. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 66*(7), 784–793.

D'Adamo, C. R., **Shardell, M. D., Hicks, G. E.,** Orwig, D. L., Hochberg, M. C., Semba, R. D., … Miller, R. R. (2011). Serum vitamin E concentrations among highly functioning hip fracture patients are higher than in nonfracture controls. *Nutrition Research (New York, N.Y.), 31*(3), 205–214.

Baumgarten, M., Rich, S. E., **Shardell, M. D.,** Hawkes, W. G., Margolis, D. J., Langenberg, P., … Magaziner, J. (2012). Care-related risk factors for hospital-acquired pressure ulcers in elderly adults with hip fracture. *Journal of the American Geriatrics Society, 60*(2), 277–283.

D'Adamo, C. R., Miller, R. R., **Shardell, M. D.,** Orwig, D. L., Hochberg, M. C., Ferrucci, L., … Hicks, G. E. (2012). Higher serum concentrations of dietary antioxidants are associated with lower levels of inflammatory biomarkers during the year after hip fracture. *Clinical Nutrition (Edinburgh, Scotland), 31*(5), 659–665.

Quinn, C. C., **Shardell, M. D.,** Terrin, M. L., Barr, E. A., Ballew, S. H., & Gruber-Baldini, A. L. (2011). Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. *Diabetes Care, 34*(9), 1934–1942.

Orwig, D. L., Hochberg, M., Yu-Yahiro, J., Resnick, B., Hawkes, W. G., **Shardell, M.,** … Magaziner, J. (2011). Delivery and outcomes of a yearlong home exercise program after hip fracture: A randomized controlled trial. *Archives of Internal Medicine, 171*(4), 323–331.

Matheny, M. E., Miller, R. R., **Shardell, M. D.,** Hawkes, W. G., Lenze, E. J., Magaziner, J. & Orwig, D. L. (2011). Inflammatory cytokine levels and depressive symptoms in older women in the year after hip fracture: Findings from the Baltimore hip studies. *Journal of the American Geriatrics Society, 59*(12), 2249–2255.

Resnick, B., Galik, E., Boltz, M., Hawkes, W., **Shardell, M.,** Orwig, D., & Magaziner, J. (2011). Physical activity in the post-hip-fracture period. *Journal of Aging and Physical Activity, 19*(4), 373–387.

Neumann, S. A., Maier, K. J., **Brown, J. P.,** Giggey, P. P., Cooper, D. C., Synowski, S. J., … Waldstein, S. R. (2011). Cardiovascular and psychological reactivity and recovery from harassment in a biracial sample of high and low hostile men and women. *International Journal of Behavioral Medicine, 18*(1), 52–64.

Ohrbach, R., Fillingim, R. B., Mulkey, F., Gonzalez, Y., **Gordon, S.,** Gremillion, H., … Slade, G. (2011). Clinical findings and pain symptoms as potential risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control study. *The Journal of Pain: Official Journal of the American Pain Society, 12*(11 Suppl), T27–T45.

Gonzalez, Y. M., Schiffman, E., **Gordon, S. M.,** Seago, B., Truelove, E. L., Slade, G., & Ohrbach, R. (2011). Development of a brief and effective temporomandibular disorder pain screening questionnaire: Reliability and validity. *Journal of the American Dental Association (1939), 142*(10), 1183–1191.

Griffith, K. A., Royak-Schaler, R., Nesbitt, K., Zhan, M., Kozlovsky, A., **Hurley, K.,** … Ryan, A. S. (2012). A culturally specific dietary plan to manage weight gain among African-American breast cancer survivors: A feasibility study. *Nutrition and Health, 21*(2), 97–105.

Hurley, K. M., & Black, M. M. (2011). Introduction to a supplement on responsive feeding: Promoting healthy growth and development for infants and toddlers. *The Journal of Nutrition, 141*(3), 489.

Black, M. M., Quigg, A. M., **Hurley, K. M.,** & Pepper, M. R. (2011). Iron deficiency and iron-deficiency anemia in the first two years of life: Strategies to prevent loss of developmental potential. *Nutrition Reviews, 69*(Suppl 1), S64–70.

Surkan, P. J., Kennedy, C. E., **Hurley, K. M.,** & Black, M. M. (2011). Maternal depression and early childhood growth in developing countries: Systematic review and meta-analysis. *Bulletin of the World Health Organization, 89*(8), 608–615.

Hurley, K. M., Cross, M. B., & Hughes, S. O. (2011). A systematic review of responsive feeding and child obesity in high-income countries. *The Journal of Nutrition, 141*(3), 495–501.

Buckingham-Howes, S., Oberlander, S. E., **Hurley, K. M.,** Fitzmaurice, S., & Black, M. M. (2011). Trajectories of adolescent mother-grandmother psychological conflict during early parenting and children's problem behaviors at age 7. *Journal of Clinical Child and Adolescent Psychology, 40*(3), 445–455.

Jones, L. P., Stefansson, S., Kim, M. S., & Ahn, S. N. (2011). Comparison of radioimmuno and carbon nanotube field-effect transistor assays for measuring insulin-like growth factor-1 in a preclinical model of human breast cancer. *Journal of Nanobiotechnology, 9*, 36.

Johnson, W., Shaya, F. T., **Khanna, N.,** Warrington, V. O., Rose, V. A., Yan, X., … Saunders, E. (2011). The Baltimore partnership to educate and achieve control of hypertension (the BPTEACH trial): A randomized trial of the effect of education on improving blood pressure control in a largely African-American population. *Journal of Clinical Hypertension (Greenwich, Conn.), 13*(8), 563–570.

Cohen, L. A., Bonito, A. J., Eicheldinger, C., Manski, R. J., Macek, M. D., Edwards, R. R., & **Khanna, N.** (2011). Behavioral and socioeconomic correlates of dental problem experience and patterns of health care-seeking. *Journal of the American Dental Association (1939), 142*(2), 137–149.

Cohen, L. A., Bonito, A. J., Eicheldinger, C., Manski, R. J., Macek, M. D., Edwards, R. R., & **Khanna, N.** (2011). Comparison of patient visits to emergency departments, physician offices, and dental offices for dental problems and injuries. *Journal of Public Health Dentistry, 71*(1), 13–22.

Cohen, L. A., Bonito, A. J., Eicheldinger, C., Manski, R. J., Edwards, R. R., & **Khanna, N.** (2011). Health literacy impact on patient-provider interactions involving the treatment of dental problems. *Journal of Dental Education, 75*(9), 1218–1224.

Markham, J. A. (2012). Sex steroids and schizophrenia. *Reviews in Endocrine & Metabolic Disorders, 13*(3), 187–207.

Heng, L. J., **Markham, J. A.,** Hu, X. T., & Tseng, K. Y. (2011). Concurrent upregulation of post-synaptic L-type ca(2+) channel function and protein kinase A signaling is required for the periadolescent facilitation of ca(2+) plateau potentials and dopamine D1 receptor modulation in the prefrontal cortex. *Neuropharmacology, 60*(6), 953–962.

Markham, J. A., & Koenig, J. I. (2011). Prenatal stress: Role in psychotic and depressive diseases. *Psychopharmacology, 214*(1), 89–106.

Taylor, S. B., **Markham, J. A.,** Taylor, A. R., Kanaskie, B. Z., & Koenig, J. I. (2011). Sex-specific neuroendocrine and behavioral phenotypes in hypomorphic type II neuregulin 1 rats. *Behavioural Brain Research, 224*(2), 223–232.

Mong, J. A., & McCarthy, M. M. (2012). Brain sexual differentiation: Clues toward the understanding of neural dysfunctions. *Reviews in Endocrine & Metabolic Disorders, 13*(3), 149.

Schwartz, M. D., & **Mong, J. A.** (2011). Estradiol suppresses recovery of REM sleep following sleep deprivation in ovariectomized female rats. *Physiology & Behavior, 104*(5), 962–971.

Thompson, L. P., Liu, H., Evans, L., & **Mong, J. A.** (2011). Prenatal nicotine increases matrix metalloproteinase 2 (MMP-2) expression in fetal guinea pig hearts. *Reproductive Sciences (Thousand Oaks, Calif.), 18*(11), 1103–1110.

Mong, J. A., Baker, F. C., Mahoney, M. M., Paul, K. N., Schwartz, M. D., Semba, K., & Silver, R. (2011). Sleep, rhythms, and the endocrine brain: Influence of sex and gonadal hormones. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 31*(45), 16107–16116.

Rattinger, G. B., Dutcher, S. K., Chhabra, P. T., Franey, C. S., Simoni-Wastila, L., Gottlieb, S. S., … Zuckerman, I. H. (2012). The effect of dementia on medication use and adherence among Medicare beneficiaries with chronic heart failure. *The American Journal of Geriatric Pharmacotherapy, 10*(1), 69–80.

Zuckerman, I. H., Yin, X., **Rattinger, G. B.,** Gottlieb, S. S., Simoni-Wastila, L., Pierce, S. A., … Stuart, B. (2012). Effect of exposure to evidence-based pharmacotherapy on outcomes after acute myocardial infarction in older adults. *Journal of the American Geriatrics Society, 60*(10), 1854–1861.

Chhabra, P. T., **Rattinger, G. B.,** Dutcher, S. K., Hare, M. E., Parsons, K. L., & Zuckerman, I. H. (2012). Medication reconciliation during the transition to and from long-term care settings: A systematic review. *Research in Social & Administrative Pharmacy: RSAP, 8*(1), 60–75.

Diamantidis, C. J., Seliger, S. L., Zhan, M., Walker, L., **Rattinger, G. B.,** Hsu, V. D., & Fink, J. C. (2012). A varying patient safety profile between black and nonblack adults with decreased estimated GFR. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation, 60*(1), 47–53.

Fialkowski, M. K., McCrory, M. A., Roberts, S. M., **Tracy, J. K.,** Grattan, L. M., & Boushey, C. J. (2012). Dietary patterns are associated with dietary recommendations but have limited relationship to BMI in the communities advancing the studies of tribal nations across the lifespan (CoASTAL) cohort. *Public Health Nutrition, 15*(10), 1948–1958.

Terplan, M., Schluterman, N., McNamara, E. J., **Tracy, J. K.,** & Temkin, S. M. (2012). Have racial disparities in ovarian cancer increased over time? An analysis of SEER data. *Gynecologic Oncology, 125*(1), 19–24.

Tracy, L., Gaff, H. D., Burgess, C., Sow, S., Gravitt, P. E., & **Tracy, J. K.** (2011). Estimating the impact of human papillomavirus (HPV) vaccination on HPV prevalence and cervical cancer incidence in Mali. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 52*(5), 641–645.

Schluterman, N. H., Terplan, M., Lydecker, A. D., & **Tracy, J. K.** (2011). Human papillomavirus (HPV) vaccine uptake and completion at an urban hospital. *Vaccine, 29*(21), 3767–3772.

Tracy, J. K., Traore, C. B., Bakarou, K., Dembele, R., Coulibaly, R. C., & Sow, S. O. (2011). Risk factors for high-risk human papillomavirus infection in unscreened Malian women. *Tropical Medicine & International Health: TM & IH, 16*(11), 1432–1438.

Li, X., Weng, H., Xu, C., Reece, E. A., & **Yang, P.** (2012). Oxidative stress-induced JNK1/2 activation triggers proapoptotic signaling and apoptosis that leads to diabetic embryopathy. *Diabetes, 61*(8), 2084–2092.

Weng, H., Li, X., Reece, E. A., & **Yang, P.** (2012). SOD1 suppresses maternal hyperglycemia-increased iNOS expression and consequent nitrosative stress in diabetic embryopathy. *American Journal of Obstetrics and Gynecology, 206*(5), 448.e1–448.e7.

Yang, P., & Reece, E. A. (2011). Role of HIF-1alpha in maternal hyperglycemia-induced embryonic vasculopathy. *American Journal of Obstetrics and Gynecology, 204*(4), 332.e1–332.e7.

Li, X., Weng, H., Reece, E. A., & **Yang, P.** (2011). SOD1 overexpression in vivo blocks hyperglycemia-induced specific PKC isoforms: Substrate activation and consequent lipid peroxidation in diabetic embryopathy. *American Journal of Obstetrics and Gynecology, 205*(1), 84.e1–84.e6.

University of Michigan

Scholars: Luyun Chen, Kelli S. Hall, Wendy Marder, and Lu Wang

Ramanah, R., Berger, M. B., **Chen, L.,** Ashton-Miller, J. A., & DeLancey, J. O. L. (2012). See it in 3D!: Researchers examined structural links between the cardinal and uterosacral ligaments. *American Journal Obstetrics Gynecology, 207*(5), 437.e1–437.e7.

Larson, K. A., Luo, J., Guire, K. E., **Chen, L.,** Ashton-Miller, J. A., & DeLancey, J. O. L. (2012). 3D analysis of cystoceles using magnetic resonance imaging assessing midline, paravaginal, and apical defects. *International Journal of Urogynecology, 23*(3), 285–293.

Hall, K. S., Moreau, C., & Trussell, J. (2012). Lower use of sexual and reproductive health services among women with frequent religious participation, regardless of sexual experience. *Journal of Women's Health, 21*(7), 739–747.

Marder, W., Ganser, M. A., Romero, V., Hyzy, M. A., Gordon, C., McCune, W. J., & Somers, E. C. (2012). In utero azathioprine exposure and increased utilization of special educational services in children born to mothers with systemic lupus erythematosus. *Arthritis Care & Research*. Advance online publication. doi:10:1002/acr21888

Marder, W., Fisseha, S., Ganser, M., & Somers, E. C. (2012). Ovarian damage during chemotherapy in autoimmune diseases: Broad health implications beyond fertility. *Clinical Medicine Insights: Reproductive Health, 6*, 9–18.

Marder, W., Khalatbari, S., Myles, J., Hench, R., Yalavarthi, S., Lustig, S., … Kaplan, M. (2011). Interleukin-17 as a novel predictor of vascular function in rheumatoid arthritis. *Annals Rheumatic Diseases, 70*(9), 1550–1555.

Marder, W., McCune, W. J., **Wang, L.,** Wing, J. J., Fisseha, S., McConnell, D. S., … Somers, E. C. (2012). Adjunctive GnRH—a treatment attenuates depletion of ovarian reserve associated with cyclophosphamide therapy in premenopausal SLE patients. *Gynecologic Endocrinology, 28*(8), 624–627.

University of Minnesota

Scholars: Daheia J. Barr-Anderson, Jerica M. Berge, Carolyn Garcia, Rahel G. Ghebre, Susanta K. Hui, Vishal Lamba, Katy B. Kozhimannil, Kristine M. Talley, and Bharat Thyagarajan

Camacho-Miñano, M. J., LaVoi, N., & **Barr-Anderson, D. J.** (2012). Interventions to promote physical activity among young and adolescent girls: A systematic review. *Health Education Research, 26*(6), 1025–1049.

Barr-Anderson, D. J., Laska, M. N., Veblen-Mortenson, S., Farbakhsh, K., Dudovitz, B., & Story, M. (2012). A school-based, peer leadership physical activity intervention for 6th graders: Feasibility and results of a pilot study. *Journal of Physical Activity and Health, 9*(4), 492–499.

Barr-Anderson, D. J., Fulkerson, J. A., Smyth, M., Himes, J. H., Hannan, P. J., Holy Rock, B., & Story, M. (2011). Associations of American Indian children's screen-time behavior with parental television behavior, parental perceptions of children's screen time, and media-related resources in the home. *Preventing Chronic Disease, 8*(5), A105.

Barr-Anderson, D. J., AuYoung, M., Whitt-Glover, M. C., Glenn, B. A., & Yancey, A. K. (2011). Integration of short bouts of physical activity into organizational routine a systematic review of the literature. *American Journal of Preventive Medicine, 40*(1), 76–93.

Patnode, C. D., Lytle, L. A., Erickson, D. J., Sirard, J. R., **Barr-Anderson, D. J.,** & Story, M. (2011). Physical activity and sedentary activity patterns among children and adolescents: A latent class analysis approach. *Journal of Physical Activity and Health, 8*(4), 457–467.

McCormack, L. A., Laska, M. N., Veblen-Mortenson, S., **Barr-Anderson, D. J.,** & Story, M. (2011). Weight-related teasing in a racially diverse sample of children. *Journal of the American Dietetic Association, 111*(3), 431–436.

Berge, J. M., Arikian, A., Doherty, W. J., Neumark-Sztainer (2012). Healthy eating and activity in the home environment: Results from multi-family focus groups. *Journal of Nutrition Education and Behavior, 44*(2), 123–131.

Berge, J. M., Larson, N., Bauer, K., & Neumark-Sztainer, D. (2011). Are parents of young children practicing healthy nutrition and physical activity behaviors? *Pediatrics, 127*(5), 881–887.

Eisenberg, M., **Berge, J. M.,** Fulkerson, J., & Neumark-Sztainer, D. (2011). Weight comments by family and significant others in young adulthood. *Body Image, 8*(1), 12–19.

Garcia, C., Hermann, D., Bartels, A., Matamoros, P., Dick-Olson, L., & Guerra de Patino, J. (2012). Development of project wings home visits, a mental health intervention for Latino families using community-based participatory research. *Health Promotion Practice, 13*(6), 755–762.

Stoddard, S., & **Garcia, C.** (2011). Hopefulness about the future among non-U.S. born Latino youth. *Journal of Child Adolescence Psychiatric Nursing, 24*(4), 216–222.

Nachreiner, N. M., **Ghebre, R. G.,** Virnig, B. A., & Shanley, R. (2012). Early work patterns for gynecological cancer survivors in the USA. *Occupational Medicine, 62*(1), 23–28.

Ghebre, R. G., Posthuma, R., Vogel, R. I., Geller, M., & Carson, L. F. (2011). Effect of age and comorbidity on the treatment and survival of elderly patients with vulvar cancer. *Gynecologic Oncology, 121*(3), 565–569.

Hui, S. K., Sharkey, L., Kidder, L. S., Zhang, Y., Fairchild, G., Coghill, K., … Yee, D. (2012). The influence of therapeutic radiation on the patterns of bone marrow in ovary-intact and ovariectomized mice. *PLOS ONE, 7*(8), e42668.

Hui, S. K., Sharma, M., & Bhattacharyya, M. (2012). Liquid scintillation based quantitative measurement of dual radioisotopes (3H and 45Ca) in biological samples for bone remodeling studies. *Applied Radiation and Isotopes, 70*(1), 63–68.

Hui, S. K., Fairchild, G. R., Kidder, L. S., Sharma, M., Bhattacharya, M., Jackson, S., … Yee, D. (2012). Time course of skeletal remodeling following clinically relevant radiation induced bone damage treated with zoledronic acid. *Osteoporosis International, 90*(1), 40–49.

Hui, S. K., Weir, V., Brown, K., & Froelich, J. (2011). Assessing the clinical utility of quantitative computed tomography with a routinely used diagnostic computed tomography scanner in a cancer center. *Journal of Clinical Densitometry, 14*(1), 41–46.

Sharma, M., Bajzer, Z., & **Hui, S. K.** (2011). Development of 41Ca-based pharmacokinetic model for the study of bone remodeling in humans. *Clinical Pharmacokinetics, 50*(3), 191–99.

Pakhomov, S., McInnes, B. T., Lamba, J., Liu, Y., Ghodke, Y., Bhise, N., **Lamba, V.,** & Birnbaum, A. K. (2012). Using PharmGKB to train text mining approaches for identifying potential gene targets for pharmacogenomics studies. *Journal of Biomedical Informatics, 45*(5), 862–869.

Kozhimannil, K. B., Abraham, J. M., & Virnig, B. A. (2012). National trends in health insurance coverage of pregnant and reproductive-age women. *Women's Health Issues, 22*(2), e135–e141.

Kozhimannil, K. B., Avery, M. D., & Terrell, C. A. (2012). Recent trends in clinicians providing care to pregnant women in the United States. *Journal of Midwifery and Women's Health, 57*(5), 433–438.

Kozhimannil, K. B., Huskamp, H. A., Graves, A. J., Soumerai, S. B., Ross-Degnan, D., & Wharam, J. F. (2011). High-deductible health plans and costs and utilization of maternity care. *American Journal of Managed Care, 17*(1), e15–e24.

Kozhimannil, K. B., Adams, A. S., Soumerai, S. B., Busch, A. B., & Huskamp, H. A. (2011). New Jersey's efforts to improve postpartum depression care did not change treatment patterns for women on Medicaid. *Health Affairs, 30*(2), 293–301.

Kozhimannil, K. B., Trinacty, C. M., Busch, A. B., Huskamp, H. A., & Adams, A. S. (2011). Racial/ethnic disparities in postpartum depression care among low-income women. *Psychiatric Services, 62*(6), 619–625.

Kane, R. L., Shamliyan, T., **Talley, K.,** & Pacala, J. (2012). The association between geriatric syndromes and survival. *Journal of the American Geriatrics Society, 60*(5), 896–904.

Shamliyan, T., **Talley, K. M.,** Ramakrishnan, R., & Kane, R. L. (2012). Association of frailty with survival: A systematic literature review. *Ageing Research Reviews.* Advance online publication. doi:10.1016/j.arr.2012.03.001

Talley, K. M. C., Wyman, J. F., Bronas, U., Olson-Kellogg, B., McCarthy, T., & Schaber, P. (2012). Feasibility of recruiting for the Defeating Urinary Incontinence with Exercise Training (DUET) study. *Journal of Women's Health, 21*(10), 1000–1001.

Talley, K. M. C., & Wyman, J. F. (2012). Toileting disabilities in older people living in residential care facilities. *The Gerontologist, 52*(S1), 205–206.

Kane, R. L., **Talley, K. M.,** Shamliyan, T., & Pacala, J. T. (2011). *Common syndromes in older adults related to primary and secondary prevention. Evidence report/technology assessment No. 87* (AHRQ Publication No. 11-05157-EF-1). Rockville, MD: Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.

McMahon, S., **Talley, K. M.,** & Wyman, J. F. (2011). Older people's perspectives on fall risk and fall prevention programs: A literature review. *International Journal of Older People Nursing, 6*(4), 289–298.

Talley, K. M., Wyman, J. F., & Shamliyan, T. A. (2011). State of the science: Conservative interventions for urinary incontinence in frail community-dwelling older adults. *Nursing Outlook, 59*(4), 215–220.

Mueller, C., Goering, M., **Talley, K.,** & Zaccagnini, M. (2011). Taking on the challenge of clinical teaching in nursing homes. *Journal of Gerontological Nursing, 37*(4), 32–38.

Butler, M., **Talley, K. M.,** Burns, R., Ripley, A., Rothman, A., Johnson, P., … Kane, R. L. (2011). *Values of older adults related to primary and secondary prevention. Evidence report/technology assessment No. 84* (Report No. 11-05154-EF-1). Rockville, MD: Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services.

Sood, A., Qualls, C., Schuyler, M., **Thyagarajan, B.,** Steffes, M. W., Smith, L. J., & Jacobs, D. R. (2012). Low serum adiponectin predicts future risk for asthma in women. *American Journal of Respiratory and Critical Care Medicine, 186*(1), 41–47.

Thyagarajan, B., Wang, R., Barcelo, H., Koh, W. P., & Yuan, J. M. (2012). Mitochondrial copy number is associated with colorectal cancer risk. *Cancer Epidemiology, Biomarkers & Prevention, 21*(9), 1574–1581.

Sood, A., Dominic, E., Qualls, C., Steffes, M. W., **Thyagarajan, B.,** Smith, L. J., … Jacobs, D. R. (2011). Serum adiponectin is associated with adverse outcomes of asthma in men but not in women. *Frontiers in Pharmacology, 2*, 55.

Thyagarajan, B., Meyer, K., Smith, L. J., Beckett, W. S., Williams, O. D., Gross, M. D., & Jacobs, D. R. (2011). Serum carotenoid concentrations predict lung function evolution in young adults: The CARDIA study. *American Journal of Clinical Nutrition, 94*(5), 1211–1218.

University of North Carolina at Chapel Hill

Scholars: Anna S. Beeber, Sarah E. Bledsoe-Mansori, Wendy F. Mathes, Eliana M. Perrin, Asheley C. Skinner, Maya Styner, and Stephanie C. Zerwas

Beeber, A. S., & Zimmerman, S. (2012). Adapting the family management style framework for families caring for older adults with dementia. *Journal of Family Nursing, 18*(1), 123–145.

Manuel, J. I., Martinson, M. L., **Bledsoe-Mansori, S. E.,** & Bellamy, J. L. (2012). The influence of stress and social support on depressive symptoms in mothers with young children. *Social Science & Medicine, 75*(11), 2013–2020.

Kanarek, R. B., **Mathes, W. F.,** & D'Anci, K. E. (2012). Exercise promotes positive impression formation towards both men and women. *Appetite, 58*(3), 786–789.

Mathes, W. F., Kelly, S. A., & Pomp, D. (2011). Advances in comparative genetics: Influence of genetics on obesity. *British Journal of Nutrition, 106*(Suppl 1), S1–S10.

Mathes, W. F., Aylor, D. L., Miller, D. R., Churchill, G. A., Chesler, E. J., de Villena, F. P., … Pomp, D. (2011). Architecture of energy balance traits in emerging lines of the Collaborative Cross. *American Journal of Physiology. Endocrinology and Metabolism, 300*(6), E1124–1134.

Aylor, D. L., Valdar, W., **Foulds-Mathes, W.,** Buus, R. J., Verdugo, R. A., Baric, R. S., … Churchill, G. A. (2011). Genetic analysis of complex traits in the emerging Collaborative Cross. *Genome Research, 21*(8), 1213–1222.

Skinner, A. C., Steiner, M. J., Chung, A. E., & **Perrin, E. M.** (2012). Cholesterol curves to identify population norms by age and sex in healthy weight children. *Clinical Pediatrics, 51*(3), 233–237.

Perrin, E. M., Skinner, A. C., & Steiner, M. J. (2012). Parental recall of doctor communication of weight status: National trends from 1999 through 2008. *Archives of Pediatrics & Adolescent Medicine, 166*(4), 317–322.

Chung, A. E., **Skinner, A. C.,** Steiner, M. J., & **Perrin, E. M.** (2012). Physical activity and BMI in a nationally representative sample of children and adolescents. *Clinical Pediatrics, 51*(2), 122–129.

Steiner, M. J., **Skinner, A. C.,** & **Perrin, E. M.** (2011). Fasting might not be necessary before lipid screening: A nationally representative cross-sectional study. *Pediatrics, 128*(3), 463–470.

Jacobson Vann, J. C., Finkle, J., Ammerman, A., Wegner, S., **Skinner, A. C.,** Benjamin, J. T., & **Perrin, E. M.** (2011). Use of a tool to determine perceived barriers to children's healthy eating and physical activity and relationships to health behaviors. *Journal of Pediatric Nursing, 26*(5), 404–415.

Skinner, A. C., Steiner, M. J., & Perrin, E. M. (2012). Self-reported energy intake by age in overweight and healthy-weight children in NHANES, 2001–2008. *Pediatrics, 130*(4), e936–e942.

Sleath, B., Blalock, S. J., Stone, J. L., **Skinner, A. C.,** Covert, D., Muir, K., & Robin, A. L. (2012). Validation of a short version of the glaucoma medication self-efficacy questionnaire. *British Journal of Ophthalmology, 96*(2), 258–262.

Skinner, A. C. (2011). Free speech and duty. Sleeping dogs should have been left to lie [Letter]. *BMJ (Clinical research edition), 342,* d1299.

Sleath, B., Blalock, S., Covert, D., Stone, J. L., **Skinner, A. C.,** Muir, K., & Robin, A. L. (2011). The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. *Ophthalmology, 118*(12), 2398–2402.

Sen, B., Xie, Z., Case, N., **Styner, M.,** Rubin, C. T., & Rubin, J. (2011). Mechanical signal influence on mesenchymal stem cell fate is enhanced by incorporation of refractory periods into the loading regimen. *Journal of Biomechanics, 44*(4), 593–599.

Bulik, C. M., Marcus, M. D., **Zerwas, S.,** Levine, M. D., Hofmeier, S., Trace, S. E., … Kordy, H. (2012). CBT4BN versus CBTF2F: Comparison of online versus face-to-face treatment for bulimia nervosa. *Contemporary Clinical Trials, 33*(5), 1056–1064.

Bulik, C. M, Marcus, M. D., **Zerwas, S.,** Levine, M. D., & La Via, M. (2012). The changing "weightscape" of bulimia nervosa. *The American Journal of Psychiatry, 169*(10), 1031–1036.

Zerwas, S., Von Holle, A., Torgersen, L., Reichborn-Kjennerud, T., Stoltenberg, C., & Bulik, C. M. (2012). Maternal eating disorders and infant temperament: Findings from the Norwegian mother and child cohort study. *International Journal of Eating Disorders, 4*5(4), 546–555.

Meltzer-Brody, S., **Zerwas, S.,** Leserman, J., Holle, A. V., Regis, T., & Bulik, C. (2011). Eating disorders and trauma history in women with perinatal depression. *Journal of Women's Health 20*(6), 863–870.

Hoffman, E. R., **Zerwas, S. C.,** & Bulik, C. M. (2011). Reproductive issues in anorexia nervosa. *Expert Review of Obstetrics & Gynecology, 6*(4), 403–414.

Kim, Y., **Zerwas, S.,** Trace, S. E., & Sullivan, P. F. (2011). Schizophrenia genetics: Where next? *Schizophrenia Bulletin, 37*(3), 456–463.

University of Pittsburgh

Scholars: Steven D. Abramowitch, Janet M. Catov, Chiara Ghetti, and Beth A. Prairie

Feola, A. J., Barone, W., Moalli, P., & **Abramowitch, S. D.** (2012). Characterizing the ex vivo textile and structural properties of synthetic prolapse meshes. *International Urogynecology Journal and Pelvic Floor Dysfunction, 24*(4), 559–564.

Barone, W., Feola, A., Moalli, P., & **Abramowitch, S. D.** (2012). The effect of pregnancy and postpartum recovery on the viscoelastic behavior of the rat cervix. *Journal of Mechanics in Medicine and Biology, 12*(1), 12500091–125000917.

Shepherd, J. P., Feola, A. J., **Abramowitch, S. D.,** & Moalli, P. (2012). Uniaxial biomechanical properties of seven different vaginally implanted meshes for pelvic organ prolapse. *International Urogynecology Journal and Pelvic Floor Dysfunction, 23*(5), 613–20.

McClure, C. K., **Catov, J. M.,** Ness, R. B., Schwarz, E. B. (2012). Lactation and maternal cardiovascular disease among premenopausal women. *American Journal of Obstetrics and Gynecology, 207*(1), 46.e1–46.e8.

Roberts, J. M., & **Catov, J. M.** (2012). Pregnancy is a screening test for later life cardiovascular disease—now what? Research recommendations. *Women's Health Issues, 22*(2), e123–e128.

McClure, C. K., Bodnar, L. M., Ness, R. B., & **Catov, J. M.** (2011). Accuracy of maternal recall of gestational weight gain 4 to 12 years after delivery. *Obesity, 19*(5), 1047–1053.

Laughon, K. S., Powers, R. W., Roberts, J. M., Parana, S., & **Catov, J.** (2011). Caffeine and insulin resistance in pregnancy. *American Journal of Perintology, 28*(7), 571–578.

Laughon, S. K., **Catov, J. M.,** Powers, R. W., Roberts, J. M., & Gandley, R. E. (2011). First trimester uric acid and adverse pregnancy outcomes. *American Journal of Hypertension, 24*(4), 489–495.

Founds, S. A., **Catov, J. M.,** Gallaher, M., Harger, G., Markovic, N., & Roberts, J. M. (2011). Is there evidence of separate inflammatory or metabolic forms of preeclampsia? *Hypertension in Pregnancy, 30*(1), 1–10.

Catov, J. M., Bodnar, L. M., Olsen, J., Olsen, S. J., Nohr, E. A. (2011). Periconceptional multivitamin use and risk of preterm or small-for-gestational-age births in the Danish National British Cohort. *American Journal of Clinical Nutrition, 94*(3), 906–912.

Catov, J. M., Dodge, R., Yamal, J. M., Roberts, J. M, Piller, L. B., Ness, R. B. (2011). Prior preterm or small gestational age birth related to maternal metabolic syndrome. *Obstetrics and Gynecology, 117*(2 Pt 1), 225–232.

Oliphant, S., Lowder, J. L., **Ghetti, C.,** & Zyczynski, H. (2012). The effect of preoperative viewing self-catherization video on anxiety: A randomized controlled trial. *International Urogynecology Journal, 24*(3), 419–424.

Lowder, J. L., **Ghetti, C.,** Nikolajski, C., Oliphant, S., & Zyczynski, H. (2011). Body image perceptions in women with pelvic organ prolapse: A qualitative study. *American Journal of Obstetrics and Gynecology, 204*(5), 441.e1–441.e5.

Okun, M. L., Luther, J. F., Wisniewski, S. R., Sit, D., **Prairie, B. A.,** & Wisner, K. L. (2012). Disturbed sleep, a novel risk factor for preterm birth? *Journal of Women's Health, 21*(1), 54–60.

Prairie, B. A., Wisniewski, S. R., Luther, J., Sit, D., & Wisner, K. L. (2012). Postpartum lipid levels in women with major depression. *Journal of Women's Health, 21*(5), 534–538.

Prairie, B. A., Scheier, M. F., Matthews, K. A., Chang, C. H., & Hess, R. (2011). A higher sense of purpose in life is associated with sexual enjoyment in midlife women. *Menopause, 18*(8), 839–844.

University of Wisconsin–Madison

Scholars: M. Alison Brooks, Sumona Saha, Sana M. Salih, and Chanel Tyler

McGuine, T. A., Hetzel, S., Wilson, J., & **Brooks, A.** (2012). The effect of lace-up ankle braces on injury rates in high school football players. *American Journal of Sports Medicine, 40*(1), 49–57.

Tarini, B. A., **Brooks, M. A.,** & Bundy, D. G. (2012). Fair or foul? A policy impact analysis of the mandatory NCAA sickle cell trait screening program. *Health Services Research, 47*(1 Pt 2), 446–461.

McGuine, T. A., **Brooks, A.,** & Hetzel, S. (2011). The effect of lace-up ankle braces on injury rates in high school basketball players. *American Journal of Sports Medicine, 39*(9), 1840–1848.

Nagle, K. B., & **Brooks, M. A.** (2011). A systematic review of bone health in cyclists. *Sports Health, 3*(3), 235–243.

Brooks, M. A., & McGuine, T. A. (2011). Translating cost-effective injury prevention research into sustainable change on the playing field: The youth injury epidemic. *Archives of Pediatric & Adolescent Medicine, 165*(11), 1049–1050.

Saha, S., Lam, M. E., Roberson, E., Shah, S., LeLeiko, N. S., Lidofsky, S., … Sands, B. E. (2012). Evaluation of possible inflammatory bowel disease: A survey of Rhode Island physicians. *Medicine and Health, Rhode Island, 95*(1), 4–8.

Ikeda, R., Vermeulen, L. S., Lau, E., Jiang, Z., **Saha, S.,** Reichelderfer, M., & Kolesar, J. M. (2012). Stability of infliximab in polyvinyl chloride bags. *American Journal of Health-System Pharmacy, 69*(17), 1509–1512.

Saha, S., Manlolo, J., McGowan, C. E., Reinert, S., & Degli Esposti, S. (2011). Gastroenterology consultations in pregnancy. *Journal of Women's Health, 20*(3), 359–363.

Lee, N. M., & **Saha, S.** (2011). Nausea and vomiting of pregnancy. *Gastroenterology Clinics of North America, 40*(2), 309–34, vii.

Saha, S., Roberson, E., Richie, K., Lindstrom, M. J., Esposti, S. D., & Wald, A. (2011). Women's health training in gastroenterology fellowship: A national survey of fellows and program directors. *Digestive Diseases and Sciences, 56*(3), 751–760.

Roti Roti, E. C., Leisman, S. K., Abbott, D. H., & **Salih S. M.** (2012). Acute doxorubicin insult in the mouse ovary is cell- and follicle-type dependent. *PLOS ONE, 7*(8), e42293.

Roti Roti, E. C., & **Salih, S. M.** (2012). Dexrazoxane ameliorates doxorubicin-induced injury in mouse ovarian cells. *Biology of Reproduction, 86*(3), 96.

Williams-Brown, M. Y., **Salih, S. M.,** Xu, X., Veenstra, T. D., Saeed, M., Theiler, S. K., … Salama, S. A. (2011). The effect of tamoxifen and raloxifene on estrogen metabolism and endometrial cancer risk. *The Journal of Steroid Biochemistry and Molecular Biology, 126*(3–5), 78–86.

Salih, S. M., Kapur, A., Albayrak, S., Salama, S. A., & Magness, R. R. (2011). Pregnancy ameliorates the inhibitory effects of 2-methoxyestradiol on angiogenesis in primary sheep uterine endothelial cells. *Reproductive Sciences, 18*(9), 858–867.

Salih, S. M. (2011). Retrovirus-mediated multidrug resistance gene (MDR1) overexpression inhibits chemotherapy-induced toxicity of granulosa cells. F*ertility and Sterility, 95*(4), 1390–1396.e1–1396.e6.

Tyler, C., Kapur, A., Felder, M., Belisle, J. A., Trautman, C., Gubbels, J. A., … Patankar, M. S. (2012). The mucin MUC16 (CA125) binds to NK cells and monocytes from peripheral blood of women with healthy pregnancy and preeclampsia. *American Journal of Reproductive Immunology, 68*(1), 28–37.

Vanderbilt University

Scholars: Alicia Beeghly-Fadiel, Richard A. Epstein, Dawn C. Newcomb, and Digna R. Velez Edwards

Deming, S. L., Lu, W., **Beeghly-Fadiel, A.,** Zheng, Y., Cai, Q., Long, J., … Zheng, W. (2012). Melatonin pathway genes and breast cancer risk among Chinese women. *Breast Cancer Research and Treatment, 132*(2), 693–699.

Ma, X., **Beeghly-Fadiel, A.,** Lu, W., Shi, J., Xiang, Y. B., Cai, Q., … Zheng, W. (2012). Pathway analyses identify TGFBR2 as potential breast cancer susceptibility gene: Results from a consortium study among Asians. *Cancer Epidemiology, Biomarkers & Prevention, 21*(7), 1176–1184.

Beeghly-Fadiel, A., Zheng, W., Lu, W., Long, J., Zheng, Y., Cai, H., … Shu, X. O. (2012). Replication study for reported SNP associations with breast cancer survival. *Journal of Cancer Research & Clinical Oncology, 138*(6), 1019–1026.

Delahanty, R. J., **Beeghly-Fadiel, A.,** Xiang, Y. B., Long, J., Cai, Q., Wen, W., … Shu, X. O. (2011). Association of obesity-related genetic variants with endometrial cancer risk: A report from the Shanghai Endometrial Cancer Genetics Study. *American Journal of Epidemiology, 174*(10), 1115–1126.

Zhang, B., **Beeghly-Fadiel, A.,** Lu, W., Zheng, Y., Long, J. R., Gu, K., … Zheng, W. (2011). Evaluation of functional genetic variants for breast cancer: Results from the Shanghai Breast Cancer Study. *American Journal of Epidemiology, 173*(10), 1159–1170.

Zhang, B., **Beeghly-Fadiel, A.,** Long, J. R., & Zheng, W. (2011). Genetic variants associated with breast-cancer risk: Comprehensive research synopsis, meta-analysis, and epidemiologic evidence. *The Lancet Oncology, 12*(5), 477–488.

Beeghly-Fadiel, A., Shu, X. O., Lu, W., Long, J. R., Cai, Q., Xiang, Y. B., … Zheng, W. (2011). Genetic variation in VEGF family genes and breast cancer risk: A report from the Shanghai Breast Cancer Genetics Study. *Cancer Epidemiology, Biomarkers & Prevention, 20*(1), 33–41.

Qian, B., Katsaros, D., Lu, L., Canuto, E. M., Benedetto, C., **Beeghly-Fadiel, A.,** Yu, H. (2011). IGF-II promoter specific methylation and expression in epithelial ovarian cancer and their associations with disease characteristics. *Oncology Reports, 25*(1), 203–213.

Beeghly-Fadiel, A., Lu, W., Shu, X. O., Long, J. R., Cai, Q., Gao, Y. T., & Zheng, W. (2011). Matrix metalloproteinase-9 polymorphisms and breast cancer risk: A report from the Shanghai Breast Cancer Study. B*reast Cancer Research and Treatment, 126*(2), 507–513.

Epstein, R. A., Feix, J., Arbogast, P. G., Beckjord, S., & Bobo, W. V. (2012). Changes to the financial responsibility for juvenile court ordered psychiatric evaluations reduces inpatient services utilization. *BMC Health Services Research, 12*(1), 136.

Epstein, R. A., Bobo, W. V., Shelton, R. C., Arbogast, P. G., Morrow, J. A., Wang, W., … Cooper, W. O. (2012). Increasing use of atypical antipsychotics and anticonvulsants during pregnancy. *Pharmacoepidemiology and Drug Safety.* Advance online publication. doi:10.1002/pds.3366

Bobo, W. V., **Epstein, R. A.,** & Shelton, R. C. (2011). Effects of orally-disintegrating versus regular olanzapine tablets on body weight, eating behavior, and glycemic and lipid indices and gastrointestinal hormones: A randomized, open comparison in outpatients with bipolar depression. *Annals of Clinical Psychiatry, 23*(3), 193–201.

Bobo, W. V., **Epstein, R. A.,** Lynch, A., Patton, T. D., Bossaller, N. A., & Shelton, R. C. (2011). A randomized, open comparison of long-acting injectable risperidone and treatment as usual for prevention of relapse, rehospitalization and urgent care referral in frequently relapsing, community-treatment patients with bipolar disorder. *Clinical Neuropharmacology, 34*(6), 224–233.

Epstein, R. A., Bobo, W. V., Cull, M. J., & Gatlin, D. (2011). Sleep and school problems among children and adolescents in state custody. *The Journal of Nervous and Mental Disease, 199*(4), 251–256.

Newcomb, D. C., Boswell, M. G., Huckabee, M. M., Goleniewska, K., Dulek, D. E., Reiss, S., … Peebles, R. S. (2012). IL-13 regulates Th17 secretion of IL-17A in an IL-10-dependent manner. *The Journal of Immunology, 188*(3), 1027–1035.

Polosukhin, V. V., Degryse, A. L., **Newcomb, D. C.,** Jones, B. R., Ware, L. B., Lee, J. W., … Lawson, W. E. (2012). Intratracheal bleomycin causes airway remodeling and airflow obstruction in mice. *Experimental Lung Research, 38*(3), 135–146.

Zhou, W., Dowell, D. R., Huckabee, M. M., **Newcomb, D. C.,** Boswell, M. G., Goleniewska, K., … Peebles, R. S. (2012). Prostaglandin I2 signaling drives Th17 differentiation and exacerbates experimental autoimmune encephalomyelitis. *PLOS ONE, 7*(5), e33518.

Stokes, K. L., Chi, M. H., Sakamoto, K., **Newcomb, D. C.,** Currier, M. G., Huckabee, M. M., … Moore, M. L. (2011). Differential pathogenesis of respiratory syncytial virus (RSV) clinical isolates in BALB/c mice. *Journal of Virology, 85*(12), 5782–5793.

Newcomb, D. C., Boswell, M. G., Zhou, W., Huckabee, M. M., Goleniewska, K., Sevin, C. M., … Peebles, R. S. (2011). Human Th17 cells express a functional IL-13 receptor and IL-13 attenuates IL-17A production. *Journal of Allergy and Clinical Immunology, 127*(4), 1006–1013.

Boswell, M. G., Zhou, W., **Newcomb, D. C.,** Peebles, R. S. (2011). PGI2 as a regulator of CD4+ subset differentiation and function. *Prostaglandins & Other Lipid Mediators, 96*(1–4), 2–6.

Johnson, M. D., Plantinga, T. S., van de Vosse, E., **Velez Edwards, D. R.,** Smith, P. B., Alexander, B. D., … Netea, M. G. (2012). Cytokine gene polymorphisms and the outcome of invasive candidiasis: A prospective cohort study. *Clinical Infectious Diseases, 54*(4), 502–510.

Velez Edwards, D. R., Baird, D. D., Hasan, R., Savitz, D. A., & Hartmann, K. E. (2012). First-trimester bleeding characteristics associate with increased risk of preterm birth: Data from a prospective pregnancy cohort. *Human Reproduction, 27*(1), 54–60.

Cummings, A. C., Jiang, L., **Velez Edwards, D. R.,** McCauley, J. L., Laux, R., McFarland, L. L., … Haines, J. L. (2012). Genome-wide association and linkage study in the Amish detects a novel candidate late-onset Alzheimer disease gene. *Annals of Human Genetics, 76*(5), 342–351.

Velez Edwards, D. R., Aldridge T, Baird DD, Funk MJ, Savitz DA, Hartmann KE. (2012). Periconceptional over-the-counter nonsteroidal anti-inflammatory drug exposure and risk for spontaneous abortion. *Obstetrics & Gynecology, 120*(1), 113–122.

Likis, F. E., **Velez Edwards, D. R.,** Andrews, J. C., Woodworth, A. L., Jerome, R. N., Fonnesbeck, C. J., … Hartmann, K. E. (2012). Progestogens for preterm birth prevention: A systematic review and meta-analysis. *Obstetrics & Gynecology, 120*(4), 897–907.

Sirugo, G., **Velez Edwards, D. R.,** Ryckman, K. K., Bisseye, C., White, M. J., Kebbeh, B., … Williams, S. M. (2012). PTX3 genetic variation and dizygotic twinning in the Gambia: Could pleiotropy with innate immunity explain common dizygotic twinning in Africa? *Annals of Human Genetics, 76*(6), 454–463.

Plantinga, T. S., Johnson, M. D., Scott, W. K., van d Vosse, E., **Velez Edwards, D. R.,** Smith, P. B., … Netea, M. G. (2012). Toll-like receptor 1 polymorphisms increase susceptibility to candidemia. *The Journal of Infectious Diseases, 205*(6), 934–943.

Rosentul, D. C., Plantinga, T. S., Oosting, M., Scott, W. K., **Velez Edwards, D. R.,** Smith, P. B., … Johnson, M. D. (2011). Genetic variation in the dectin-1/CARD9 recognition pathway and susceptibility to candidemia. *The Journal of Infectious Diseases, 204*(7), 1138–1145.

Velez Edwards, D. R., Romero, R., Kusanovic, J. P., Hassan, S. S., Mazaki-Tovi, S., Vaisbuch, E., … Williams, S. M. (2011). Polymorphisms in maternal and fetal genes encoding for proteins involved in extracellular matrix metabolism alter the risk for small-for-gestational-age. *Journal of Maternal-Fetal and Neonatal Medicine, 24*(2), 362–380.

Velez Edwards, D. R., Gilbert, J. R., Jiang, L., Gallins, P. J., Caywood, L., Creason, M., … Scott, W. K. (2011). Successful aging shows linkage to chromosomes 6, 7, and 14 in the Amish. *Annals of Human Genetics, 75*(4), 516–528.

Virginia Commonwealth University

Scholars: Keith D. Baker, Amelia C. Grover, Briana Mezuk, Lora B. Sweeney, and Kazuaki Takabe

Tennessen, J. M., **Baker, K. D.,** Lam, G., Evans, J., & Thummel, C. S. (2011). The Drosophila estrogen-related receptor directs a metabolic switch that supports developmental growth. *Cell Metabolism, 13,* 139–148.

Stevenson, C. E., Gardner, D. F., & **Grover, A. C.** (2012). Patient factors affecting operative times for single-incision trans-axillary robotic-assisted (STAR) thyroid lobectomy: Does size matter? *Annals of Surgical Oncology, 19*(5), 1460–1465.

Ferrada, P. A, Anand, R. J, & **Grover, A. C.** (2011). Virginia Commonwealth University: Committed to the professional growth of women in surgery. *The American Journal of Surgery, 77*(11), 1430–1431.

Mezuk, B., Golden, S. H., Eaton, W. W., & Lee, H. B. (2012). Depression and body composition among older adults. *Aging & Mental Health, 16*(2), 167–172.

Mezuk, B., Edwards, L., Choi, M., Lohman, M., & Lapane, K. L. (2012). Depression and frailty in later life: A synthetic review. *International Journal of Geriatric Psychiatry, 27*(9), 879–892.

Choi, M., Betts Adams, K., & **Mezuk, B.** (2012). Examining the aging process through the stress-coping framework: Application to driving cessation in later life. *Aging & Mental Health, 16*(1), 75–83.

Mezuk, B. (2011). Depression and type 2 diabetes: A call to explore the common cause hypothesis. *Archives of Internal Medicine, 171*, 1040–1041.

Vieweg, W. V., Hasnain, M., **Mezuk, B.,** Levy, J. R., Lesnefsky, E. J., & Pandurangi, A. K. (2011). Depression, stress, and heart disease in earthquakes and takotsubo cardiomyopathy. *American Journal of Medicine, 124*(10), 900–907.

Mezuk, B., Bohnert, A., Ratliff, S., & Zivin, K. (2011). Job strain, depressive symptoms, and drinking behavior among older adults: Results from the Health and Retirement Study. *Journal of Gerontology Series B: Psychological Sciences and Social Sciences, 66B*(4), 426–434.

Mezuk, B., Kershaw, K. N., Hudson, D., Lim, K. A., & Ratliff, S. (2011). Job strain, workplace discrimination and hypertension among older workers: The Health & Retirement Study. *Race and Social Problems, 3*(1), 38–50.

Scott, T., Maysuyama, R., & **Mezuk, B.** (2011). The relationship between treatment settings and diagnostic attributions of depression among African-Americans. *General Hospital Psychiatry, 33*(1), 66–74.

Parsons, P., **Mezuk, B.,** Ratliff, S., & Lapane, K. L. (2011). Subsidized housing not subsidized health: Health status and fatigue among elders in public housing and other community settings. *Ethnicity & Disease, 21*, 85–90.

Wu, Z., **Sweeney, L. B.,** Ayoob, J. C., Chak, K., Andreone, B. J., Ohyama, T., … Kolodkin, A. L. (2011). A combinatorial semaphorin code instructs the initial steps of sensory circuit assembly in the Drosophila CNS. *Neuron, 70*(2), 281–298.

Sweeney, L. B., Chou, Y. H., Wu, Z., Joo, W., Komiyama, T., Potter, C. J., … Luo, L. (2011). Secreted semaphorins from degenerating larval ORN axons direct adult projection neuron dendrite targeting. *Neuron, 72*(5), 734–747.

Rashid, O., & **Takabe, K.** (2012). The evolution of the role of surgery in the management of breast cancer lung metastasis. *Journal of Thoracic Disease, 4*(4), 420–424.

Rashid, O., Nagahashi, M., & **Takabe, K.** (2012). Management of massive soft tissue defects: The use of INTEGRA® artificial skin after necrotizing soft tissue infection of the chest. *Journal of Thoracic Disease, 4*(3), 331–335.

Nagahashi, M., Ramachandran, S., Kim, E. Y., Allegood, J. C., Rashid, O. M., Yamad, A., … **Takabe, K.** (2012). Sphingosine-1-phosphate produced by sphingosine kinase 1 promotes breast cancer progression by stimulating angiogenesis and lymphangiogenesis. *Cancer Research, 72*(3), 726–735.

Takabe, K. (2011). Is T790M mutation the key in development of resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR–TKIs)? *Journal of Thoracic Disease, 3*(1), 1–3.

Washington University in St. Louis

Scholars: Christina A. Gurnett, Jeffrey P. Henderson, Jonas Marschall, Tessa Madden, Joan K. Riley, and Julie K. Schwarz

Dobbs M. B., & **Gurnett C. A.** (2012). Genetics of clubfoot. *Journal of Pediatric Orthopaedics, Part B, 21*(1), 7–9.

Alvarado, D. H., McCall, K., Aferol, H., Silva, M. J., Garbow, J. R., Spees, W. M., … , **Gurnett, C. A.** (2011). Pitx1 haploinsufficiency causes clubfoot in humans and a clubfoot-like phenotype in mice. *Human Molecular Genetics, 20*(20), 3943–3952.

Marschall, J., Zhang, L., Foxman, B., Warren, D. K., **Henderson J. P.,** & CDC Prevention Epicenters Program. (2012). Both host and pathogen factors predispose to *Escherichia coli* urinary-source bacteremia in hospitalized patients. *Clinical Infectious Diseases, 54*(12), 1692–1698.

Hadjifrangiskou, M., Kostakioti, M., Chen, S. L., **Henderson, J. P.,** Greene, S. E., & Hultgren, S. J. (2011). A central metabolic circuit controlled by QseC in pathogenic *Escherichia coli. Molecular Microbiology, 80*(6), 1516–1529.

Lv, H., Hung, C. S., Chaturvedi, K. S., Hooton, T. M., & **Henderson, J. P.** (2011). Development of an integrated metabolomic profiling approach for infectious diseases research. *The Analyst, 136*(22), 4752–4763.

Cusumano, C. K., Pinkner, J. S., Han Z., Greene, S. E., Crowley, J. R., **Henderson J. P.,** … Hultgren, S. J. (2011). Treatment and prevention of urinary tract infection with orally active FimH inhibitors. *Science Translational Medicine, 3*(109), 109ra115.

Lv, H., & **Henderson, J. P.** (2011). Yersinia high pathogenicity island genes modify the *Escherichia coli* primary metabolome independently of siderophore production. *Journal of Proteome Research, 10*(12), 5547–5554.

Marschall, J., Ota, K. N., **Henderson, J. P.,** & Warren, D. K. (2011). Not all nosocomial *Escherichia coli* bacteriurias are catheter associated. *Infection Control and Hospital Epidemiology, 32*(11), 1140–1142.

Xu, H., Wade, J. A., Peipert, J. F., Zhao, Q., **Madden, T.,** & Secura, G. M. (2012). Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstetrics & Gynecology, 120*(1), 21–26.

McNicholas, C., Hotchkiss, T., **Madden, T.,** Zhao, Q., Allsworth, J., & Peipert J. F. (2012). Immediate postabortion intrauterine device insertion: Continuation and satisfaction. *Women's Health Issues, 22*(4), e365–e369.

Madden, T., Proehl, S., Allsworth, J. E., Secura, G. M., & Peipert, J. F. (2012). Naproxen or estradiol for bleeding and spotting with the Levonorgestrel Intrauterine System: A randomized controlled trial. *American Journal of Obstetrics & Gynecology, 206*(2), 129–130.

Shih, S. L., Kebodeaux, C. A., Secura, G. M., Allsworth, J. E., **Madden T.,** & Peipert J. F. (2011). Baseline correlates of inconsistent and incorrect condom use among sexually active women in the Contraceptive CHOICE Project. *Sexually Transmitted Diseases, 38*(11), 1012–1019.

Rose, J. A., Rabenold, J. J., Parast, M. M., Milstone, D. S., Abrahams, V. M., & **Riley J. K.** (2012). Peptidoglycan induces necrosis and regulates cytokine production in murine trophoblast stem cells. *American Journal of Reproductive Immunology, 66*(3), 209–222.

Jungheim, E. S., Louden, E. D., Chi, M. M., Frolova, A. I., **Riley, J. K.,** & Moley K. H. (2011). Preimplantation exposure of mouse embryos to palmitic acid results in fetal growth restriction followed by catch-up growth in the offspring. *Biology of Reproduction, 85*(4), 678–683.

Shokeen, M., Zheleznyak, A., Wilson, J. M., Jiang, M., Liu, R., **Schwarz, J. K.,** … Anderson, C. J. (2012). Molecular imaging of very late antigen-4 (α4β1 integrin) in the premetastatic niche. *Journal of Nuclear Medicine, 53*(5), 779–786.

Yale University

Scholars: Elise E. DeVito, Megan V. Smith, Azure B. Thompson, and Tomoko Udo

Sofuoglu, M., **DeVito, E. E.,** Waters, A. J., & Carroll, K. M. (2012). Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology, 64*(1), 452–463.

Jamadar, S., **DeVito, E. E.,** Jiantonio, R. E., Meda, S. A., Stevens, M. C., Potenza, M. N., … Pearlson, G. D. (2012). Memantine, an NMDA-receptor antagonist, differentially influences fMRI activity in individuals with and without a family history of alcoholism. *Psychopharmacology, 222*(1), 129–140.

DeVito, E. E., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., Kober, H., & Potenza, M. N. (2012). A preliminary study of the neural effects of behavioral therapy for substance use disorders. *Drug and Alcohol Dependence, 122*(3), 228–235.

de Wit, S., Standing, H. R., **DeVito, E. E.,** Robinson, O. J., Ridderinkhof, K. R., Robbins, T. W., & Sahakian B. J. (2012). Reliance habits at the expense of goal-directed control following dopamine precursor depletion. *Psychopharmacology, 219*(2), 621–631.

Yonkers, K. A., Norwitz, E. R., **Smith, M. V.,** Lockwood, C. J., Gotman, N., Lin, H., … Belanger, K. (2012). Major depressive disorder and serotonin reuptake inhibitor treatment as risk factors for preterm birth. *Epidemiology, 23*(5), 677–685.

Smith, M. V., Mayes, L. C., Sung, A., Shah, B., Klein, D. S., & Yonkers, K. A. (2012). Neurobehavioral assessment of infants born at term and in utero exposure to serotonin reuptake inhibitors. *Early Human Development.* Advance online publication. doi:10.1016/j.earlhumdev.2012.08.001

Yonkers, K. A., Gotman, N., **Smith, M. V.,** Forray, A., Belanger, K., Brunetto, W., … Lockwood, C. J. (2011). Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? *Epidemiology, 22,* 848–854.

Smith, M. V., & Lincoln, A. K. (2011). Integrating social epidemiology into public health research and practice: The case of maternal depression. *American Journal of Public Health, 101*(6), 990–994.

Smith, M. V., Shao, L., Lin, H., Howell, H., & Yonkers, K. A. (2011). Perinatal depression and birth outcomes in a Healthy Start project. *Maternal and Child Health Journal, 15*(3), 401–409.

Melnick, G., Duncan, A., **Thompson, A.,** Wexler, H. K., Chaple, M., & Cleland, C. M. (2011). Racial disparities in substance abuse treatment and the ecological fallacy. *Journal of Ethnicity in Substance Abuse, 10*(3), 226–245.

Thompson, A. B., Moon-Howard, J., & Messeri, P. A. (2011). Smoking cessation advantage among adult initiators: Does it apply to black women? *Nicotine & Tobacco Research, 13*(1), 15–21.

Cohn, A. M., Cameron, A. Y., **Udo, T.,** Hagman, B. T., & Mitchell, J. (2012). Delineating potential mechanisms of implicit alcohol cognitions: Drinking restraint, negative affect, and their relationship with approach alcohol associations. *Psychology of Addictive Behaviors, 26*(2), 318–324.

Ray, S., Mun, E. Y., Buckman, J. B., **Udo, T.,** & Bates, M. E. (2012). Memory for emotional picture cues during acute alcohol intoxication. *Journal of Studies on Alcohol and Drugs, 73*(5), 718–725.

APPENDIX E

Selected FY 2011–FY 2012 SCOR Publications, Including Sex and Gender Analyses

Harvard University SCOR—PI: Jill Goldstein, Ph. D.

Alim, Z., Hartshorn, C., Mai, O., Stitt I., Clay, C., Tobet, S., & Boehm, U. (2012). Gonadotrope plasticity at cellular and population levels. *Endocrinology, 153*, 4729–4739.

Anastario, M., Salafia, C. M., Fitzmaurice, G., & Goldstein, J. M. (2012). Impact of fetal versus perinatal hypoxia on sex differences in childhood outcomes: developmental timing matters. *Social Psychiatry and Psychiatric Epidemiology, 47*, 455–464.

Boersma, G. J., Salton, S. R., Spritzer, P. M., Steele, C. T., & Carbone, D. L. (2012). Models and mechanisms of metabolic disease: genes, stress and the HPA and HPG axes. *Hormone and Metabolic Research, 44*, 598–606.

Carbone, D. L., Zuloaga, D. G., Hiroi, R., Foradori, C. D., LeGare, M. E., & Handa, R. J. (2012). Prenatal dexamethasone exposure potentiates diet-induced hepatosteatosis and decreases plasma IGF-1 in a sex specific fashion. *Endocrinology, 153*, 295–306.

Carbone, D. L., Zuloaga, D. G., Lacagnina, A. F., & Handa, R. J. (2012). A unique population of prepro-thyrotropin releasing hormone expressing neurons in the lateral hypothalamus that are activated by leptin and altered by prenatal glucocorticoid exposure. *Brain Research, 1477*, 19–26.

Carbone, D. L., Zuloaga, D. G., Lacagnina, A. F., McGivern, R. F., & Handa, R. J. (2012). Exposure to dexamethasone during late gestation causes female-specific decreases in core body temperature and prepro-thyrotopin releasing hormone expression in the paraventricular nucleus of the hypothalamus in rats. *Physiology & Behavior, 108*, 6–12.

Fernández-Guasti, A., Fiedler J., Herrera L., & Handa, R. J. (2012). Sex, stress and mood disorders: at the intersection of adrenal and gonadal hormones. *Hormone and Metabolic Research, 44*, 607–618.

Frahm, K. A., Schow, M. J., & Tobet, S. A. (2012). The vasculature within the paraventricular nucleus of the hypothalamus in mice varies as a function of development, subnuclear location, and GABA signaling. *Hormone and Metabolic Research, 44*, 1–6.

Goldstein, J. M., Cherkerzian, S., Buka, S., Fitzmaurice, G., Susser, E., Hornig, M., Gillman, M., Factor-Litvak, P., & Sloan, R. P. (2012). Sex-specific impact of maternal-fetal risk factors on depression and cardiovascular risk 40 years later. *Journal of Developmental Origins of Health and Disease, 2*, 353–364.

Goldstein, J. M., Holsen, L., Handa, R., & Tobet, S. (2012). Sex differences in HPA and HPG axes dysregulation in major depressive disorder: The role of shared brain circuitry between hormones and mood. In D. Pfaff & Y. Christen (Eds.), *Research and perspectives in endocrine Interactions: Multiple origins of sex differences in brain: Neuroendocrine functions and their pathologies* (pp. 139–163). Heidelberg, Germany: Springer-Verlag.

Holsen, L. M., Lee, J.-H., Spaeth, S. B., Ogden, L. A., Klibanski, A., Whitfield-Gabrieli, S., Sloan, R., & Goldstein, J. M. (In press). Brain hypoactivation, autonomic nervous system dysregulation, and gonadal hormones in depression: a preliminary study. *Neuroscience Letters, 514*, 57–61.

Holsen, L. M., Spaeth, S. B., Lee, J.-H., Ogden, L. A., Klibanski, A., Whitfield-Gabrieli, S., & Goldstein, J. M. (2011). Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. *Journal of Affective Disorders, 131*, 379–387.

Lebron-Milad, K., Abbs, B., Milad, M., Linman, C., Rougemount-Bücking, A., Zeidan, M. A., Holt, D. J., & Goldstein, J. M. (2012). Sex differences in the neurobiology of fear conditioning and extinction: a preliminary fMRI study of shared sex differences with stress-arousal circuitry. *Biology of Mood and Anxiety Disorders, 2*, 7.

Lynn, N. S., Tobet, S., Henry, C. S., & Dandy, D. S. (2012). Mapping spatiotemporal molecular distributions using a microfluidic array. *Analytical Chemistry, 84*, 1360–1366.

Nugent, B. M., Tobet, S. A., Lara, H. E., Lucion, A. B., Wilson, M. E., Recabarren, S. E., & Paredes, A. H. (2012). Hormonal programming across the lifespan. *Hormone and Metabolic Research, 44*, 577–586.

Pettine, W., Jibson, M., Chen, T., Tobet, S., Nikkel P., & Henry, C. S. (2012). Characterization of a novel microelectrode array and sensor geometries for detection of neurotransmitters. *Sensors Journal, 12*, 1187–1192.

Stratton, M. S., Searcy, B. T., & Tobet, S. A. (2011). GABA regulates corticotropin releasing hormone levels in the paraventricular nucleus of the hypothalamus in newborn mice. *Physiology & Behavior, 104*, 327–333.

Zhang, Q., Bouma, G. J., McClellan, K., & Tobet, S. (2012). Hypothalamic expression of snoRNA Snord116 is consistent with a link to the hyperphagia and obesity symptoms of Prader-Willi syndrome. *International Journal of Developmental Neuroscience, 30*, 479–485.

Zuloaga, D. G., Carbone, D. L., & Handa, R. J. (2012). Prenatal dexamethasone selectively decreases calretinin expression in the adult female lateral amygdala. *Neuroscience Letters, 521*, 109–114.

Zuloaga, D. G., Carbone, D. L., Hiroi, R., Chong, D. L., & Handa, R. J. (2011). Dexamethasone induces apoptosis in the developing rat amygdala in an age-, region-, and sex-specific manner. *Neuroscience, 199*, 535–547.

Zuloaga, D. G., Carbone, D. L., Quihuis, A., Chong, D. L., & Handa, R. J. (2012). Perinatal dexamethasone-induced alterations in apoptosis within the hippocampus and paraventricular nucleus of the hypothalamus are age- and sex-dependent. *Journal of Neuroscience Research, 90*, 1403–1412.

Zuloaga, K. L., O'Connor, D. T., Handa, R. J., & Gonzales, R. J. (2012). Estrogen receptor beta dependent attenuation of cytokine-induced cyclooxygenase-2 by androgens in human brain vascular smooth muscle cells and rat mesenteric arteries. *Steroids, 77*, 835–844.

Zuloaga, K. L., Swift S. N., Gonzales, R. J., Wu, T. J., & Handa, R. J. (2012). The androgen metabolite, 5α-androstane-3β, 17β-diol, decreases cytokine-induced cyclooxygenase-2, vascular cell adhesion molecule-1 expression, and P-glycoprotein expression in human brain microvascular endothelial cells. *Endocrinology, 153*, 5949–5960.

Medical University of South Carolina SCOR—PI: Kathleen Brady, M.D., Ph.D.

Back, S. E., Lawson, K. M., Singleton, L. M., & Brady, K. T. (2011). Characteristics and correlates of men and women with prescription opioid dependence. *Addictive Behaviors, 36*, 829–834.

Back, S. E., Payne, R. L., Wahlquist, A. H., Carter, R. E., Stroud, Z., Haynes, L., Hillhouse, M., Brady, K. T., & Ling, W. (2011). Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. *American Journal of Drug Alcohol Abuse, 37*, 313–323.

Becker, H. C., Lopez, M. F., & Doremus-Fitzwater, T. L. (2011). Effects of stress on alcohol drinking: a review of animal studies. *Psychopharmacology (Berlin, Germany), 218*, 131–156.

Boger, H. A., Mannangatti, P., Samuvel, D. J., Saylor, A. J., Bender, T. S., McGinty, J. F., Fortress, A. M., & Brady, K. T. (2011). Stress- and cue-elicited craving and reactivity in marijuana-dependent individuals. *Psychopharmacology (Berlin, Germany), 218*, 49–58.

Buffalari, D. M., Baldwin, C. K., Feltenstein, M. W., & See, R. E. (2012). Corticotrophin releasing factor (CRF) induced reinstatement of cocaine-seeking in male and female rats. *Physiology and Behavior, 105*, 209–214.

Buffalari, D. M., & See, R. E. (2011). Inactivation of the bed nucleus of the stria terminalis attenuates conditioned cue-induced reinstatement and its potentiation by yohimbine in an animal model of relapse. *Psychopharmacology, 213*, 19–27.

Carpenter, M. J., Sterba, K. R., Boatright, A. S., & West, R. (2011). 'Closet' quit attempts: prevalence, correlates and association with outcome. *Addiction, 106*, 2214–2220.

Cason, A. M., Fallon, R. V., & Aston-Jones, G. (2012). Role of orexin/hypocretin in conditioned sucrose-seeking. *Psychopharmacology (Berlin, Germany), 226*, 155-165.

Cropsey, K. L., Jackson, D. O., Hale, G. J., Carpenter, M. J., & Stitzer, M. L. (2011). Impact of self-initiated pre-quit smoking reduction on cessation rates: results of a clinical trial of smoking cessation among female prisoners. *Addictive Behaviors, 36*, 73–78.

De Bellis, M. D., Spratt, E. G., & Hooper, S. R. (2011). Neurodevelopmental biology associated with childhood sexual abuse. *Journal of Child Sexual Abuse, 20*, 548–587.

DeSantis, S. M., Baker, N. L., Back, S. E., Spratt, E., Ciolino, J. D., Moran-Santa Maria, M. M., Dipankar, B., & Brady, K. T. (2011). Gender differences in the effect of early life trauma on hypothalamic-pituitary-adrenal axis functioning. *Depression and Anxiety, 28*, 383–392.

Farrugia, P. L., Mills, K. L., Barrett, E., Back, S. E., Teesson, M., Baker, A., Sannibale, C., Hopwood, S., Rosenfeld, J., Merz, S., & Brady, K. T. (2011). Childhood trauma among individuals with co-morbid substance use and post-traumatic stress disorder. *Mental Health and Substance Use, 4*, 314–326.

Feltenstein, M. W., Ghee, S. M., & See, R. E. (2012). Nicotine self-administration and reinstatement of nicotine-seeking in male and female rats. *Drug and Alcohol Dependence, 121*, 240–246.

Feltenstein, M. W., Henderson, A. R., & See, R. E. (2011). Enhancement of cue reinstatement of cocaine-seeking in rats by yohimbine: sex differences and the role of the estrous cycle. *Psychopharmacology, 216*, 53–62.

Guille, C., & Sen, S. (2012). Prescription drug use and self-prescription among training physicians. *JAMA Internal Medicine, 172*, 371-372.

Hartwell, K. J., Back, S. E., McRae-Clark, A. L., Shaftman, S., & Brady, K. T. (2012). Motives for using: a comparison of opiate, marijuana and cocaine dependent individuals. *Addictive Behaviors, 37*, 373–378.

Jardin, B. F., & Carpenter, M. J. (2012). Predictors of quit attempts and abstinence among smokers not currently interested in quitting. *Nicotine & Tobacco Research, 14*, 1197–1204

Lopez, M. F., Doremus-Fitzwater, T. L., & Becker, H. C. (2011). Chronic social isolation and chronic variable stress during early development induce later elevated ethanol intake in adult C57BL/6J mice. *Alcohol, 45*, 355–364.

Lopez, M. F., Grahame, N. J., & Becker, H. C. (2011). Development of ethanol withdrawal-related sensitization and relapse drinking in mice selected for high- or low-ethanol preference. *Alcoholism: Clinical and Experimental Research, 35*, 953–962.

Lopez, M. F., Griffin, W. C., 3rd, Melendez, R. I., & Becker, H. C. (2012). Repeated cycles of chronic intermittent ethanol exposure leads to the development of tolerance to aversive effects of ethanol in C57BL/6J mice. *Alcoholism: Clinical and Experimental Research, 36*, 1180–1187.

McCart, M. R., Zajac, K., Danielson, C. K., Strachan, M., Ruggiero, K. J., Smith, D. W., Saunders, B. E., & Kilpatrick, D. G. (2011). Interpersonal victimization, posttraumatic stress disorder, and change in adolescent substance use prevalence over a ten-year period. *Journal of Clinical Child & Adolescent Psychology, 40*, 136–143.

McRae-Clark, A. L., Carter, R. E., Price, K. L., Baker, N. L., Thomas, S., Saladin, M. E., Giarla, K., Nicholas, K., Reichel, C. M., Ramsey, L. A., Schwendt, M., McGinty, J. F., & See, R. E. (2012). Methamphetamine-induced changes in the object recognition memory circuit. *Neuropharmacology, 62*, 1119–1126.

Prisciandaro, J. J., McRae-Clark, A. L., Moran-Santa Maria, M. M., Hartwell, K. J., & Brady, K. T. (2011). Psychoticism and neuroticism predict cocaine dependence and future cocaine use via different mechanisms. *Drug and Alcohol Dependence, 116*, 80–85.

Reichel, C. M., Schwendt, M., McGinty, J. F., Olive, M. F., & See, R. E. (2011). Loss of object recognition memory produced by extended access to methamphetamine self-administration is reversed by positive allosteric modulation of metabotropic glutamate receptor 5. *Neuropsychopharmacology, 36*, 782–792.

Reichel, C. M., & See, R. E. (2011). Chronic modafinil effects on drug-seeking following methamphetamine self-administration in rats. *International Journal of Neuropsychopharmacology, 15*, 919–929.

Richardson, K. A., & Aston-Jones, G. (2012). Lateral hypothalamic orexin/hypocretin neurons that project to ventral tegmental area are differentially activated with morphine preference. *Journal of Neuroscience, 32*, 3809–3817.

Saladin, M. E., Gray, K. M., Carpenter, M. J., LaRowe, S. D., DeSantis, S. M., & Upadhyaya, H. P. (2012). Gender differences in reactivity to smoking and negative affect/stress cues. *American Journal on Addictions, 21*, 210–220.

Schwendt, M., Reichel, C. M., & See, R. E. (2012). Extinction-dependent alterations in corticostriatal mGluR2/3 and mGluR7 receptors following chronic methamphetamine self-administration in rats. *PLOS ONE, 7*(3), e34299.

See, R. E., & Waters, R. P. (2011). Pharmacologically-induced stress: a cross-species probe for translational research in drug addiction and relapse. *American Journal of Translational Research, 3*, 81–89.

Spratt, E. G., Friedenberg, S., LaRosa, A., De Bellis, M. D., Macias, M. M., Summer, A. P., Hulsey, T. C., Runyan, D. K., & Brady, K. T. (2012). The effects of early neglect on cognitive, language, and behavioral functioning in childhood. *Psychology, 3*, 175–182.

Zaman, V., Huang, P., Middaugh, L. D., Randall, P. K., Jayanthi, L. D., Rohrer, B., Helke, K. L., Granholm, A. C., & Ramamoorthy, S. (2011). Effects of brain-derived neurotrophic factor on dopaminergic function and motor behavior during aging. *Genes, Brain, and Behavior, 10*, 186–198.

Zhou, L., Ghee, S. M., Chan, C., Lin, L., Cameron, M. D., Kennym P. J., & See, R. E. (2012). Orexin-1 receptor mediation of cocaine-seeking in male and female rats. *Journal of Pharmacology and Experimental Therapeutics, 340*, 801–809.

Zhou, L., Sun, W. L., & See, R. E. (2011). Orexin receptor targets for anti-relapse medication development. *Pharmaceuticals, 4*, 804–821.

Northwestern University SCOR—PI: Andrea Dunaif, M.D.

Mauvais-Jarvis, F. (2012). Estrogen sulfotransferase: Intracrinology meets metabolic diseases. *Diabetes, 61*, 1353–1354.

Taylor, M. C., Kar, A. R., Kunselman, A. R., Stetter, C. M., Dunaif, A., & Legro, R. S. (2011). Evidence for increased cardiovascular events in the fathers but not mothers of women with polycystic ovary syndrome. *Human Reproduction, 26*, 2226–2231.

Tiano, J., & Mauvais-Jarvis, F. (2012). Selective estrogen receptor modulation in pancreatic β-cells and the prevention of type 2 diabetes. *Islets, 4*, 173–176.

Tiano, J. P., & Mauvais-Jarvis, F. (2012). Molecular mechanisms of estrogen receptors' suppression of lipogenesis in pancreatic β-cells. *Endocrinology, 153*, 2997–3005.

University of California, Los Angeles SCOR—PI: Emeran Mayer, M.D.

Birder, L. A., & de Groat, W. C. (2011). Autonomic control of the lower urinary tract. In D. Robertson, I. Biaggioni, G. Burnstock, P. Low, & J. Paton (Eds.), *Primer of the autonomic nervous system, 3rd edition* (pp. 225–228). London, England: Academic Press.

Birder, L. A., Hanna-Mitchell, A. T., Mayer, E., & Buffington, C. A. (2011). Cystitis, co-morbid disorders and associated epithelial dysfunction. *Neurourology and Urodynamics, 30*, 668–672.

Bradford, K., Shih, W., Videlock, E. J., Presson, A. P., Naliboff, B. D., Mayer, E. A., & Chang, L. (2012). Association between early adverse life events and irritable bowel syndrome. *Clinical Gastroenterology and Hepatology, 10*, 385–390.

Chang, L., Adeyemo, M., Karagiannidis, I., Videlock, E. J., Bowe, C., Shih, W., Presson, A. P., Yuan, P. Q., Cortina, G., Gong, H., Singh, S., Licudine, A., Mayer, M., Taché, Y., Pothoulakis, C., & Mayer, E. A. (2012). Serum and colonic mucosal immune markers in irritable bowel syndrome. *American Journal of Gastroenterology, 107*, 262–272.

Craske, M. G., Wolitzky-Taylor, K. B., Labus, J., Wu, S., Frese, M., Mayer, E. A., & Naliboff, B. D. (2011). A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. *Behaviour Research and Therapy, 49*, 413–421.

Hubbard, C., Labus, J. S., Bueller, J., Stains, J., Suyenobu, B., Dukes, G., Kelleher, D., Tillisch, K., Naliboff, B., & Mayer, E. A. (2011). Corticotropin-releasing factor receptor 1 antagonist alters regional activation and effective connectivity in an emotional-arousal circuit during expectation of abdominal pain. *Journal of Neuroscience, 31*, 12491–12500.

Hubbard, C. S., Ornitz, E., Gaspar, J. X., Smith, S., Amin, J., Labus, J. S., Kilpatrick, L. A., Rhudy, J. L., Mayer, E. A., & Naliboff, B. D. (2011). Modulation of nociceptive and acoustic startle responses to an unpredictable threat in men and women. *Pain, 152*, 1632–1640.

Jarcho, J. M., Mayer, E. A., Jiang, Z. K., Feier, N. A., & London, E. D. (2012). Pain, affective symptoms, and cognitive deficits in patients with cerebral dopamine dysfunction. *Pain, 153*, 744–754.

Kanai, A., Zabbarova, I., Ikeda, Y., Yoshimura, N., Birder, L., Hanna-Mitchell, A., & de Groat, W. (2011). Sophisticated models and methods for studying neurogenic bladder dysfunction. *Neurourology and Urodynamics, 30*, 658–667.

Kilpatrick, L. A., Labus, J. S., Coveleskie, K., Hammer, C., Rappold, G., Tillisch, K., Bueller, J. A., Suyenobu, B., Jarcho, J. M., McRoberts, J. A., Niesler, B., & Mayer, E. A. (2011). The HTR3A polymorphism c. -42C>T is associated with amygdala responsiveness in patients with irritable bowel syndrome. *Gastroenterology, 140*, 1943–1951.

Labus, J. S., Mayer, E. A., Jarcho, J., Kilpatrick, L. A., Kilkens, T. O., Evers, E. A., Backes, W. H., Brummer, R. J., & van Nieuwenhoeven, M. A. (2011). Acute tryptophan depletion alters the effective connectivity of emotional arousal circuitry during visceral stimuli in healthy women. *Gut, 60*, 1196–1203.

Larauche, M., Mulak, A., & Taché, Y. (2012). Stress and visceral pain: From animal models to clinical therapies. *Experimental Neurology, 233*, 49–67.

Larauche, M., Mulak, A., & Taché, Y. (2011). Stress-related alterations of visceral sensation: animal models for irritable bowel syndrome study. *Journal of Neurogastroenterology and Motility, 17*, 213–234.

Larauche, M., Mulak, A., Yuan, P. Q., Kanauchi, O., & Taché, Y. (2012). Stress-induced visceral analgesia assessed non-invasively in rats is enhanced by prebiotic diet. *World Journal of Gastroenterology, 18*, 225–236.

Mayer, E. A. (2011). Neurobiology gut feelings: the emerging biology of gut-brain communication. *Nature Reviews Neuroscience, 12*, 453–466.

Mayer, E. A., & Brunnhuber, S. (2012). Gastrointestinal disorders. In T. E. Schlaepfer & C. B. Nemeroff (Eds.), *Handbook of Clinical Neurology 3rd Series, Volume 106, Neurobiology of Psychiatric Disorders* (pp. 607–631). London, England: Elsevier.

Mayer, E. A., & Tillisch, K. (2012). Functional gastrointestinal disorders: Irritable bowel syndrome, dyspepsia, and noncardiac chest pain. In L. Goldman & A.I. Schafer (Eds.), *Goldman's Cecil medicine.* Philadelphia, PA: Saunders.

Mulak, A., Larauche, M., & Taché, Y. (2012). Modulation of visceral pain by stress: implication in irritable bowel syndrome. In G. Lule (Ed.), *Current concepts in colonic disorders* (pp. 251–260). New York, NY: InTech.

Mulak, A., Larauche, M., & Taché, Y. (2012). Psychological stress induces visceral analgesic or hyperalgesic response in rodents. A role of preconditions. In L. P. Filaretova & K. Takeuchi (Eds.), *Cell/tissue injury and cytoprotection/organoprotection in the gastrointestinal tract: Mechanisms, prevention and treatment* (pp. 106–114). Basel, Switzerland: Karger.

Smith, A. L., Leung, J., Kun, S., Zhang, R., Karagiannides, I., Raz, S., Lee, U., Golovatscka, V., Pothoulakis, C., Bradesi, S., Mayer, E. A., & Rodriguez, L. V. (2011). The effects of acute and chronic psychological stress on bladder function in a rodent model. *Urology, 78*, 967.e1–967.e7.

Tillisch, K., Labus, J. S., Mayer, E. A., & Naliboff, B. D. (2012). Neuroimaging of brain-gut interactions in functional gastrointestinal disorders. In L. Johnson (Ed.), *Physiology of the gastrointestinal tract, 5th edition* (pp. 733–740). London, England: Academic Press.

Wang, L., Goebel-Stengel M., Stengel A., Wu, S. V., Ohning, G., & Taché, Y. (2011). Comparison of CRF-immunoreactive neurons distribution in mouse and rat brains and selective induction of Fos in rat hypothalamic CRF neurons by abdominal surgery. *Brain Research, 1415*, 34–46.

University of California, San Francisco SCOR—PI: Jeanette Brown, M.D.

Copeland, K. L., Brown, J. S., Creasman, J. M., Van Den Eeden, S. K., Subak, L. L., Thom, D. H., Ferrara, A., & Huang, A. J. (2012). Diabetes mellitus and sexual function in middle-aged and older women. *Obstetrics and Gynecology, 120*, 331–340.

Farhat, G. N., Cummings, S. R., Chlebowski, R. T., Parimi, N., Cauley, J. A., Rohan, T. E., Huang, A. J., Vitolins, M., Hubbell, A., Manson, J. E., Cochrane, B. B., Lane, D. S., & Lee, J. S. (2011). Sex hormones and risk of estrogen receptor-negative and estrogen receptor-positive breast cancer. *Journal of the National Cancer Institute, 103*, 562–570.

Huang, A. J., Brown, J. S., Boyko, E. J., Moore, E. E., Scholes, E., Walter, L. C., Lin, F. Vittinghoff, E., & Fihn, S. D. (2011). Clinical significance of postvoid residual volume in older ambulatory women. *Journal of the American Geriatrics Society, 59*, 1452–1458.

Markland, A. D., Richter, H. E., Burgio, K. L., Myers, D. L., Hernandez, A. L., & Subak, L. L. (2011). Weight loss improves fecal incontinence severity in overweight and obese women with urinary incontinence. *International Urogynecology Journal of Pelvic Floor Dysfunction, 22*, 1151–1157.

Phelan, S., Kanaya, A. M., Subak, L. L., Hogan, P. E., Espeland, M. A., Wing, R. R., Burgio, K. L., Dilillo, V., Gorin, A. A., West, D. S., & Brown, J. S. (2012). Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the look ahead trial. The Look AHEAD Research Group. *Journal of Urology, 187*, 939–944.

Pinto, A. M., Kuppermann, M., Nakagawa, S., Vittinghoff, E., Wing, R. R., Kusek, J. W., Herman, W. H., & Subak, L. L. (2011). Comparison and correlates of three preference-based health-related quality-of-life measures among overweight and obese women with urinary incontinence. *Quality of Life Research, 20*, 1655–1662.

Pinto, A. M., Kuppermann, M., Nakagawa, S., Vittinghoff, E., Wing, R. R., Kusek, J. W., Herman, W. H., & Subak, L. L. (2012). The effect of weight loss and change in urinary incontinence frequency on health-related quality of life. *Quality of Life Research, 21*, 1685–1694.

Thom, D. H., Brown, J. S., Schembri, M., Ragins, A. I., Creasman, J. M., & Van Den Eeden, S. K. (2011). Parturition events and risk of urinary incontinence in later life. *Neurourology and Urodynamics, 30*, 1456–1461.

Whitcomb, E. L., & Subak, L. L. (2011). Effect of weight loss on urinary incontinence in women. *Journal of Urology, 3*, 123–132.

University of Kansas Medical Center SCOR—PI: Hong Wen Deng, Ph.D.

Deng, F. Y., Lei S. F., Chen, X. D., Tan, L. J., Zhu, X. Z., & Deng, H. W. (2011). An integrative study ascertained SOD2 as a susceptibility gene for osteoporosis in Chinese. *Journal of Bone and Mineral Research, 26*, 2695–2701.

Deng, F. Y., Lei, S. F., Zhang, Y., Zhang, Y. L., Zheng, Y. P., Zhang, L. S., Pan, R., Wang, L., Tian, Q., Shen, H., Zhao, M., Lundberg Y. W., Liu, Y. Z., Papasian, C. J., & Deng, H. W. (2011). Peripheral blood monocyte-expressed ANXA2 gene is involved in pathogenesis of osteoporosis in humans. *Molecular & Cellular Proteomics, 10*, M111.011700.

Guo, Y., Liu, H., Yang, T. L., Li, S. M., Li, S. K., Tian, Q., Liu, Y. J., & Deng, H. W. (2011). The fat mass and obesity associated gene, FTO, is also associated with osteoporosis phenotypes. *PLOS ONE, 6*(11), e27312.

Liu, Y. Z., Li, J., Pan, R., Shen, H., Tian, Q., Zhou, Y., Liu, Y. J., & Deng, H. W. (2012). Genome-wide copy number variation association analyses for age at menarche. *Journal of Clinical Endocrinology & Metabolism, 97*, E2133–E2139.

Pan, R., Liu, Y. Z., Deng, H. W., & Dvornyk, V. (2012). Association analyses suggest the effects of RANK and RANKL on age at menarche in Chinese women. *Climacteric, 15*, 75–81.

Sun L., Tan, L., Yang F., Luo, Y., Li, X., Deng, H. W., & Dvornyk, V. (2012). Meta-analysis suggests that smoking is associated with an increased risk of early natural menopause. *Menopause, 19*, 126–132.

Zhang, L. S., Hu, H. G., Liu, Y. J., Li, J., Yu, P., Zhang, F., Yang, T. L., Tian, Q., Zheng, Y. P., Guo, Y., & Deng, H. W. (2012) A follow-up association study of two genetic variants for bone mineral density variation in Caucasians. *Osteoporosis International, 23*, 1867–1875.

Zhang, Y. P., Deng, F. Y., Yang, T. L., Zhang, F., Chen, X. D., Shen, H., Zhu, X. Z., Tian, Q., & Deng, H. W. (2012). Genome-wide association study identified CNP12587 region underlying height variation in Chinese females. *PLOS ONE, 7*, e44292.

University of Miami SCOR—PI: Emmalee Bandstra, M.D.

Accornero, V. H., Anthony, J. C., Morrow, C. E., Xue, L., Mansoor, E., Johnson, A. L., McCoy, C. B., & Bandstra, E. S. (2011). Estimated effect of prenatal cocaine exposure on examiner-rated behavior at age 7 years. *Neurotoxicology and Teratology, 33*, 370–378.

Dow-Edwards, D., & Izenwasser, S. (2012). Pretreatment with Delta 9-tetrahydrocannibinol (THC) increases cocaine-stimulated activity in adolescent but not adult male rats. *Pharmacology Biochemistry and Behavior, 100*, 587–591.

Mansoor, E., Morrow, C. E., Accornero, V. H., Xue, L., Johnson, A. L., Anthony, J. C., & Bandstra, E. S. (2012). Longitudinal effects of prenatal cocaine use on mother-child interactions at ages 3 and 5. *Journal of Developmental & Behavioral Pediatrics, 33*, 32–41.

Messiah, S. E., Arheart, K. L., Lipshultz, S. E., Bandstra, E. S., & Miller, T. L. (2012). Perinatal factors associated with cardiovascular disease risk among preschool-age children in the United States: An analysis of 1999–2008 NHANES data. *International Journal of Pediatrics,* 157237.

Messiah, S. E., Lipshultz, S. E., Miller, R. L., Accornero, V. H., & Bandstra, E. S. (2012). Assessing latent effects of prenatal cocaine exposure on growth and risk of cardiovascular disease in late adolescence: design and methods. *International Journal of Pediatrics,* 467918.

Zakharova, E., Starosciak, A., Wade, D., & Izenwasser, S. (2012). Sex differences in the effects of social and physical environment on novelty-induced exploratory behavior and cocaine-stimulated locomotor activity in adolescent rats. *Behavioural Brain Research, 230*, 92–09.

University of Michigan SCOR—PI: John O. L. DeLancey, M.D.

Berger, M. B., Patel, D. A., Miller, J. M., DeLancey, J. O. L., & Fenner, D. E. (2011). Racial differences in self-reported healthcare seeking and treatment for urinary incontinence in community-dwelling women from the EPI Study. *Neurourology and Urodynamics, 30*, 1442–1447.

Brandon, C., Jacobson, J. A., Low, L. K., Park, L., DeLancey, J., & Miller, J. (2012). Pubic bone injuries in primiparous women: magnetic resonance imaging in detection of differential diagnosis of structural injury. *Ultrasound in Obstetrics & Gynecology, 39*, 444–451.

Brincat, C. A., DeLancey, J. O. L., & Miller, J. M. M. (2011). Urethral closure pressures among primiparous women with and without levator ani muscle defects. *International Urogynecology Journal, 22*,1491–1495.

DeLancey, J. O., Sorensen, H. C., Lewicky-Gaupp, C., & Smith, T. M. (2012). Comparison of the puborectal muscle on MRI in women with POP and levator ani defects with those with normal support and no defect. *International Urogynecology Journal, 23*, 73–77.

Jing, D., Ashton-Miller, J. A., & DeLancey, J. O. L. (2012). A subject-specific anisotropic visco-hyperelastic finite element model of the female pelvic floor stress and strain during the second stage of labor. *Journal of Biomechanics, 45*, 455–460.

Kim, J., Ramanah, R., DeLancey, J. O., & Ashton-Miller, J. A. (2011). On the anatomy and histology of pubovisceral muscle enthesis in women. *Neurourology and Urodynamics, 30*, 1366–1370.

Larson, K. A., Luo, J., Guire, K. E., Chen, L., Ashton-Miller, J. A., & DeLancey J. O. (2012). 3D analysis of cystoceles using magnetic resonance imaging assessing midline, paravaginal and apical defects. *International Urogynecology Journal, 23*, 285–293.

Larson, K. A., Luo, J., Yousuf, A., Ashton-Miller, J. A., & DeLancey, J. O. (2012). Measurement of the 3D geometry of the fascial arches in women with a unilateral levator defect and "architectural distortion." *International Urogynecology Journal, 23*, 57–63.

Luo, J., Ashton-Miller, J. A., & DeLancey, J. O. (2011). A model patient: Female pelvic anatomy can be viewed in diverse 3-dimensional images with a new interactive tool. *American Journal of Obstetrics & Gynecology, 205*, 391.e1–e2.

Morris, V. C., Murray, M. P., DeLancey, J. O., & Ashton-Miller, J. A. (2012). A comparison of the effect of age on levator ani and obturator internus muscle cross-sectional areas and volumes in nulliparous women. *Neurourology and Urodynamics, 31*, 481–486.

Zielinski, R., Kane-Low, L., Miller, J. M., & Sampselle, C. (2012). Validity and reliability of a scale to measure genital body image. *Journal of Sex & Marital Therapy, 38*, 309–324.

Washington University SCOR—PI: Scott Hultgren, Ph.D.

Chaturvedi, K. S., Hung, C. S., Crowley, J. R., Stapleton, A. E., & Henderson, J. P. (2012). The siderophore yersiniabactin binds copper to protect pathogens during infection. *Nature Chemical Biology, 8*, 731–736.

Cusumano, C. K., Pinkner, J. S., Han, Z., Greene, S. E., Ford, B. A., Crowley, J. R., Henderson, J. P., Janetka, J. W., & Hultgren, S. J. (2011). Treatment and prevention of UTI with orally active mannoside FimH inhibitors. *Science Translational Medicine, 3*, 109ra115.

Floyd, R. V., Upton, M., Hultgren, S. J., Wray, S., Burdyga, T. V., & Winstanley, C. (2012). Escherichia coli-mediated impairment of ureteric contractility is uropathogenic *E. coli* specific. *Journal of Infectious Disease, 206*, 1589–1596.

Guiton, P. S., Cusumano, C. K., Kline, K. A., Dodson, K. W., Han, Z., Janetka, J. W., Henderson, J. P., Caparon, M. G., & Hultgren, S. J. (2012). Combinatorial small-molecule therapy prevents uropathogenic *Escherichia coli* catheter-associated urinary tract infections in mice. *Antimicrobial Agents and Chemotherapy, 56*, 4738–4745.

Hadjifrangiskou, M., Gu, A. P., Pinkner, J. S., Kostakioti, M., Zhang, E. W., Greene, S. E, Hultgren, S. J. (2012). Transposon mutagenesis identifies uropathogenic *Escherichia coli* biofilm factors. *Journal of Bacteriology, 194*, 6195–6205.

Hadjifrangiskou, M., Kostakioti, M., Chen, S. L., Henderson, J. P., Greene, S. E., & Hultgren, S. J. (2011). A central metabolic circuit controlled by QseC in pathogenic *Escherichia coli*. *Molecular Microbiology, 7*, 345–347.

Hadjifrangiskou, M., Kostakioti, M., & Hultgren, S. J. (2011). Antitoxins: Therapy for stressed bacteria. *Nature Chemical Biology, 7*, 345–347.

Horvath, D. L., Li, B., Partida-Sanchez, S., Hunstad, D. A., Hultgren, S. J., & Justice, S. S. (2011). Morphological plasticity promotes resistance to phagocyte killing of uropathogenic Escherichia coli. *Microbes and Infection, 13*, 426–437.

Kostakioti, M., Hadjifrangiskou, M., Cusumano, C. K., Hannan, T. J., Janetka, J. W, & Hultgren, S. J. (2012). Distinguishing the contribution of type 1 pili from that of other QseB-misregulated factors when QseC is absent during urinary tract infection. *Infection and Immunity, 80*, 2826–2834.

Schwartz, D. J., Chen, S. L., Hultgren, S. J., & Seed, P. C. (2011). Population dynamics and niche distribution of uropathogenic *E. coli* during acute and chronic urinary tract infection. *Infection and Immunity, 79,* 4250–4259.

Stapleton, A. E., Au-Yeung, M., Hooton, T. M., Fredricks, D. N., Roberts, P. L., Czaja, C. A., Yarova-Yarovaya, Y., Fiedler, T., Cox, M., & Stamm, W. E. (2011). Randomized, placebo-controlled phase 2 trial of a *Lactobacillus crispatus* probiotic given intravaginally for prevention of recurrent urinary tract infection. *Clinical Infectious Diseases, 52,* 1212–1217

Tenke, P., Koves, B., Nagy, K., Hultgren, S. J., Mendling, W., Wullt, B., Grabe, M., Wagenlehner, F. M., Cek, M., Pickard, R., Botto, H., Naber, K. G., & Bjerklund Johansen, T. E. (2011). Update on biofilm infections in the urinary tract. *World Journal of Urology, 30,* 51–57.

Tenke, P., Koves, B., Nagy, K., Uehara, S., Kumon, H., Hultgren, S., Hung, C., & Mendling, W. (2011). Biofilm and urogenital infections. In A. Nikibakhsh (Ed.), *Clinical Management of Complicated Urinary Tract Infection.* New York, NY: InTech.

Vigil, P. D., Stapleton, A. E., Johnson, J. R., Hooton, T. M., Hodges, A. P., He, Y., & Mobley, H. L. T. (2011). Putative repeat-intoxin (RTX) gene tosA of *Escherichia coli* predicts successful colonization of the urinary tract. *mBio, 2*(3), e00066–11.

Yale University SCOR—PI: Rajita Sinha, Ph.D.

Axelrod, S. R., Perepletchikova, F., Holtzman, K., & Sinha, R. (2011). Emotion regulation and substance use frequency in women with substance dependence and borderline personality disorder receiving dialectical behavior therapy. *American Journal of Drug and Alcohol Abuse, 37,* 37–42.

Lou, X., Zhang, S., Hu, S., Bednarski, S. R., Erdman, E., Farr, O. M., & Chiang-Shan, R. (2013). Error processing and gender shared and specific neural predictors of relapse in cocaine dependence. *Brain: a journal of neurology, 9,* 457.

Potenza, M. N., Hong, K. A., Lacadie, C. M., Fulbright, R. K., Tuit, K. L., & Sinha, R. (2012). Neural correlates of stress induced drug craving: influences of sex and cocaine dependence. *American Journal of Psychiatry, 169*(4), 406–414.

Rando, K., Tuit, K., Hannestsad, J., Guarnaccia, J., & Sinha R. (2013). Sex differences in decreased limbic and cortical grey matter volume in cocaine dependence: a voxel based morphometric study. *Addiction Biology, 4,* 833.

Schepis, T. S., Desai, R. A., Cavallo, D. A., Smith, A. E., McFetridge, A., Liss, T. B., Potenza, M. N., & Krishnan-Sarin, S. (2011). Gender differences in adolescent marijuana use and associated psychosocial characteristics. *Journal of Addiction Medicine, 5,* 65–73.

Seo, D., Jia, Z., Lacadie, C. M., Tsou, K. A., Bergquist, K., & Sinha, R. (2011). Sex differences in neural responses to stress and alcohol context cues. *Human Brain Mapping, 32,* 1998–2013.

APPENDIX F

NIH Working Group on Women in Biomedical Careers

FY 2011

Co-Chairs

Francis S. Collins, M.D., Ph.D., Director, NIH

Janine Austin Clayton, M.D., Director, ORWH

Institute and Center Directors

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S., Director, NIEHS

Patricia Grady, Ph.D., R.N., F.A.A.N., Director, NINR

Judith H. Greenberg, Ph.D., Acting Director, NIGMS

Alan E. Guttmacher, M.D., Director, NICHD

Story Landis, Ph.D., Director, NINDS

Donald Lindberg, M.D., Director, NLM

Griffin P. Rodgers, M.D., M.A.C.P., Director, NIDDK

Office of the Director

Lawrence Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

Joyce Rudick, Director, Programs and Management, ORWH

Benjamin Butler, J.D., Senior Attorney, Office of the General Council *(Ex-Officio member)*

Intramural Research

Michael Gottesman, M.D., Deputy Director for Intramural Research, NIH

Joan Schwartz, Ph.D., Special Volunteer, Office of Intramural Research

Edward Giniger, Ph.D., Investigator, NINDS

Elaine Ostrander, Ph.D., Chief & Senior Investigator, Cancer Genetics Branch, NHGRI

Kathryn Zoon, Ph.D., Scientific Director, NIAID

Extramural Research

Sally Rockey, Ph.D., Deputy Director for Extramural Research, NIH

Walter Schaffer, Ph.D., Senior Scientific Advisor for Extramural Research, Office of Extramural Research

Pamela Marino, Ph.D., Program Director, Pharmacology, Physiology, and Biological Chemistry Division; Co-Director, Pharmacology Research Associate Program, NIGMS

Belinda Seto, Ph.D., Deputy Director, NIBIB

Staff to Working Group

Keren Witkin, Ph.D., American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow, ORWH

FY 2012

Co-Chairs

Francis S. Collins, M.D., Ph.D., Director, NIH

Janine Austin Clayton, M.D., Director, ORWH

Institute and Center Directors

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S., Director, NIEHS

Patricia Grady, Ph.D., R.N., F.A.A.N., Director, NINR

Judith H. Greenberg, Ph.D., Acting Director, NIGMS

Alan E. Guttmacher, M.D., Director, NICHD

Story Landis, Ph.D., Director, NINDS

Donald Lindberg, M.D., Director, NLM

Griffin P. Rodgers, M.D., M.A.C.P., Director, NIDDK

Office of the Director

Lawrence Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

Joyce Rudick, Director, Programs and Management, ORWH

Benjamin Butler, J.D., Senior Attorney, Office of the General Council *(Ex-Officio member)*

Debra Chu, J.D., Director, Office of Equal Opportunity and Diversity Management

Intramural Research

Michael Gottesman, M.D., Deputy Director for Intramural Research, NIH

Joan Schwartz, Ph.D., Special Volunteer, Office of Intramural Research

Edward Giniger, Ph.D., Investigator, NINDS

Elaine Ostrander, Ph.D., Chief & Senior Investigator, Cancer Genetics Branch, NHGRI

Kathryn Zoon, Ph.D., Scientific Director, NIAID

Meghan Mott, Ph.D., Postdoctoral Fellow, NIAAA

Extramural Research

Sally Rockey, Ph.D., Deputy Director for Extramural Research, NIH

Walter Schaffer, Ph.D., Senior Scientific Advisor for Extramural Research, Office of Extramural Research

Pamela Marino, Ph.D., Program Director, Pharmacology, Physiology, and Biological Chemistry Division; Co-Director, Pharmacology Research Associate Program, NIGMS

Belinda Seto, Ph.D., Deputy Director, NIBIB

Marie Bernard, M.D., Deputy Director, NIA

Staff to Working Group

Keren Witkin, Ph.D., American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow, ORWH

APPENDIX G

Intramural Program on Research on Women's Health Steering Committee

FY 2011

Esther Sternberg, M.D., NIMH, *Co-chair*

Maria Morasso, Ph.D., NIAMS, *Co-chair*

Joyce Rudick, OD/ORWH, *ORWH Liaison*

Rosemarie Filart, M.D., M.P.H., NCRR, *Chair, WHSIG Lecture Series*

Lawrence Nelson, M.D., NICHD, *Chair, Training*

Cherié Butts, Ph.D., FDA

Janine Austin Clayton, M.D., OD/ORWH

Wendy Fibison, Ph.D., NIAID

Gretchen Gierach, Ph.D., M.P.H., NCI

Kenneth Korach, Ph.D., NIEHS

Joslyn Kravitz, Ph.D., OD/ORWH

Pamela Robey, Ph.D., NIDCR

Marian Young, Ph.D., NIDCR

Ex-Officio Members

Michael Gottesman, M.D., OD/OIR

Vivian Pinn, M.D., OD/ORWH

FY 2012

Esther Sternberg, M.D., NIMH, *Co-chair*

Maria Morasso, Ph.D., NIAMS, *Co-chair*

Joyce Rudick, OD/ORWH, *ORWH Liaison*

Rosemarie Filart, M.D., M.P.H., NCRR, *Chair, WHSIG Lecture Series*

Lawrence Nelson, M.D., NICHD, *Chair, Training*

Remy Brim, Ph.D., NIH, *Bioethics Fellow*

Wendy Fibison, Ph.D., NIAID

Gretchen Gierach, Ph.D., M.P.H., NCI

Kenneth Korach, Ph.D., NIEHS

Pamela Robey, Ph.D., NIDCR

Keren Witkin, Ph.D., OD/ORWH

Marian Young, Ph.D., NIDCR

Ex-Officio Members

Michael Gottesman, M.D., OD/OIR

Janine Austin Clayton, M.D., OD/ORWH

APPENDIX H

NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended October 2001

NOTE: Additional information concerning the NIH Policy on Inclusion of Women and Minorities as Subjects in Clinical Research is available at *http://grants.nih.gov/grants/funding/women_min/women_min.htm*.

SUMMARY: This notice updates the NIH policy on the inclusion of women and minorities as subjects in clinical research. It supersedes the 1994 Federal Register notice (*http://grants.nih.gov/grants/guide/notice-files/not94-100.html*) and the August 2000 notice in the NIH Guide to Grants and Contracts (*http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html*). It incorporates the definition of clinical research as reported in the 1997 Report of the NIH Director's Panel on Clinical research. Also, this notice provides additional guidance on reporting analyses of sex/gender and racial/ethnic differences in intervention effects for NIH-defined Phase III clinical trials. The guidelines ensure that all NIH-funded clinical research will be carried out in a manner sufficient to elicit information about individuals of both sexes/genders and diverse racial and ethnic groups and, particularly in NIH-defined Phase III clinical trials, to examine differential effects on such groups. Since a primary aim of research is to provide scientific evidence leading to a change in health policy or standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently.

In June 2001, NIH adopted the definition of clinical research as: (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; (2) Epidemiologic and behavioral studies; and (3) Outcomes research and health services research, *http://www.nih.gov/news/crp/97report/execsum.htm*.

EFFECTIVE DATE: This amended policy is effective immediately and applies to all grants and cooperative agreements currently active and to be awarded. Contract solicitations issued as of October 2001 must adhere to the amended policy.

I. Legislative Background

The NIH Revitalization Act of 1993, PL 103-43, signed into law on June 10, 1993, directed the NIH to establish guidelines for inclusion of women and minorities in clinical research.

The statute states that:

> In conducting or supporting clinical research for the purposes of this title, the Director of NIH shall ... ensure that (a) women are included as subjects in each project of such research; and (b) members of minority groups are included in such research. 492B(a)(1)

The statute further directed the NIH to establish guidelines to specify:

(a) the circumstances under which the inclusion of women and minorities as subjects in projects of clinical research is inappropriate;

(b) the manner in which clinical trials are required to be designed and carried out; and

(c) the operation of outreach programs, 492B(d)(1)

The statute defines "clinical research" to include "clinical trials" and states that:

> In the case of any clinical trial in which women or members of minority groups will be included as subjects, the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial. 492B(c)

Specifically addressing the issue of minority groups, the statute states that:

> The term "minority group" includes subpopulations of minority groups. The Director of NIH shall, through the guidelines established … define the terms "minority group" and "subpopulation" for the purposes of the preceding sentence. 492B(g)(2)

The statute speaks specifically to outreach and states that:

> The Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in the projects of clinical research. 492B(a)(2)

The statute includes a specific provision pertaining to the cost of clinical research and, in particular clinical trials.

(A)(i) In the case of a clinical trial, the guidelines shall provide that the costs of such inclusion in the trial is (sic) not a permissible consideration in determining whether such inclusion is inappropriate. 492B(d)(2)

(ii) In the case of other projects of clinical research, the guidelines shall provide that the costs of such inclusion in the project is (sic) not a permissible consideration in determining whether such inclusion is inappropriate unless the data regarding women or members of minority groups, respectively, that would be obtained in such project (in the event that such inclusion were required) have been or are being obtained through other means that provide data of comparable quality. 492B(d)(2)

Exceptions to the requirement for inclusion of women and minorities are stated in the statute, as follows:

> The requirements established regarding women and members of minority groups shall not apply to the project of clinical research if the inclusion, as subjects in the project, of women and members of minority groups, respectively—
>
> (1) is inappropriate with respect to the health of the subjects;
>
> (2) is inappropriate with respect to the purpose of the research; or
>
> (3) is inappropriate under such other circumstances as the Director of NIH may designate. 492B(b)
>
> (B) In the case of a clinical trial, the guidelines may provide that such inclusion in the trial is not required if there is substantial scientific data demonstrating that there is no significant difference between—
>
> (i) the effects that the variables to be studied in the trial have on women or members of minority groups, respectively; and
>
> (ii) the effects that the variables have on the individuals who would serve as subjects in the trial in the event that such inclusion were not required. 492B(d)(2)

II. Policy

A. Inclusion of Women and Minorities as Subjects in Clinical Research

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy applies to research subjects of all ages in all NIH-supported clinical research studies.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract proposal appropriate to the scientific objectives of the study/contract. The research plan/proposal should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

B. NIH-Defined Phase III Clinical Trials: Planning, Conducting, and Reporting of Analyses for Sex/Gender and Race/Ethnicity Differences

When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

Investigators must consider the following when planning, conducting, analyzing, and reporting an NIH-Defined Phase III clinical trial. Based on prior studies, one of the three situations below will apply:

1. Prior Studies Support the Existence of Significant Differences

If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, the primary question(s) to be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this. For example, if men and women are thought to respond differently to an intervention, then the Phase III clinical trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.

The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct analyses to detect significant differences in intervention effect (see "Significant Difference" under IV. Definitions) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable. The final protocol(s) approved by the Institutional Review Board (IRB) must include these plans for analysis. The award will require that for each funded protocol, investigators must report in their annual Progress Report cumulative subject accrual and progress in conducting analyses for sex/gender and race/ethnicity differences. If final analyses of sex/gender and race/ethnicity are not available at the time of the Final Progress Report or Competing Continuation for the grant, a justification and plan ensuring completion and reporting of the analyses are required. If final analyses are required as part of the contract, these analyses must be included as part of the deliverables. These requirements will be cited in the

terms and conditions of all awards for grants, cooperative agreements and contracts supporting NIH-defined Phase III clinical trials.

Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

2. Prior Studies Support No Significant Differences

If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and/or relevant subpopulation comparisons, then sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

3. Prior Studies Neither Support nor Negate Significant Differences

If the data from prior studies neither strongly support nor strongly negate the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, then the NIH-defined Phase III clinical trial will be required to include sufficient and appropriate entry of sex/gender and racial/ethnic participants, so that valid analysis of the intervention effects can be performed. However, the trial will not be required to provide high statistical power for these comparisons.

The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct valid analysis (see "Valid Analysis" under IV. Definitions) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable. The final protocol(s) approved by the Institutional Review Board (IRB) must include these plans for analysis. The award will require that for each funded protocol, investigators must report in their annual Progress Report cumulative subject accrual and progress in conducting analyses for sex/gender and race/ethnicity differences. If final analyses of sex/gender and race/ethnicity are not available at the time of the Final Progress Report or Competing Continuation for the grant, a justification and plan ensuring completion and reporting of the analyses are required. If final analyses are required as part of the contract, these analyses must be included as part of the deliverables. These requirements will be cited in the terms and conditions of all awards for grants, cooperative agreements and contracts supporting NIH-defined Phase III clinical trials.

Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

For all three situations, cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

III. Roles and Responsibilities

While this policy applies to all applicants/offerors for NIH-supported clinical research, certain individuals and groups have special roles and responsibilities with regard to its implementation.

1. NIH Staff

The NIH staff provides educational opportunities for the extramural and intramural communities concerning this policy; monitor its implementation during the development, review, award and conduct of research; and manage the NIH research portfolio to comply with the policy.

2. Principal Investigators

Principal investigators should assess the theoretical and/or scientific linkages between sex/gender, race/ethnicity, and their topic of study. Following this assessment, the principal

investigator and the applicant/offeror institution will address the policy in each application and proposal, providing the required information on inclusion of women and minorities and their subpopulations in clinical research projects, and any required justifications for exceptions to the policy.

For foreign awards and domestic awards with a foreign component, the NIH policy on inclusion of women and minority groups in research is the same as that for research conducted in the U.S. If there is scientific rationale for examining subpopulation group differences within the foreign population, investigators should consider designing their studies to accommodate these differences.

Investigators and their staff(s) are urged to develop appropriate and culturally sensitive outreach programs and activities commensurate with the goals of the study or objectives of the contract. The objective should be to actively recruit and retain the most diverse study population consistent with the purposes of the research project. Indeed, the purpose should be to establish a relationship between the investigator(s) and staff(s) and populations and community(ies) of interest such that mutual benefit is derived for participants in the study. Investigator(s) should take precautionary measures to ensure that ethical issues are considered, such that there is minimal possibility of coercion or undue influence in the incentives or rewards offered in recruiting into or retaining participants in studies.

To assist investigators and potential study participants, NIH staff have prepared educational materials, including a notebook titled the, "NIH Outreach Notebook on the Inclusion of Women and Minorities in Biomedical and Behavioral Research." The notebook as well as the Frequently Asked Questions document, is located at the following URL: *http://grants.nih.gov/grants/funding/women_min/women_min.htm*.

3. Institutional Review Boards (IRBs)

It is the responsibility of the IRBs to address the ethical issues as outlined in Section IV(2) for Principal Investigators. As the IRBs implement the regulation for the protection of human subjects as described in Title 45 CFR Part 46, "Protection of Human Subjects," *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html*, they must also attend to the guidelines for the inclusion of women and minorities and their subpopulations in clinical research. They should take into account the Food and Drug Administration's "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," Vol. 58 Federal Register 39406, *http://www.fda.gov/cder/guidance/old036fn.pdf*.

4. Peer Review Groups

In conducting peer review for scientific and technical merit, appropriately constituted initial review groups (including study sections), technical evaluation groups, and intramural review panels are instructed, as follows:

- To evaluate the proposed plan for the inclusion of minorities and both genders for appropriate representation or to evaluate the proposed justification when representation is limited or absent;
- To evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects;
- To evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the purpose of the research;
- To determine whether the design of clinical trials is adequate to measure differences when warranted,
- To evaluate the plans for valid analysis for NIH-defined Phase III clinical trials;

- To evaluate the plans for recruitment/outreach for study participants; and
- To include these criteria as part of the scientific assessment and evaluation.

The review instructions for grants are available on line at the following URL: *http://grants.nih.gov/grants/peer/hs_review_inst.pdf*

For contracts, the contracting officer will provide instructions for contract reviewers. Further information on instructions for contracts may be obtained at the following URL: *http://oa.od.nih.gov/oamp/index.html*.

Or contact:

National Institutes of Health
Division of Acquisition Policy and Evaluation
Office of Acquisition Management and Policy
6100 Executive Boulevard, Room 6C01
Phone: 301–496–6014
Fax: 301–402–1199

5. NIH Advisory Councils

In addition to other responsibilities for review of projects where the peer review groups have raised questions about the appropriate inclusion of women and minorities, the Advisory Council/Board of each Institute/Center shall prepare biennial reports, for inclusion in the overall NIH Director's biennial report, describing the manner in which the Institute/Center has complied with the provisions of the statute.

6. Institute/Center Directors

Institute/Center Directors and their staff shall ensure compliance with the policy.

7. NIH Director

The NIH Director may approve, on a case-by-case basis, the exclusion of projects, as recommended by the Institute/Center Director, that may be inappropriate to include within the requirements of these guidelines on the basis of circumstances other than the health of the subjects, the purpose of the research, or costs.

IV. Definitions

Throughout the section of the statute pertaining to the inclusion of women and minorities, terms are used which require definition for the purpose of implementing these guidelines. These terms, drawn directly from the statute, are defined below.

A. Clinical Research

Clinical research is defined as:

(1) Patient-oriented research: Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes:

   (a) Mechanisms of human disease;

   (b) Therapeutic interventions;

   (c) Clinical trials; and

(d) Development of new technologies.

(2) Epidemiologic and behavioral studies; and

(3) Outcomes research and health services research: *http://www.nih.gov/news/crp/97report/execsum.htm*

B. NIH-Defined Clinical Trial

For the purpose of these guidelines, an NIH-defined "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

C. Valid Analysis

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- Allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization;
- Unbiased evaluation of the outcome(s) of study participants; and
- Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

D. Significant Difference

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

E. Racial and Ethnic Categories

1. Minority Groups

A minority group is a readily identifiable subset of the U.S. population that is distinguished by racial, ethnic, and/or cultural heritage.

The Office of Management and Budget (OMB) Directive No. 15 *http://www.whitehouse.gov/omb/fedreg/ombdir15.html* defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The categories in this classification are social-political constructs and should not be interpreted as anthropological in nature.

When an investigator is planning data collection on race and ethnicity, these categories shall be used. The collection of greater detail is encouraged. However, more detailed items should be designed in a way that they can be aggregated into these required categories. Using respondent self-report or self-identification to collect an individual's data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation. Respondents shall be offered the opportunity to select more than one racial designation. When data are collected separately, provision shall be made to report the number of respondents in each racial category who are Hispanic or Latino.

The following definitions apply for ethnic categories.

Hispanic or Latino—a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

The following definitions apply for racial categories.

American Indian or Alaska Native—a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian—a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African-American—a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African-American."

Native Hawaiian or Other Pacific Islander—a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

2. Majority Group

White—a person having origins in any of the original peoples of Europe, the Middle East, or North Africa

NIH recognizes the diversity of the U.S. population and that changing demographics are reflected in the changing racial and ethnic composition of the population. The terms "minority groups" and "minority subpopulations" are meant to be inclusive, rather than exclusive, of differing racial and ethnic categories.

3. Subpopulations

Each racial and ethnic group contains subpopulations that are delimited by geographic origins, national origins and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self-identify with more than one race or ethnicity. Researchers should be cognizant of the possibility that these racial/ethnic combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study.

F. Outreach Strategies

These are outreach efforts by investigators and their staff(s) to appropriately recruit and retain populations of interest into research studies. Such efforts should represent a thoughtful and culturally sensitive plan of outreach and generally include involvement of other individuals and organizations relevant to the populations and communities of interest, e.g., family, religious organizations, community leaders and informal gatekeepers, and public and private institutions and organizations. The objective is to establish appropriate lines of communication and cooperation to build mutual trust and cooperation such that both the study and the participants benefit from such collaboration.

APPENDIX I

NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research

Release Date: August 8, 2001

NOTICE: NOT-OD-01-053

National Institutes of Health

POLICY: The NIH has adopted the 1997 Office of Management and Budget (OMB) revised minimum standards for maintaining, collecting, and presenting data on race and ethnicity for all grant applications, contract and intramural proposals and for all active research grants, cooperative agreements, contract and intramural projects. The minimum standards are described in the 1997 OMB Directive 15, *http://www.whitehouse.gov/omb/fedreg/directive_15.html*.

SUMMARY: This document provides additional guidance and instruction for using the revised minimum standards for maintaining, collecting, and presenting data on race and ethnicity found in the PHS 398 (rev. 5/01) and PHS 2590 (rev.5/01) instructions and forms *http://grants.nih.gov/grants/forms.htm*. Comparable information will be provided in research and development contract solicitations and awards for intramural projects. This document should be used in conjunction with the instructions in the PHS 398 and PHS 2590 instructions and forms.

The 1997 OMB revised minimum standards include two ethnic categories (Hispanic or Latino, and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African-American, Native Hawaiian or Other Pacific Islander, and White). The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. Using self-reporting or self-identification to collect an individual's data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation.

Collection of this information and use of these categories is required for research that meets the NIH definition of clinical research.

EFFECTIVE DATE: This policy applies to all new applications and proposals, annual progress reports, competing continuation applications, competing supplement applications for research grants, contracts, and intramural projects as of January 10, 2002.

I. Revised Minimum Standards for Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity

The following are the ethnic and racial definitions for the minimum standard categories (1997 OMB Directive 15)

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African-American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African-American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Using respondent self-report or self-identification to collect an individual's data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation.

When reporting these data in the aggregate, investigators should report: (a) the number of respondents in each ethnic category; (b) the number of respondents who selected only one category for each of the five racial categories; (c) the total number of respondents who selected multiple racial categories reported as the "number selecting more than one race"; and, (d) the number of respondents in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed items should be designed in a way that they can be aggregated into the required categories for reporting purposes. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. Federal agencies will not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

II. Guidance on Reporting Ethnicity/Race and Sex/Gender in Clinical Research

NIH requires all grants, contracts, and intramural projects conducting clinical research to address the Inclusion of Women and Minorities (see *http://grants.nih.gov/grants/funding/women_min/women_min.htm*). NIH defines clinical research as: (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. (2) Epidemiologic and behavioral studies. (3) Outcomes research and health services research.

New Applications (type 1), Competing Continuations (type 2), Requests for Proposals, and Intramural Projects

Submitting Applications or Proposals Involving the Collection of New/Additional Data in Clinical Research:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender. This information must be reported using the newly revised categories and according to the new format provided in the Targeted/Planned Enrollment table *http://grants.nih.gov/grants/funding/phs398/enrollment.pdf*.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories. If the existing data on ethnicity and race allows accurate correspondence with the new categories, the investigator can use the format in the Targeted/Planned Enrollment table. However, if the existing data do not allow accurate correspondence with the new categories, information may be reported using the former categories and according to the format in the 4/98 Version of the Inclusion Table *http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf*.

Annual Progress Reports (type 5) and Competing Supplement Applications

In Annual Progress Reports and Competing Supplement Applications, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date (as well as any proposed additions to the Targeted/Planned enrollment in the case of Competing Supplement Applications) and to present the distribution by ethnic/racial categories and sex/gender.

If Data Collection Is Ongoing, Such that New Subjects Will be Enrolled and/or Additional Data Will Be Collected from Human Subjects:

Investigators may choose to report ethnicity/race and sex/gender sample composition using EITHER the format in the former 4/98 Version of the Inclusion Table OR the new Inclusion Enrollment Report *http://grants.nih.gov/grants/funding/phs398/enrollmentreport.pdf*. [Note: If investigators with on-going data collection choose to report information using the new Inclusion Enrollment Report, they must continue to use this format for the remaining years of the project.]

If Data Collection Is Complete, Such that No New/Additional Subject Contact Is Planned:

Investigators may EITHER continue to report using the former categories and according to the 4/98 Version of the Inclusion Table, OR, if data allow accurate correspondence with the new categories, use the format in the new Inclusion Enrollment Report.

III. Frequently Asked Questions

1. What categories should I use in my application to estimate race and ethnicity, given the new OMB standards?

Investigators should use the categories described in the PHS 398 instructions and listed in the table "Targeted/Planned Enrollment Table" for New Applications. First, the investigator should report the anticipated total number of males and females to be enrolled by Ethnicity (Hispanic or Latino, Not Hispanic or Latino). Then, the investigator should report the anticipated total number of males and females by Racial Categories (American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African-American, White). The total number of subjects in the Ethnic Category section of the table should equal the total number of subjects in the Racial Categories section. Investigators do not need to estimate the anticipated number of individuals reporting multiple racial categories (either total number reporting multiple categories or number reporting specific combinations) for New Applications. However, the investigator must follow the OMB guidelines, which include allowing respondents to select multiple race categories, once data collection commences.

2. What if my new application involves analyzing secondary data in which the race and ethnicity categories do not comply with the new OMB guidelines?

If an investigator is using secondary data sets that do not conform to the new OMB guidelines and does not plan to collect any new/additional data from the subjects, this should be noted in the New Application. In this circumstance, the investigator should complete the "Targeted/ Planned Enrollment Table" for a New Application and the "Inclusion Enrollment Report" for Continuation Applications, Competing Supplement Applications, and Annual Grant Progress Reports if the data allow. However, if the existing data do not allow accurate correspondence with the new categories, the investigator should report the information using the prior categories and use the 4/98 Version of the Inclusion Table.

3. There are many ways of tabulating the multiple race and ethnicity responses, particularly since the race and ethnicity categories are not mutually exclusive. Do the numbers I report have to "add up"?

The numbers in several parts of the two tables must be the same. In both the "Targeted/ Planned Enrollment Table" for a New Application and the "Inclusion Enrollment Report" for Continuation Applications, Competing Supplement Applications, and Annual Progress Reports, the sum in "Ethnic Category: Total of All Subjects" must equal the sum in "Racial Categories: Total of All Subjects." In addition, the "Racial Categories: Total Hispanics or Latinos" in Part B of the "Inclusion Enrollment Report Table" must equal the Total Hispanic or Latino number reported in Part A of the "Inclusion Enrollment Report." Footnotes in the tables clearly identify which numbers must be the same.

4. Can I use the Targeted/Planned Enrollment Table or the Enrollment Inclusion Report to collect data from individuals?

Neither the Targeted/Planned Enrollment Tablet nor the Enrollment Inclusion Report should be used for collecting data from individuals. These tables are only to be used for reporting aggregate data.

To collect data from an individual respondent, investigators should use respondent self-report or self-identification and use two separate questions. The first question should be about ethnicity, followed by a question that provides the option of selecting one or more racial designations. An example of a format for collecting information from an individual can be found in the "Ethnic Origin and Race" section of the Personal Data Form Page in the PHS 398 (rev. 5/01) *http://grants.nih.gov/grants/funding/phs398/personal.pdf.*

5. Can I ask more detailed questions about ethnicity and race than these guidelines indicate?

The revised OMB guidelines provide minimal standards for data collection. Indeed, researchers are encouraged to explore collecting additional types of information on race and ethnicity that will provide additional insights into the relationships between race and ethnicity and health. For example, after asking the ethnicity and then the race questions, researchers may opt to ask study participants who choose multiple categories to identify the group that they identify with primarily. Further questions identifying membership in subpopulations within the ethnic and racial categories provided by OMB may also be considered. The scientific question being addressed in the study should guide investigators' decisions regarding collection of any additional information on ethnicity or race. Information on subpopulations may be reported by listing the information in an attachment to the required table.

6. I have already begun data collection and my categories do not comply with the new OMB standards. Do I need to change my questions on race and ethnicity in the middle of the study?

If data collection has already begun, we do not expect investigators to change their questions on race and ethnicity prior to the completion of the study. For Annual Progress Reports, in this circumstance, investigators should note that the research project was initiated prior to the implementation of the new reporting guidelines. If the data do not accurately correspond with the new categories, the investigator may continue to use the format in the 4/98 Version of the Inclusion Table.

7. I began data collection prior to the new standards, but my race and ethnicity questions comply with the new standards. I submitted my original estimates of the study composition using the old standards. How should I present the data in the progress report?

If you began your data collection prior to the implementation of the new standards but your questions on race and ethnicity comply with the new standards, the choice is left up to the investigator as to how to present the data for Annual Progress Reports. We suggest completion of the new Inclusion Enrollment Report.

8. How should I report race and ethnicity data when my research involves a foreign population?

Investigators are encouraged to design their data collection instruments in ways that allow respondent self-identification of their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables, investigators should asterisk and footnote the table indicating that data includes foreign participants. If the aggregated data only includes foreign participants, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign participants, we suggest the investigator complete two separate tables—one for domestic data and one for foreign data, with an asterisk and footnote accompanying the table with foreign data.

9. How do the 1997 OMB revised standards differ from the previous standards?

OMB issued the previous standards for maintaining, collecting, and presenting data on race and ethnicity in 1977. The minimum acceptable categories were: American Indian or Alaska Native; Asian or Pacific Islander; Black, not of Hispanic origin; Hispanic; White, not of Hispanic origin.

The 1997 OMB revised standards now include two ethnic categories (Hispanic or Latino or Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African-American, Native Hawaiian or Other Pacific Islander, and White). When using self-reporting or self-identification to collect data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation.

APPENDIX J

Aggregate Enrollment Tables and Trend Data

Section 1: Metrics Based on Data Records

Table 1A: Total Number of Data Records for All NIH Clinical Research Reported from FY2003–FY2012

Fiscal Year (FY)	Total Number of Data Records	Data Records without Enrollment	Data Records with Enrollment	Domestic Data Records	Foreign Data Records	Data Records for Female-Only Studies	Data Records for Male-Only Studies	Data Records for Studies Excluding Male-only and Female-only studies*
FY2003	14,041	3,825	10,216	9,578	638	1,404	614	8,198
FY2004	14,512	4,387	10,125	9,760	365	1,470	511	8,144
FY2005	14,798	4,565	10,233	9,862	371	1,326	559	8,348
FY2006	15,320	4,562	10,758	10,294	464	1,338	581	8,839
FY2007	15,567	4,653	10,914	10,463	451	1,340	517	9,057
FY2008	15,598	4,553	11,045	10,548	497	1,272	529	9,244
FY2009	16,689	5,518	11,171	10,269	902	1,356	624	9,191
FY2010	17,251	5,172	12,079	11,189	890	1,373	691	10,015
FY2011	15,843	4,547	11,296	10,500	796	1,286	617	9,393
FY2012	15,541	4,767	10,774	9,982	792	1,222	618	8,934

* Data records excluding male-only and female-only include unknown gender, and combination of unknown and any gender(s).

Table 1B: Total Number of Data Records for All NIH-Defined Phase III Clinical Trials Reported from FY2003–FY2012

Fiscal Year (FY)	Total Number of Data Records	Data Records without Enrollment	Data Records with Enrollment	Domestic Data Records	Foreign Data Records	Data Records for Female-Only Studies	Data Records for Male-Only Studies	Data Records for Studies Excluding Male-only and Female-only studies*
FY2003	965	113	852	643	209	189	84	591
FY2004	689	116	573	549	24	147	34	395
FY2005	665	118	547	517	30	127	34	386
FY2006	760	136	624	564	60	118	47	459
FY2007	749	96	653	609	44	121	41	491
FY2008	726	87	639	585	54	126	42	471
FY2009	662	32	630	457	173	151	48	431
FY2010	743	47	696	540	156	140	61	495
FY2011	628	46	582	461	121	109	36	437
FY2012	565	17	548	441	107	95	31	422

* Data records excluding male-only and female-only include unknown gender, and combination of unknown and any gender(s).

Table 2A: Total Enrollment for All NIH Clinical Research from FY2003–FY2012 (10 Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/ Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2003	14,772,254	8,514,481	57.6	6,121,496	41.4	136,277	0.9	3,044,558	20.6	351,987	2.4	5,469,923	37.0	5,769,509	39.1
FY2004	18,923,920	10,889,097	57.5	7,741,892	40.9	292,931	1.5	3,256,634	17.2	245,482	1.3	7,632,463	40.3	7,496,410	39.6
FY2005	15,722,752	9,503,922	60.4	5,941,907	37.8	276,923	1.8	3,469,692	22.1	317,697	2.0	6,034,230	38.4	5,624,210	35.8
FY2006	14,830,930	9,473,273	63.9	5,172,205	34.9	185,452	1.3	4,120,055	27.8	336,717	2.3	5,353,218	36.1	4,835,488	32.6
FY2007	17,448,458	10,152,589	58.2	6,887,791	39.5	408,078	2.3	9,000,648	51.6	377,803	2.2	1,151,941	6.6	6,509,988	37.3
FY2008	15,412,355	9,243,966	60.0	5,991,739	38.9	176,650	1.1	7,507,149	48.7	361,434	2.3	1,736,817	11.3	5,630,305	36.5
FY2009	19,138,738	11,439,143	59.8	7,570,646	39.6	128,949	0.7	4,830,093	25.2	396,076	2.1	6,609,050	34.5	7,174,570	37.5
FY2010	23,363,635	13,102,832	56.1	10,044,444	43.0	216,359	0.9	4,440,402	19.0	1,328,551	5.7	8,662,430	37.1	8,715,893	37.3
FY2011	15,992,456	9,499,682	59.4	6,287,306	39.3	205,468	1.3	4,562,652	28.5	1,210,876	7.6	4,937,030	30.9	5,076,430	31.7
FY2012	17,655,238	10,071,897	57.0	7,382,884	41.8	200,457	1.1	3,713,994	21.0	1,096,914	6.2	6,357,903	36.0	6,285,970	35.6

Table 2B: Total Enrollment for Domestic NIH Clinical Research from FY 2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/ Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2008	14,134,627	8,514,768	60.2	5,451,624	38.6	168,235	1.2	7,206,906	51.0	322,164	2.3	1,307,156	9.2	5,130,166	36.3
FY2009	17,962,879	10,748,744	59.8	7,093,702	39.5	120,433	0.7	4,619,125	25.7	347,894	1.9	6,129,619	34.1	6,745,808	37.6
FY2010	21,523,076	12,018,942	55.8	9,301,128	43.2	203,006	0.9	4,202,962	19.5	1,286,256	6.0	7,815,980	36.3	8,014,872	37.2
FY2011	13,470,269	7,974,958	59.2	5,314,952	39.5	180,359	1.3	4,318,845	32.1	1,172,588	8.7	3,656,113	27.1	4,142,364	30.8
FY2012	15,077,760	8,490,785	56.3	6,408,209	42.5	178,766	1.2	3,471,881	23.0	1,064,581	7.1	5,018,904	33.3	5,343,628	35.4

Table 2C: Total Enrollment for Domestic Extramural NIH Clinical Research from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/ Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2008	11,797,605	7,618,658	64.6	4,043,042	34.3	135,905	1.2	6,805,570	57.7	314,494	2.7	813,088	6.9	3,728,548	31.6
FY2009	15,546,350	9,842,191	63.3	5,624,890	36.2	79,269	0.5	4,460,062	28.7	338,422	2.2	5,382,129	34.6	5,286,468	34.0
FY2010	18,974,363	11,039,610	58.2	7,795,110	41.1	139,643	0.7	4,004,391	21.1	1,274,647	6.7	7,035,219	37.1	6,520,463	34.4
FY2011	10,853,602	6,961,241	64.1	3,779,319	34.8	113,042	1.0	4,108,737	37.9	1,162,408	10.7	2,852,504	26.3	2,616,911	24.1
FY2012	11,066,707	6,173,108	55.8	4,770,436	43.1	123,163	1.1	2,089,973	18.9	1,054,158	9.5	4,083,135	36.9	3,716,278	33.6

Table 2D: Total Enrollment for Domestic Intramural NIH Clinical Research from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/ Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2008	2,337,022	895,404	38.3	1,409,288	60.3	32,330	1.4	401,336	17.2	7,670	0.3	494,068	21.1	1,401,618	60.0
FY2009	2,416,529	906,553	37.5	1,468,812	60.8	41,164	1.7	159,063	6.6	9,472	0.4	747,490	30.9	1,459,340	60.4
FY2010	2,548,713	979,332	38.4	1,506,018	59.1	63,363	2.5	198,571	7.8	11,609	0.5	780,761	30.6	1,494,409	58.6
FY2011	2,616,667	1,013,717	38.7	1,535,633	58.7	67,317	2.6	210,108	8.0	10,180	0.4	803,609	30.7	1,525,453	58.3
FY2012	4,011,053	2,317,677	57.8	1,637,773	40.8	55,603	1.4	1,381,908	34.5	10,423	0.3	935,769	23.3	1,627,350	40.6

Table 2E: Total Enrollment for All NIH-Defined Phase III Clinical Trials from FY2003–FY2012 (10 Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2003	536,267	294,950	55.0	239,403	44.6	1,914	0.4	163,220	30.4	71,985	13.4	131,730	24.6	167,418	31.2
FY2004	545,367	301,353	55.3	242,913	44.5	1,101	0.2	160,148	29.4	72,762	13.3	141,205	25.9	170,151	31.2
FY2005	493,000	290,977	59.0	197,300	40.0	4,723	1.0	157,329	31.9	56,191	11.4	133,648	27.1	141,109	28.6
FY2006	499,430	314,066	62.9	179,975	36.0	5,389	1.1	167,624	33.6	27,723	5.6	146,442	29.3	152,252	30.5
FY2007	591,159	324,694	54.9	249,633	42.2	16,832	2.8	181,625	30.7	79,434	13.4	143,069	24.2	170,199	28.8
FY2008	792,578	455,612	57.5	319,732	40.3	17,234	2.2	219,673	27.7	79,613	10.0	235,939	29.8	240,119	30.3
FY2009	652,300	345,748	53.0	276,159	42.3	30,393	4.7	141,892	21.8	65,516	10.0	203,856	31.3	210,643	32.3
FY2010	769,885	408,181	53.0	330,808	43.0	30,896	4.0	119,103	15.5	62,315	8.1	289,078	37.5	268,493	34.9
FY2011	584,278	333,293	57.0	222,060	38.0	28,925	5.0	82,315	14.1	26,229	4.5	250,978	43.0	195,831	33.5
FY2012	603,136	374,819	62.1	197,019	32.7	31,298	5.2	58,916	9.8	10,288	1.7	315,903	52.4	186,731	31.0

Table 2F: Total Enrollment for Domestic NIH-Defined Phase III Clinical Trials from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2008	591,105	347,982	58.9	226,266	38.3	16,857	2.9	199,380	33.7	76,537	12.9	148,602	25.1	149,729	25.3
FY2009	590,886	347,533	58.8	226,715	38.4	16,638	2.8	123,192	20.8	59,643	10.1	224,341	38.0	167,072	28.3
FY2010	392,867	197,608	50.3	165,205	42.1	30,054	7.6	89,500	22.8	56,281	14.3	108,108	27.5	108,924	27.7
FY2011	303,916	160,644	52.9	116,345	38.3	26,927	8.9	64,095	21.1	24,337	8.0	96,549	31.8	92,008	30.3
FY2012	280,932	146,991	52.3	106,842	38.0	27,099	9.6	48,345	17.2	10,002	3.6	98,646	35.1	96,840	34.5

Table 2G: Total Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2008	585,023	345,372	59.0	223,021	38.1	16,630	2.8	199,371	34.1	76,378	13.1	146,001	25.0	146,643	25.1
FY2009	584,886	345,144	59.0	223,117	38.1	16,625	2.8	123,187	21.1	59,488	10.2	221,957	37.9	163,629	28.0
FY2010	382,998	190,415	49.7	162,542	42.4	30,041	7.8	84,405	22.0	56,117	14.7	106,010	27.7	106,425	27.8
FY2011	293,864	153,306	52.2	113,644	38.7	26,914	9.2	58,915	20.0	24,179	8.2	94,391	32.1	89,465	30.4
FY2012	270,082	138,811	51.4	104,185	38.6	27,086	10.0	42,375	15.7	9,837	3.6	96,436	35.7	94,348	34.9

Table 2H: Total Enrollment for Domestic Intramural NIH-Defined Phase III Clinical Trials from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Total Number of Females	Total % of Females	Total Number of Males	Total % of Males	Total Number of Unknown Sex/Gender	Total % of Unknown Sex/Gender	Number Enrolled in Female-only Studies	% Enrolled in Female-only Studies	Number Enrolled in Male-only Studies	% Enrolled in Male-only Studies	Number of Females, Excluding Female-only Studies	% of Females, Excluding Female-only Studies	Number of Males, Excluding Male-only Studies	% of Males, Excluding Male-only Studies
FY2008	6,082	2,610	42.9	3,245	53.4	227	3.7	9	0.1	159	2.6	2,601	42.8	3,086	50.7
FY2009	6,000	2,389	39.8	3,598	60.0	13	0.2	5	0.1	155	2.6	2,384	39.7	3,443	57.4
FY2010	9,869	7,193	72.9	2,663	27.0	13	0.1	5,095	51.6	164	1.7	2,098	21.3	2,499	25.3
FY2011	10,052	7,338	73.0	2,701	26.9	13	0.1	5,180	51.5	158	1.6	2,158	21.5	2,543	25.3
FY2012	10,850	8,180	75.4	2,657	24.5	13	0.1	5,970	55.0	165	1.5	2,210	20.4	2,492	23.0

Section 3: Metrics Based on Aggregate Enrollment of Race and Ethnicity: Clinical Research

Table 3A: Total Enrollment and Minority Enrollment for All NIH Clinical Research from FY2003–FY2012 (10 Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
FY2003	14,772,254	5,387,692	36.5
FY2004	18,923,920	7,611,611	40.2
FY2005	15,722,752	6,245,436	39.7
FY2006	14,830,930	6,388,316	43.1
FY2007	17,448,458	5,216,434	29.9
FY2008	15,412,355	4,412,106	28.6
FY2009	19,138,738	5,783,543	30.2
FY2010	23,363,635	7,510,763	32.1
FY2011	15,992,456	6,488,223	40.6
FY2012	17,655,238	6,446,175	36.5

Table 3B: Total Enrollment and Minority Enrollment for Domestic NIH Clinical Research (Old and New Forms) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
FY2008	14,134,627	3,521,691	24.1
FY2009	17,962,879	4,998,599	27.8
FY2010	21,523,076	6,041,531	28.1
FY2011	13,470,269	4,390,764	32.6
FY2012	15,077,760	4,332,559	28.7

Table 3C: Total Enrollment and Minority Enrollment for Domestic Extramural NIH Clinical Research (Old and New Forms) FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
FY2008	11,797,605	3,092,465	26.2
FY2009	15,546,350	4,419,314	28.4
FY2010	18,974,363	5,423,294	28.6
FY2011	10,853,602	3,746,667	34.5
FY2012	11,066,707	3,634,100	32.8

Table 3D: Total Enrollment and Minority Enrollment for Domestic Intramural NIH Clinical Research (Old and New Forms) FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
FY2008	2,337,022	459,360	19.7
FY2009	2,416,529	579,285	24.0
FY2010	2,548,713	618,237	24.3
FY2011	2,616,667	644,097	24.6
FY2012	4,011,053	698,459	17.4

Table 3E: Total Enrollment for All NIH Clinical Research Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	626,419	146,171	23.3	1,930	0.3	16,258	2.6	99,164	15.8	28,819	4.6	460,533	73.5	19,715	3.1
FY2009	389,466	74,571	19.1	1,213	0.3	11,652	3.0	42,405	10.9	19,301	5.0	299,115	76.8	15,780	4.1
FY2010	266,757	57,755	21.7	682	0.3	9,081	3.4	32,551	12.2	15,441	5.8	203,303	76.2	5,699	2.1
FY2011	18,294	3,824	20.9	60	0.3	382	2.1	1,787	9.8	1,595	8.7	13,950	76.3	520	2.8
FY2012	7,163	3,250	45.4	55	0.8	281	3.9	1,478	20.6	1,436	20.0	3,636	50.8	277	3.9

Table 3F: Total Enrollment for All NIH Clinical Research Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	14,785,936	4,265,935	28.9	134,494	0.9	1,168,053	7.9	1,835,035	12.4	48,560	0.3	9,651,267	65.3
FY2009	18,749,272	5,708,972	30.4	154,515	0.8	1,840,539	9.8	2,287,577	12.2	50,339	0.3	12,790,945	68.2
FY2010	23,096,878	7,453,008	32.3	361,229	1.6	2,133,596	9.2	2,949,614	12.8	150,856	0.7	15,278,117	66.1
FY2011	15,974,162	6,484,399	40.6	360,626	2.3	2,351,721	14.7	2,112,553	13.2	47,794	0.3	9,154,454	57.3
FY2012	17,648,075	6,442,925	36.5	335,460	1.9	2,157,236	12.2	2,140,641	12.1	56,721	0.3	9,070,528	51.4

Table 3F (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	181,941	1.2	1,766,586	11.9
FY2009	323,839	1.7	1,301,518	6.9
FY2010	358,946	1.6	1,864,520	8.1
FY2011	349,281	2.2	1,597,733	10.0
FY2012	355,539	2.0	3,531,950	20.0

Table 3G: Total Enrollment for All NIH Clinical Research Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	11,881,644	80.4	1,116,699	7.6	1,787,594	12.1
FY2009	16,033,547	85.5	1,302,944	6.9	1,412,781	7.5
FY2010	18,962,836	82.1	1,958,060	8.5	2,175,982	9.4
FY2011	12,687,228	79.4	1,641,383	10.3	1,645,551	10.3
FY2012	12,091,772	68.5	1,778,148	10.1	3,778,155	21.4

Table 3H: Total Enrollment for Domestic NIH Clinical Research Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic, not White	% Hispanic, not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	622,354	111,795	18.0	12,505	2.0	11,366	1.8	62,753	10.1	25,171	4.0	350,300	56.3	160,259	25.8
FY2009	372,018	72,601	19.5	1,165	0.3	11,204	3.0	42,213	11.3	18,019	4.8	284,717	76.5	14,700	4.0
FY2010	256,522	55,229	21.5	656	0.3	8,510	3.3	31,785	12.4	14,278	5.6	195,779	76.3	5,514	2.1
FY2011	17,878	3,723	20.8	60	0.3	380	2.1	1,730	9.7	1,553	8.7	13,663	76.4	492	2.8
FY2012	7,163	3,250	45.4	55	0.8	281	3.9	1,478	20.6	1,436	20.0	3,636	50.8	277	3.9

Table 3I: Total Enrollment for Domestic NIH Clinical Research Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	13,512,273	3,409,896	25.2	111,668	0.8	719,287	5.3	1,582,616	11.7	41,780	0.3	9,256,041	68.5
FY2009	17,590,861	4,925,998	28.0	145,541	0.8	1,396,409	7.9	2,066,817	11.7	47,981	0.3	12,387,427	70.4
FY2010	21,266,554	5,986,302	28.1	180,458	0.8	1,396,324	6.6	2,521,997	11.9	150,539	0.7	14,917,917	70.1
FY2011	13,452,391	4,387,041	32.6	153,066	1.1	1,234,591	9.2	1,610,345	12.0	47,247	0.4	8,731,310	64.9
FY2012	15,070,597	4,329,309	28.7	123,329	0.8	1,033,995	6.9	1,665,516	11.1	56,474	0.4	8,598,595	57.1

Table 3I (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	168,750	1.2	1,632,131	12.1
FY2009	302,563	1.7	1,244,123	7.1
FY2010	333,164	1.6	1,766,155	8.3
FY2011	325,613	2.4	1,350,219	10.0
FY2012	329,050	2.2	3,263,638	21.7

Table 3J: Total Enrollment for Domestic NIH Clinical Research Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	10,871,618	80.5	945,603	7.0	1,695,053	12.5
FY2009	15,090,139	85.8	1,142,171	6.5	1,358,551	7.7
FY2010	17,523,002	82.4	1,650,926	7.8	2,092,626	9.8
FY2011	10,765,968	80.0	1,151,089	8.6	1,535,334	11.4
FY2012	10,115,385	67.1	1,263,122	8.4	3,692,090	24.5

Table 3K: Total Enrollment for Domestic Extramural NIH Clinical Research Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	424,022	70,168	16.5	1,610	0.4	9,483	2.2	39,092	9.2	19,983	4.7	337,016	79.5	16,838	4.0
FY2009	210,541	34,534	16.4	884	0.4	4,456	2.1	20,257	9.6	8,937	4.2	163,706	77.8	12,301	5.8
FY2010	92,838	16,843	18.1	348	0.4	1,554	1.7	9,305	10.0	5,636	6.1	73,120	78.8	2,875	3.1
FY2011	17,878	3,723	20.8	60	0.3	380	2.1	1,730	9.7	1,553	8.7	13,663	76.4	492	2.8
FY2012	7,163	3,250	45.4	55	0.8	281	3.9	1,478	20.6	1,436	20.0	3,636	50.8	277	3.9

Table 3L: Total Enrollment for Domestic Extramural NIH Clinical Research Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	11,373,583	3,022,297	26.6	91,219	0.8	682,794	6.0	1,342,138	11.8	37,213	0.3	7,673,578	67.5
FY2009	15,335,809	4,384,780	28.6	124,638	0.8	1,359,843	8.9	1,806,313	11.8	46,579	0.3	10,854,012	70.8
FY2010	18,881,525	5,406,451	28.6	157,306	0.8	1,357,807	7.2	2,241,304	11.9	146,735	0.8	13,331,570	70.6
FY2011	10,835,724	3,742,944	34.5	127,914	1.2	1,182,405	10.9	1,295,314	12.0	42,554	0.4	6,986,561	64.5
FY2012	11,059,544	3,630,850	32.8	96,939	0.9	969,446	8.8	1,340,160	12.1	50,939	0.5	6,736,548	60.9

Table 3L (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	158,379	1.4	1,388,262	12.2
FY2009	157,430	1.0	986,976	6.4
FY2010	180,093	1.0	1,466,710	7.8
FY2011	178,911	1.7	1,022,065	9.4
FY2012	181,044	1.6	1,684,468	15.2

Table 3M: Total Enrollment for Domestic Extramural NIH Clinical Research Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	9,045,771	79.5	867,052	7.6	1,460,761	12.8
FY2009	13,306,619	86.8	1,061,093	6.9	968,097	6.3
FY2010	15,672,806	83.0	1,560,272	8.3	1,648,447	8.7
FY2011	8,715,026	80.4	1,044,252	9.6	1,076,446	9.9
FY2012	8,047,787	72.8	1,128,442	10.2	1,883,315	17.0

Table 3N: Total Enrollment for Domestic Intramural NIH Clinical Research Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)[1]

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	197,916	74,958	37.9	291	0.1	6,681	3.4	60,038	30.3	7,948	4.0	120,201	60.7	2,757	1.4
FY2009	161,477	38,067	23.6	281	0.2	6,748	4.2	21,956	13.6	9,082	5.6	121,011	74.9	2,399	1.5
FY2010	163,684	38,386	23.5	308	0.2	6,956	4.2	22,480	13.7	8,642	5.3	122,659	74.9	2,639	1.6
FY2011	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

[1] Data have zeroes for FY 2011 and FY 2012 because the intramural programs have migrated all data to the new data form (1997 OMB definitions).

Table 3O: Total Enrollment for Domestic Intramural NIH Clinical Research Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	2,139,106	384,402	18.0	21,335	1.0	36,225	1.7	237,793	11.1	4,556	0.2	1,575,167	73.6
FY2009	2,255,052	541,218	24.0	20,903	0.9	36,566	1.6	260,504	11.6	1,384	0.1	1,533,415	68.0
FY2010	2,385,029	579,851	24.3	23,152	1.0	38,517	1.6	280,693	11.8	3,804	0.2	1,586,347	66.5
FY2011	2,616,667	644,097	24.6	25,152	1.0	52,186	2.0	315,031	12.0	4,693	0.2	1,744,749	66.7
FY2012	4,011,053	698,459	17.4	26,390	0.7	64,549	1.6	325,356	8.1	5,535	0.1	1,862,047	46.4

Table 3O (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	10,157	0.5	253,873	11.9
FY2009	145,133	6.4	257,147	11.4
FY2010	153,071	6.4	299,445	12.6
FY2011	146,702	5.6	328,154	12.5
FY2012	148,006	3.7	1,579,170	39.4

Table 3P: Total Enrollment for Domestic Intramural NIH Clinical Research Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	1,817,816	85.0	77,927	3.6	243,363	11.4
FY2009	1,783,520	79.1	81,078	3.6	390,454	17.3
FY2010	1,850,196	77.6	90,654	3.8	444,179	18.6
FY2011	2,050,942	78.4	106,837	4.1	458,888	17.5
FY2012	2,067,598	51.5	134,680	3.4	1,808,790	45.1

Section 4: Metrics Based on Aggregate Enrollment of Race and Ethnicity: NIH-Defined Phase III Clinical Trials

Table 4A: Total Enrollment and Minority Enrollment for All NIH-Defined Phase III Clinical Trials from FY2003–FY2012 (10 Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
FY2003	536,267	132,302	24.7
FY2004	545,367	150,456	27.6
FY2005	493,000	154,191	31.3
FY2006	499,430	167,446	33.5
FY2007	591,159	244,932	41.4
FY2008	792,578	270,899	34.2
FY2009	652,300	291,949	44.8
FY2010	769,885	447,187	58.1
FY2011	584,278	347,770	59.5
FY2012	603,136	396,714	65.8

Table 4B: Total Enrollment and Minority Enrollment for Domestic NIH-Defined Phase III Clinical Trials (Old and New Forms) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
FY2008	591,105	119,582	20.2
FY2009	433,895	97,079	22.4
FY2010	392,867	92,509	23.5
FY2011	303,916	76,415	25.1
FY2012	280,932	81,420	29.0

Table 4C: Total Enrollment and Minority Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials (Old and New Forms) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
FY2008	585,023	117,869	20
FY2009	427,895	95,512	22
FY2010	382,998	89,006	23
FY2011	293,864	72,819	25
FY2012	270,082	77,371	29

Table 4D: Total Enrollment and Minority Enrollment for Domestic Intramural NIH-Defined Phase III Clinical Trials (Old and New Forms) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Number Enrolled	Number of Minorities Enrolled	% of Minorities Enrolled
2008	6,082	1,713	28.2
2009	6,000	1,567	26.1
2010	9,869	3,503	35.5
2011	10,052	3,596	35.8
2012	10,850	4,049	37.3

Table 4E: Total Enrollment for All NIH-Defined Phase III Clinical Trials Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Data Records	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	232,544	164	37,529	16.1	900	0.4	4,542	2.0	22,445	9.7	9,642	4.1	190,753	82.0	4,262	1.8
FY2009	165,737	196	25,344	15.3	613	0.4	3,291	2.0	14,956	9.0	6,484	3.9	136,082	82.1	4,311	2.6
FY2010	78,435	62	11,601	14.8	296	0.4	1,192	1.5	6,888	8.8	3,225	4.1	66,085	84.3	749	1.0
FY2011	1,159	3	13	1.1	1	0.1	3	0.3	9	0.8	0	0.0	1,088	93.9	58	5.0
FY2012	0	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 4F: Total Enrollment for All NIH-Defined Phase III Clinical Trials Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Protocols	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	560,034	475	270,889	48.4	15,006	2.7	95,296	17.0	103,166	18.4	716	0.1	281,344	50.2
FY2009	486,563	434	266,605	54.8	17,509	3.6	92,868	19.1	116,233	23.9	859	0.2	189,527	39.0
FY2010	691,450	634	435,586	63.0	15,846	2.3	113,042	16.3	254,738	36.8	936	0.1	229,410	33.2
FY2011	583,119	579	347,757	59.6	26,035	4.5	179,062	30.7	89,538	15.4	1,043	0.2	213,182	36.6
FY2012	603,136	548	396,714	65.8	28,352	4.7	214,542	35.6	96,158	15.9	967	0.2	182,936	30.3

Table 4F (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	12,136	2.2	52,370	9.4
FY2009	4,676	1.0	64,891	13.3
FY2010	8,258	1.2	69,220	10.0
FY2011	7,668	1.3	66,591	11.4
FY2012	6,398	1.1	73,783	12.2

Table 4G: Total Enrollment for All NIH-Defined Phase III Clinical Trials Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	11,881,644	80.4	1,116,699	7.6	1,787,594	12.1
FY2009	16,033,547	85.5	1,302,944	6.9	1,412,781	7.5
FY2010	18,962,836	82.1	1,958,060	8.5	2,175,982	9.4
FY2011	12,687,228	79.4	1,641,383	10.3	1,645,551	10.3
FY2012	12,091,772	68.5	1,778,148	10.1	3,778,155	21.4

Table 4H: Total Enrollment for Domestic NIH-Defined Phase III Clinical Trials Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	229,348	37,458	16.3	885	0.4	4,506	2.0	22,431	9.8	9,636	4.2	187,719	81.8	4,171	1.8
FY2009	150,439	24,468	16.3	569	0.4	2,861	1.9	14,768	9.8	6,270	4.2	122,713	81.6	3,258	2.2
FY2010	70,513	11,268	16.0	270	0.4	1,026	1.5	6,816	9.7	3,156	4.5	58,678	83.2	567	0.8
FY2011	929	12	1.3	1	0.1	2	0.2	9	1.0	0	0.0	882	94.9	35	3.8
FY2012	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 4I: Total Enrollment for Domestic NIH-Defined Phase III Clinical Trials Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	361,757	81,924	22.6	2,256	0.6	6,314	1.7	25,753	7.1	713	0.2	276,406	76.4
FY2009	283,456	72,611	25.6	5,349	1.9	11,752	4.1	23,520	8.3	844	0.3	183,320	64.7
FY2010	322,354	81,241	25.2	3,231	1.0	6,899	2.1	32,467	10.1	901	0.3	217,844	67.6
FY2011	302,987	76,403	25.2	3,390	1.1	7,720	2.5	27,134	9.0	1,014	0.3	204,315	67.4
FY2012	280,932	81,420	29.0	3,397	1.2	5,504	2.0	34,495	12.3	943	0.3	176,627	62.9

Table 4I (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	11,836	3.3	38,479	10.6
FY2009	4,672	1.6	53,999	19.1
FY2010	6,326	2.0	54,686	17.0
FY2011	6,142	2.0	53,272	17.6
FY2012	6,396	2.3	53,570	19.1

Table 4J: Total Enrollment for Domestic NIH-Defined Phase III Clinical Trials Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	289,525	80.0	42,003	11.6	30,229	8.4
FY2009	212,327	74.9	32,101	11.3	39,028	13.8
FY2010	246,756	76.5	34,635	10.7	40,963	12.7
FY2011	230,759	76.2	34,308	11.3	37,920	12.5
FY2012	205,055	73.0	34,255	12.2	41,622	14.8

Table 4K: Total Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	226,137	36,952	16.3	880	0.4	4,442	2.0	22,069	9.8	9,561	4.2	185,032	81.8	4,153	1.8
FY2009	147,399	24,097	16.3	565	0.4	2,799	1.9	14,542	9.9	6,191	4.2	120,068	81.5	3,234	2.2
FY2010	67,454	10,894	16.2	265	0.4	963	1.4	6,586	9.8	3,080	4.6	56,016	83.0	544	0.8
FY2011	929	12	1.3	1	0.1	2	0.2	9	1.0	0	0.0	882	94.9	35	3.8
FY2012	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 4L: Total Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	358,886	80,917	22.5	2,449	0.7	6,192	1.7	24,843	6.9	636	0.2	275,071	76.6
FY2009	280,496	71,415	25.5	5,173	1.8	11,727	4.2	22,694	8.1	843	0.3	182,692	65.1
FY2010	315,544	78,112	24.8	2,947	0.9	6,700	2.1	30,058	9.5	900	0.3	213,988	67.8
FY2011	292,935	72,807	24.9	3,092	1.1	7,451	2.5	24,435	8.3	1,011	0.3	197,742	67.5
FY2012	270,082	77,371	28.6	3,091	1.1	5,207	1.9	31,609	11.7	938	0.3	169,553	62.8

Table 4L (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	11,832	3.3	37,863	10.6
FY2009	4,668	1.7	52,699	18.8
FY2010	6,321	2.0	54,630	17.3
FY2011	6,131	2.1	53,073	18.1
FY2012	6,377	2.4	53,307	19.7

Table 4M: Total Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	287,156	80.0	41,914	11.7	29,816	8.3
FY2009	209,846	74.8	31,936	11.4	38,714	13.8
FY2010	240,203	76.1	34,403	10.9	40,938	13.0
FY2011	221,136	75.5	33,942	11.6	37,857	12.9
FY2012	194,915	72.2	33,657	12.5	41,510	15.4

Table 4N: Total Enrollment for Domestic Intramural NIH-Defined Phase III Clinical Trials Racial Categories (Old Form, 1977 OMB Definitions) from FY2008–FY2012 (Five Year Trend)[2]

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic, not White	% Hispanic, not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2008	3,211	506	15.8	5	0.2	64	2.0	362	11.3	75	2.3	2,687	83.7	18	0.6
FY2009	3,040	371	12.2	4	0.1	62	2.0	226	7.4	79	2.6	2,645	87.0	24	0.8
FY2010	3,059	374	12.2	5	0.2	63	2.1	230	7.5	76	2.5	2,662	87.0	23	0.8
FY2011	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

[2] Data have zeroes for FY 2011 and FY 2012 because the intramural programs have migrated all data to the new data form (1997 OMB definitions).

Table 4O: Total Enrollment for Domestic Intramural NIH-Defined Phase III Clinical Trials Racial Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Total Enrollment	Number of Minorities Enrolled	% of Minorities Enrolled	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White
FY2008	2,871	1,207	42.0	7	0.2	122	4.2	910	31.7	77	2.7	1,335	46.5
FY2009	2,960	1,196	40.4	176	5.9	25	0.8	826	27.9	1	0.0	628	21.2
FY2010	6,810	3,129	45.9	284	4.2	199	2.9	2,409	35.4	1	0.0	3,856	56.6
FY2011	10,052	3,596	35.8	298	3.0	269	2.7	2,699	26.9	3	0.0	6,573	65.4
FY2012	10,850	4,049	37.3	306	2.8	297	2.7	2,886	26.6	5	0.0	7,074	65.2

Table 4O (continued)

Fiscal Year (FY)	More than one race	% More than one race	Unknown/Not Reported	% Unknown/Not Reported
FY2008	4	0.1	416	14.5
FY2009	4	0.1	1,300	43.9
FY2010	5	0.1	56	0.8
FY2011	11	0.1	199	2.0
FY2012	19	0.2	263	2.4

Table 4P: Total Enrollment of Domestic Intramural NIH-Defined Phase III Clinical Trials Ethnic Categories (New Form, 1997 OMB Definitions) from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2008	2,369	82.5	89	3.1	413	14.4
FY2009	2,481	83.8	165	5.6	314	10.6
FY2010	6,553	96.2	232	3.4	25	0.4
FY2011	9,623	95.7	366	3.6	63	0.6
FY2012	10,140	93.5	598	5.5	112	1.0

Section 5: Metrics Based on Aggregate Enrollment: Sex/Gender by Race and Ethnicity for NIH Clinical Research

Table 5A: Minority Enrollment by Sex/Gender for All NIH Clinical Research from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	9,243,966	60.0	86,903	59.5	2,522,763	59.1
FY2008	Male	5,991,739	38.9	59,249	40.5	1,725,239	40.4
FY2008	Unknown Sex/ Gender	176,650	1.1	19	0.0	17,933	0.4
FY2009	Female	3,438,992	59.5	38,109	51.1	3,400,883	59.6
FY2009	Male	2,325,402	40.2	36,455	48.9	2,288,947	40.0
FY2009	Unknown Sex/ Gender	19,149	0.3	7	0.0	19,142	0.0
FY2010	Female	4,423,474	58.9	27,730	48.0	4,395,744	59.0
FY2010	Male	3,041,396	40.5	29,882	51.7	3,011,514	40.4
FY2010	Unknown Sex/ Gender	45,893	0.6	143	0.2	45,750	0.6
FY2011	Female	4,018,450	62.3	1,619	49.8	4,016,831	62.3
FY2011	Male	2,430,139	37.7	2,204	67.8	2,427,935	37.7
FY2011	Unknown Sex/ Gender	39,634	0.6	1	0.0	39,633	0.6
FY2012	Female	3,742,903	58.1	1,333	41.0	3,741,570	58.1
FY2012	Male	2,661,413	41.3	1,916	59.0	2,659,497	41.3
FY2012	Unknown Sex/ Gender	41,859	0.6	1	0.0	41,858	0.6

Table 5B: FY2011 and FY2012 Enrollment for All NIH Clinical Research: Sex/Gender by Race (Old Form, 1977 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	28	0.3	192	2.3	676	8.1	723	8.7	6,545	78.6	167	2.0
FY2011	Male	32	0.3	189	1.9	1,111	11.2	872	8.8	7,402	74.5	332	3.3
FY2011	Unknown Sex/Gender	0	0.0	1	4.0	0	0.0	0	0.0	3	12.0	21	84.0
FY2012	Female	27	0.9	134	4.3	516	16.4	656	20.8	1,697	53.8	122	3.9
FY2012	Male	28	0.7	146	3.7	962	24.1	780	19.5	1,939	48.5	142	3.6
FY2012	Unknown Sex/Gender	0	0.0	1	7.1	0	0.0	0	0.0	0	0.0	13	92.9

Table 5C: FY2011 and FY2012 Enrollment for All NIH Clinical Research: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	215,720	2.3	1,607,044	16.9	1,181,791	12.5	27,304	0.3	5,342,673	56.3	197,882	2.1	918,937	9.7
FY2011	Male	144,147	2.3	732,466	11.7	911,489	14.5	20,374	0.3	3,790,071	60.4	150,575	2.4	528,246	8.4
FY2011	Unknown Sex/Gender	759	0.4	12,211	5.9	19,273	9.4	116	0.1	21,710	10.6	824	0.4	150,550	73.3
FY2012	Female	188,522	1.9	1,380,540	13.7	1,189,565	11.8	33,115	0.3	4,734,414	47.0	196,008	1.9	2,346,581	23.3
FY2012	Male	146,418	2.0	758,732	10.3	937,078	12.7	23,490	0.3	4,308,675	58.4	158,484	2.1	1,046,010	14.2
FY2012	Unknown Sex/Gender	520	0.3	17,964	9.0	13,998	7.0	116	0.1	27,439	13.7	1,047	0.5	139,359	69.5

Table 5D: FY2011 and FY2012 Enrollment for All NIH Clinical Research: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	7,651,179	80.6	995,980	10.5	844,192	8.9
FY2011	Male	4,990,330	79.5	636,549	10.1	650,489	10.4
FY2011	Unknown Sex/ Gender	45,719	22.3	8,854	4.3	150,870	73.4
FY2012	Female	6,490,049	64.5	967,926	9.6	2,610,770	25.9
FY2012	Male	5,544,566	75.1	801,398	10.9	1,032,923	14.0
FY2012	Unknown Sex/ Gender	57,157	28.5	8,824	4.4	134,462	67.1

Table 5E: Minority Enrollment by Sex/Gender for Domestic NIH Clinical Research from FY2008-FY2012 (Five Year Trend)

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	2,121,057	60.2	86,451	77.3	2,034,606	59.7
FY2008	Male	1,386,456	39.4	25,121	22.5	1,361,335	39.9
FY2008	Unknown Sex/ Gender	14,178	0.4	223	0.2	13,955	0.4
FY2009	Female	2,924,019	59.9	36,421	50.2	2,887,598	60.0
FY2009	Male	1,943,741	39.8	36,174	49.8	1,907,567	39.6
FY2009	Unknown Sex/ Gender	16,034	0.3	6	0.0	16,028	0.3
FY2010	Female	3,557,029	58.9	25,909	46.9	3,531,120	59.0
FY2010	Male	2,444,784	40.5	29,177	52.8	2,415,607	40.4
FY2010	Unknown Sex/ Gender	39,718	0.7	143	0.3	39,575	0.7
FY2011	Female	2,744,151	62.5	1,567	42.1	2,742,584	62.5
FY2011	Male	1,625,743	37.0	2,155	57.9	1,623,588	37.0
FY2011	Unknown Sex/ Gender	20,870	0.5	1	0.0	20,869	0.5
FY2012	Female	2,423,584	55.9	1,333	41.0	2,422,251	56.0
FY2012	Male	1,882,114	43.4	1,916	59.0	1,880,198	43.4
FY2012	Unknown Sex/ Gender	26,861	0.6	1	0.0	26,860	0.6

Table 5F: FY2011 and FY2012 Enrollment for Domestic NIH Clinical Research: Sex/Gender by Race (Old Form, 1977 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	28	0.3	190	2.3	647	7.9	702	8.6	6,420	78.9	155	1.9
FY2011	Male	32	0.3	189	1.9	1,083	11.2	851	8.8	7,242	74.6	316	3.3
FY2011	Unknown Sex/Gender	0	0.0	1	4.3	0	0.0	0	0.0	1	4.3	21	91.3
FY2012	Female	27	0.9	134	4.3	516	16.4	656	20.8	1,697	53.8	122	3.9
FY2012	Male	28	0.7	146	3.7	962	24.1	780	19.5	1,939	48.5	142	3.6
FY2012	Unknown Sex/Gender	0	0.0	1	7.1	0	0.0	0	0.0	0	0.0	13	92.9

Table 5G: FY2011 and FY2012 Enrollment for Domestic NIH Clinical Research: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	99,355	1.2	900,326	11.3	883,925	11.1	27,038	0.3	5,087,456	63.9	185,336	2.3	783,380	9.8
FY2011	Male	53,107	1.0	331,188	6.2	714,528	13.5	20,093	0.4	3,625,113	68.3	139,495	2.6	421,715	7.9
FY2011	Unknown Sex/Gender	604	0.3	3,077	1.7	11,892	6.6	116	0.1	18,741	10.4	782	0.4	145,124	80.5
FY2012	Female	66,154	0.8	662,431	7.8	887,422	10.5	32,962	0.4	4,465,700	52.6	179,017	2.1	2,193,947	25.8
FY2012	Male	56,695	0.9	363,506	5.7	767,298	12.0	23,396	0.4	4,107,877	64.1	149,024	2.3	936,416	14.6
FY2012	Unknown Sex/Gender	480	0.3	8,058	4.5	10,796	6.0	116	0.1	25,018	14.0	1,009	0.6	133,275	74.6

Table 5H: FY2011 and FY2012 Enrollment for Domestic NIH Clinical Research: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	6,453,744	81.0	721,924	9.1	791,148	9.9
FY2011	Male	4,282,102	80.7	422,490	8.0	600,647	11.3
FY2011	Unknown Sex/ Gender	30,122	16.7	6,675	3.7	143,539	79.6
FY2012	Female	5,246,806	61.8	671,787	7.9	2,569,040	30.3
FY2012	Male	4,825,831	75.4	584,353	9.1	994,028	15.5
FY2012	Unknown Sex/ Gender	42,748	23.9	6,982	3.9	129,022	72.2

Table 5I: Minority Enrollment by Sex/Gender for Domestic Extramural NIH Clinical Research from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	1,946,882	63.0	47,117	67.1	1,899,765	62.9
FY2008	Male	1,131,742	36.6	23,032	32.8	1,108,710	36.7
FY2008	Unknown Sex/ Gender	13,841	0.4	19	0.0	13,822	0.5
FY2009	Female	2,697,251	62.8	15,710	45.5	2,681,541	62.8
FY2009	Male	1,595,146	37.2	18,821	54.5	1,576,325	36.9
FY2009	Unknown Sex/ Gender	1,211	0.0	3	0.0	12,109	0.3
FY2010	Female	3,304,953	60.9	4,986	29.6	3,299,967	61.0
FY2010	Male	2,084,271	38.4	11,718	69.6	2,072,553	38.3
FY2010	Unknown Sex/ Gender	34,070	0.6	139	0.8	33,931	0.6
FY2011	Female	2,478,812	66.2	1,567	42.1	2,477,245	66.2
FY2011	Male	1,254,173	33.5	2,155	57.9	1,252,018	33.5
FY2011	Unknown Sex/ Gender	13,682	0.4	1	0.0	13,681	0.4
FY2012	Female	2,128,669	58.6	1,333	41.0	2,127,336	58.6
FY2012	Male	1,480,077	40.7	1,916	59.0	1,478,161	40.7
FY2012	Unknown Sex/ Gender	25,354	0.7	1	0.0	25,353	0.7

Table 5J: FY2011 and FY2012 Enrollment for Domestic Extramural NIH Clinical Research: Sex/Gender by Race (Old Form, 1977 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	28	0.3	190	2.3	647	7.9	702	8.6	6,420	78.9	155	1.9
FY2011	Male	32	0.3	189	1.9	1,083	11.2	851	8.8	7,242	74.6	316	3.3
FY2011	Unknown Sex/Gender	0	0.0	1	4.3	0	0.0	0	0.0	1	4.3	21	91.3
FY2012	Female	27	0.9	134	4.3	516	16.4	656	20.8	1,697	53.8	122	3.9
FY2012	Male	28	0.7	146	3.7	962	24.1	780	19.5	1,939	48.5	142	3.6
FY2012	Unknown Sex/Gender	0	0.0	1	7.1	0	0.0	0	0.0	0	0.0	13	92.9

Table 5K: FY2011 and FY2012 Enrollment for Domestic Extramural NIH Clinical Research: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	87,237	1.3	874,313	12.6	786,178	11.3	24,616	0.4	4,388,684	63.1	108,137	1.6	683,934	9.8
FY2011	Male	40,101	1	305,047	8	504,320	13	17,823	0	2,584,091	69	70,006	2	248,218	7
FY2011	Unknown Sex/Gender	576	0.5	3,045	2.7	4,816	4.3	115	0.1	13,786	12.2	768	0.7	89,913	79.6
FY2012	Female	53,419	0.9	630,562	10.2	780,065	12.6	30,096	0.5	3,715,392	60.2	101,137	1.6	859,285	13.9
FY2012	Male	43,046	0.9	331,040	6.9	550,500	11.5	20,728	0.4	3,001,289	63.0	78,915	1.7	740,921	15.5
FY2012	Unknown Sex/Gender	474	0.4	7,844	6.4	9,595	7.8	115	0.1	19,867	16.1	992	0.8	84,262	68.4

Table 5L: FY2011 and FY2012 Enrollment for Domestic Extramural NIH Clinical Research: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	5,654,058	81.3	669,615	9.6	629,426	9.1
FY2011	Male	3,042,902	81	368,001	10	358,703	10
FY2011	Unknown Sex/ Gender	18,066	16.0	6,636	5.9	88,317	78.1
FY2012	Female	4,425,687	71.7	607,349	9.8	1,136,920	18.4
FY2012	Male	3,585,665	75.2	514,185	10.8	666,589	14.0
FY2012	Unknown Sex/ Gender	36,435	29.6	6,908	5.6	79,806	64.8

Table 5M: Minority Enrollment by Sex/Gender for Domestic Intramural NIH Clinical Research from FY2008–FY2012 (Five Year Trend)[3]

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	172,273	37.5	39,295	52.4	132,978	34.6
FY2008	Male	286,978	62.5	35,663	47.6	251,315	65.4
FY2008	Unknown Sex/ Gender	109	0.0	0	0.0	109	0.0
FY2009	Female	226,768	39.1	20,711	54.4	206,057	38.1
FY2009	Male	348,595	60.2	17,353	45.6	331,242	61.2
FY2009	Unknown Sex/ Gender	3,922	0.7	3	0.0	3,919	0.7
FY2010	Female	252,076	40.8	20,923	54.5	231,153	39.9
FY2010	Male	360,513	58.3	17,459	45.5	343,054	59.2
FY2010	Unknown Sex/ Gender	5,648	0.9	4	0.0	5,644	1.0
FY2011	Female	265,339	41.2	0	0.0	265,339	41.2
FY2011	Male	371,570	57.7	0	0.0	371,570	57.7
FY2011	Unknown Sex/ Gender	7,188	1.1	0	0.0	7,188	1.1
FY2012	Female	294,915	42.2	0	0.0	294,915	42.2
FY2012	Male	402,037	57.6	0	0.0	402,037	57.6
FY2012	Unknown Sex/ Gender	1,507	0.2	0	0.0	1,507	0.2

[3] Data have zeroes for FY 2011 and FY 2012 because the intramural programs have migrated all data to the new data form (1997 OMB definitions).

Table 5N: FY2011 and FY2012 Enrollment for Domestic Intramural NIH Clinical Research: Sex/Gender by Race (Old Form, 1977 OMB Definitions)[4]

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2011	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2011	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

[4] Data have zeroes for FY 2011 and FY 2012 because the intramural programs have migrated all data to the new data form (1997 OMB definitions).

Table 5O: FY2011 and FY2012 Enrollment for Domestic Intramural NIH Clinical Research: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	12,118	1.2	26,013	2.6	97,747	9.6	2,422	0.2	698,772	68.9	77,199	7.6	99,446	9.8
FY2011	Male	13,006	1	26,141	2	210,208	14	2,270	0	1,041,022	68	69,489	5	173,497	11.3
FY2011	Unknown Sex/Gender	28	0.0	32	0.0	7,076	10.5	1	0.0	4,955	7.4	14	0.0	55,211	82.0
FY2012	Female	12,735	0.5	31,869	1.4	107,357	4.6	2,866	0.1	750,308	32.4	77,880	3.4	1,334,662	57.6
FY2012	Male	13,649	0.8	32,466	2.0	216,798	13.2	2,668	0.2	1,106,588	67.6	70,109	4.3	195,495	11.9
FY2012	Unknown Sex/Gender	6	0.0	214	0.4	1,201	2.2	1	0.0	5,151	9.3	17	0.0	49,013	88.1

Table 5P: FY2011 and FY2012 Enrollment for Domestic Intramural NIH Clinical Research: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	799,686	78.9	52,309	5.2	161,722	16.0
FY2011	Male	1,239,200	122	54,489	4	241,944	15.8
FY2011	Unknown Sex/ Gender	12,056	1.2	39	0.1	55,222	82.0
FY2012	Female	821,119	35.4	64,438	2.8	1,432,120	61.8
FY2012	Male	1,240,166	75.7	70,168	4.3	327,439	20.0
FY2012	Unknown Sex/ Gender	6,313	11.4	74	0.1	49,216	88.5

Section 6: Metrics Based on Aggregate Enrollment: Sex/Gender by Race and Ethnicity NIH-Defined Phase III Clinical Trials

Table 6A: Minority Enrollment by Sex/Gender for All NIH-Defined Phase III Clinical Trials from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	169,540	55.0	23,466	62.5	146,074	53.9
FY2008	Male	137,983	44.7	14,062	37.5	123,921	45.7
FY2008	Unknown Sex/ Gender	895	0.3	1	0.0	894	0.3
FY2009	Female	157,952	54.1	11,213	44.2	146,739	55.0
FY2009	Male	133,282	45.7	14,129	55.7	119,153	44.7
FY2009	Unknown Sex/ Gender	715	0.2	2	0.0	713	0.3
FY2010	Female	250,716	56.1	2,741	23.6	247,975	56.9
FY2010	Male	195,249	43.7	8,860	76.4	186,389	42.8
FY2010	Unknown Sex/ Gender	1,222	0.3	0	0.0	1,222	0.3
FY2011	Female	214,756	61.8	6	46.2	214,750	61.8
FY2011	Male	130,546	37.5	7	53.8	130,539	37.5
FY2011	Unknown Sex/ Gender	2,468	0.7	0	0.0	2,468	0.7
FY2012	Female	273,477	68.9	0	0.0	273,477	68.9
FY2012	Male	118,517	29.9	0	0.0	118,517	29.9
FY2012	Unknown Sex/ Gender	4,720	1.2	0	0.0	4,720	1.2

Table 6B: FY2011 and FY2012 Enrollment for All NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (Old Form, 1977 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	1	0.2	3	0.6	2	0.4	0	0.0	468	94.2	23	4.6
FY2011	Male	0	0.0	0	0.0	7	1.1	0	0.0	617	93.6	35	5.3
FY2011	Unknown Sex/Gender	0	0	0	0	0	0	0	0	3	0.455235	0	0.0
FY2012	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 6C: FY2011 and FY2012 Enrollment for All NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	15,546	4.7	109,835	33.0	55,397	16.6	553	0.2	121,282	36.4	2,995	0.9	27,188	8.2
FY2011	Male	10,424	4.7	67,414	30.4	33,897	15.3	483	0.2	90,997	41.1	4,602	2.1	13,584	6.1
FY2011	Unknown Sex/Gender	65	0.2	1,813	6.3	244	0.8	7	0.0	903	3.1	71	0.2	25,819	89.3
FY2012	Female	20,461	5.5	147,568	39.4	67,023	17.9	482	0.1	103,716	27.7	3,252	0.9	32,317	8.6
FY2012	Male	7,854	4.0	63,009	32.0	28,797	14.6	478	0.2	78,254	39.7	3,073	1.6	15,554	7.9
FY2012	Unknown Sex/Gender	37	0.1	3,965	12.7	338	1.1	7	0.0	966	3.1	73	0.2	25,912	82.8

Table 6D: FY2011 and FY2012 Enrollment for All NIH-Defined Phase III Clinical Trials: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	277,170	83.3	45,823	13.8	9,803	2.9
FY2011	Male	185,527	83.8	25,827	11.7	10,047	4.5
FY2011	Unknown Sex/ Gender	3,017	10.4	348	1.2	25,557	88.4
FY2012	Female	310,773	82.9	55,079	14.7	8,967	2.4
FY2012	Male	161,842	82.1	23,366	11.9	11,811	6.0
FY2012	Unknown Sex/ Gender	5,293	16.9	352	1.1	25,653	82.0

Table 6E: Minority Enrollment by Sex/Gender for Domestic NIH-Defined Phase III Clinical Trials from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	68,672	57.4	23,397	62.5	45,275	55.1
FY2008	Male	50,392	42.1	14,060	37.5	36,332	44.2
FY2008	Unknown Sex/ Gender	518	0.4	1	0.0	517	0.6
FY2009	Female	58,301	60.1	10,580	43.2	47,721	65.7
FY2009	Male	38,266	39.4	13,887	56.8	24,379	33.6
FY2009	Unknown Sex/ Gender	512	0.5	1	0.0	511	0.7
FY2010	Female	52,003	56.2	2,522	22.4	49,481	60.9
FY2010	Male	40,099	43.3	8,746	77.6	31,353	38.6
FY2010	Unknown Sex/ Gender	407	0.4	0	0.0	407	0.5
FY2011	Female	46,895	61.4	5	41.7	46,890	61.4
FY2011	Male	29,040	38.0	7	58.3	29,033	38.0
FY2011	Unknown Sex/ Gender	480	0.6	0	0.0	480	0.6
FY2012	Female	48,783	59.9	0	0.0	48,783	59.9
FY2012	Male	32,106	39.4	0	0.0	32,106	39.4
FY2012	Unknown Sex/ Gender	531	0.7	0	0.0	531	0.7

Table 6F: FY2011 and FY2012 Enrollment for Domestic NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (Old Form, 1977 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	1	0.0	2	0.0	2	0.0	0	0.0	372	0.0	12	0.0
FY2011	Male	0	0.0	0	0.0	7	0.0	0	0.0	509	0.0	23	0.0
FY2011	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0
FY2012	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 6G: FY2011 and FY2012 Enrollment for Domestic NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	1,820	1.1	4,857	3.0	17,929	11.2	539	0.3	116,491	72.7	2,991	1.9	15,628	9.8
FY2011	Male	1,542	1.3	2,822	2.4	9,138	7.9	468	0.4	86,926	75.1	3,080	2.7	11,830	10.2
FY2011	Unknown Sex/Gender	28	0.1	41	0.2	67	0.2	7	0.0	898	3.3	71	0.3	25,814	95.9
FY2012	Female	1,821	1.2	3,091	2.1	21,849	14.9	471	0.3	100,857	68.6	3,250	2.2	15,652	10.6
FY2012	Male	1,548	1.4	2,371	2.2	12,549	11.7	465	0.4	74,810	70.0	3,073	2.9	12,026	11.3
FY2012	Unknown Sex/Gender	28	0.1	42	0.2	97	0.4	7	0.0	960	3.5	73	0.3	25,892	95.5

Table 6H: FY2011 and FY2012 Enrollment for Domestic NIH-Defined Phase III Clinical Trials: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	132,640	82.8	20,393	12.7	7,222	4.5
FY2011	Male	97,050	83.8	13,606	11.7	5,150	4.4
FY2011	Unknown Sex/ Gender	1,069	4.0	309	1.1	25,548	94.9
FY2012	Female	119,053	81.0	20,066	13.7	7,872	5.4
FY2012	Male	84,873	79.4	13,862	13.0	8,107	7.6
FY2012	Unknown Sex/ Gender	1,129	4.2	327	1.2	25,643	94.6

Table 6I: Minority Enrollment by Sex/Gender for Domestic Extramural NIH-Defined Phase III Clinical Trials from FY2008–FY2012 (Five Year Trend)

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	67,801	57.5	23,224	62.8	44,577	55.1
FY2008	Male	49,563	42.0	13,727	37.1	35,836	44.3
FY2008	Unknown Sex/ Gender	505	0.4	1	0.0	504	0.6
FY2009	Female	57,483	60.2	10,461	43.4	47,022	65.8
FY2009	Male	37,530	39.3	13,635	56.6	23,895	33.5
FY2009	Unknown Sex/ Gender	499	0.5	1	0.0	498	0.7
FY2010	Female	49,166	55.2	2,402	22.0	46,764	59.9
FY2010	Male	39,446	44.3	8,492	78.0	30,954	39.6
FY2010	Unknown Sex/ Gender	394	0.4	0	0.0	394	0.5
FY2011	Female	43,996	60.4	5	41.7	43,991	60.4
FY2011	Male	28,356	38.9	7	58.3	28,349	38.9
FY2011	Unknown Sex/ Gender	467	0.6	0	0.0	467	0.6
FY2012	Female	45,421	58.7	0	0.0	45,421	58.7
FY2012	Male	31,432	40.6	0	0.0	31,432	40.6
FY2012	Unknown Sex/ Gender	518	0.7	0	0.0	518	0.7

Table 6J: FY2011 and FY2012 Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (Old Form, 1977 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	1	0.0	2	0.0	2	0.0	0	0.0	372	0.0	12	0.0
FY2011	Male	0	0.0	0	0.0	7	0.0	0	0.0	509	0.0	23	0.0
FY2011	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0
FY2012	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 6K: FY2011 and FY2012 Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	1,578	1.0	4,658	3.0	15,727	10.3	538	0.4	111,919	73.2	2,983	2.0	15,514	10.1
FY2011	Male	1,486	1.3	2,752	2.4	8,654	7.7	466	0.4	84,925	75.1	3,077	2.7	11,745	10.4
FY2011	Unknown Sex/Gender	28	0.1	41	0.2	54	0.2	7	0.0	898	3.3	71	0.3	25,814	95.9
FY2012	Female	1,575	1.1	2,863	2.1	19,453	14.0	468	0.3	95,753	69.0	3,237	2.3	15,462	11.1
FY2012	Male	1,488	1.4	2,302	2.2	12,072	11.6	463	0.4	72,840	69.9	3,067	2.9	11,953	11.5
FY2012	Unknown Sex/Gender	28	0.1	42	0.2	84	0.3	7	0.0	960	3.5	73	0.3	25,892	95.6

Table 6L: FY2011 and FY2012 Enrollment for Domestic Extramural NIH-Defined Phase III Clinical Trials: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	125,630	82.2	20,098	13.1	7,189	4.7
FY2011	Male	94,450	83.5	13,535	12.0	5,120	4.5
FY2011	Unknown Sex/ Gender	1,056	3.9	309	1.1	25,548	94.9
FY2012	Female	111,487	80.3	19,532	14.1	7,792	5.6
FY2012	Male	82,312	79.0	13,798	13.2	8,075	7.8
FY2012	Unknown Sex/ Gender	1,116	4.1	327	1.2	25,643	94.7

Table 6M: Minority Enrollment by Sex/Gender for Domestic Intramural NIH-Defined Phase III Clinical Trials from FY2008-FY2012 (Five Year Trend)[5]

Fiscal Year (FY)	Sex/Gender	Total Number of Minorities Enrolled	% of Minorities Enrolled	Number of Minorities Enrolled and Reported on OLD Form	% of Minorities Enrolled and Reported on OLD Form	Number of Minorities Enrolled and Reported on NEW Form	% of Minorities Enrolled and Reported on NEW Form
FY2008	Female	871	50.8	173	34.2	698	57.8
FY2008	Male	829	48.4	333	65.8	496	41.1
FY2008	Unknown Sex/ Gender	13	0.8	0	0.0	13	1.1
FY2009	Female	818	52.2	119	32.1	699	58.4
FY2009	Male	736	47.0	252	67.9	484	40.5
FY2009	Unknown Sex/ Gender	13	0.8	0	0.0	13	1.1
FY2010	Female	2,837	81.0	120	32.1	2,717	86.8
FY2010	Male	653	18.6	254	67.9	399	12.8
FY2010	Unknown Sex/ Gender	13	0.4	0	0.0	13	0.4
FY2011	Female	2,899	80.6	0	0.0	2,899	80.6
FY2011	Male	684	19.0	0	0.0	684	19.0
FY2011	Unknown Sex/ Gender	13	0.4	0	0.0	13	0.4
FY2012	Female	3,362	83.0	0	0.0	3,362	83.0
FY2012	Male	674	16.6	0	0.0	674	16.6
FY2012	Unknown Sex/ Gender	13	0.3	0	0.0	13	0.3

[5] Data have zeroes for FY 2011 and FY 2012 because the intramural programs have migrated all data to the new data form (1997 OMB definitions).

Table 6N: FY2011 and FY2012 Enrollment for Domestic Intramural NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (Old Form, 1977 OMB Definitions)[6]

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian/ Pacific Islander	% Asian/ Pacific Islander	Black or African American	% Black or African American	Hispanic not White	% Hispanic not White	White	% White	Unknown/ Other	% Unknown/ Other
FY2011	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2011	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2011	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Female	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Male	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Unknown Sex/Gender	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

[6] Data have zeroes for FY 2011 and FY 2012 because the intramural programs have migrated all data to the new data form (1997 OMB definitions).

Table 6O: FY2011 and FY2012 Enrollment for Domestic Intramural NIH-Defined Phase III Clinical Trials: Sex/Gender by Race (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	American Indian/ Alaska Native	% American Indian/ Alaska Native	Asian	% Asian	Black or African American	% Black or African American	Native Hawaiian or Pacific Islander	% Native Hawaiian or Pacific Islander	White	% White	More than one race	% More than one race	Unknown/ Not Reported	% Unknown/ Not Reported
FY2011	Female	242	3.3	199	2.7	2,202	30.0	1	0.0	4,572	62.3	8	0.1	114	1.6
FY2011	Male	56	2.1	70	2.6	484	17.9	2	0.1	2,001	74.1	3	0.1	85	3.1
FY2011	Unknown Sex/Gender	0	0.0	0	0.0	13	100.0	0	0.0	0	0.0	0	0.0	0	0.0
FY2012	Female	246	3.0	228	2.8	2,396	29.3	3	0.0	5,104	62.4	13	0.2	190	2.3
FY2012	Male	60	2.3	69	2.6	477	18.0	2	0.1	1,970	74.1	6	0.2	73	2.7
FY2012	Unknown Sex/Gender	0	0.0	0	0.0	13	100.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 6P: FY2011 and FY2012 Enrollment for Domestic Intramural NIH-Defined Phase III Clinical Trials: Sex/Gender by Ethnicity (New Form, 1997 OMB Definitions)

Fiscal Year (FY)	Sex/Gender	Not Hispanic	% Not Hispanic	Hispanic or Latino	% Hispanic or Latino	Unknown/Not Reported	% Unknown/Not Reported
FY2011	Female	7,010	95.5	295	4.0	33	0.4
FY2011	Male	2,600	96.3	71	2.6	30	1.1
FY2011	Unknown Sex/ Gender	13	100.0	0	0.0	0	0.0
FY2012	Female	7,566	92.5	534	6.5	80	1.0
FY2012	Male	2,561	96.4	64	2.4	32	1.2
FY2012	Unknown Sex/ Gender	13	100.0	0	0.0	0	0.0

Acronyms and Abbreviations

4-OHT	4-hydroxtamoxifen
AA	African-American
AA	allergic asthmatics
AAA	abdominal aortic aneurysm
AAAS	American Association for the Advancement of Science
AADCRC	Asthma and Allergic Diseases Cooperative Research Center
AAN	American Academy of Neurology
AAV	adeno-associated virus
ACA	acetaldehyde
ACCN	Appalachia Community Cancer Network
ACCORD	Action to Control Cardiovascular Risk in Diabetes lipid trial
ACCURE	Accountability for Cancer Care Through Undoing Racism and Equity
ACE	angiotensin converting enzyme
ACE	Autoimmunity Center of Excellence
ACL	anterior cruciate ligament
ACR	American College of Rheumatology
ACRWH	Advisory Committee on Research on Women's Health
ACTG	AIDS Clinical Trials Group
AD	Alzheimer's disease
ADEA	American Dental Education Association
ADEAR Center	Alzheimer's Disease Education and Referral Center
ADH	atypical ductal hyperplasia
ADHD	attention deficit hyperactivity disorder
AED	antiepileptic drug
AEP	alcohol-exposed pregnancy
AERD	aspirin-exacerbated respiratory disease
AES	American Epilepsy Society
AGE	advanced glycation end-product
AH	actinohivin
AHD	American Hospital Dictionary
AHEAD	Actions for Health in Diabetes
AHRQ	Agency for Healthcare Research and Quality
AI	aromatase inhibitor
AI/AN	American Indian/Alaska Native
AID	activated cytidine deaminase
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program
AL	allostatic load
AMA	American Medical Association
AMC	AIDS Malignancy Clinical Trials Consortium
AMD	age-related macular degeneration
ANA	allergic nonasthmatics
ANA	antinuclear antibody
ANSWHR	Advancing Novel Science in Women's Health Research
AOM	azoxymethane
AP-3	Adaptor Protein-3
APC	adenomatous polyposis coli
API	active pharmaceutical ingredient
APOE	apolipoprotein E
APPLE	Atherosclerosis Prevention in Pediatric Lupus Erythematosus
APS	antiphospholipid syndrome

AR	Andean region
AR	androgen receptor
ARDS	acute respiratory distress syndrome
AREA	Academic Research Enhancement Award
AREDS	Age-Related Eye Disease Study
ARND	alcohol-related neurodevelopmental disorder
ARRA	American Recovery and Reinvestment Act
ART	antiretroviral therapy
ART	assisted reproductive technology
ARV	antiretroviral
ASCB	American Society for Cell Biology
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
ATO	atomoxetine
ATP	adenosine triphosphate
AWIS	Association of Women in Science
BAC	blood alcohol concentration
BACH	Boston Area Community Health
BAH	bilateral adrenocortical hyperplasia
BASIC	Brain Attack Surveillance in Corpus Christi
BC	breast cancer
BCC	basal cell carcinoma
BCE	black cohosh extract
BCERP	Breast Cancer and the Environment Research Program
BCRAT	Breast Cancer Risk Assessment Tool
BDNF	brain-derived neurotrophic factor
BE-DRI	Behavior Enhances Drug Reduction of Incontinence
BIRCWH	Building Interdisciplinary Research Careers in Women's Health
BLOC-2	Biogenesis of Lysosome-related Organelles Complex-2
BMD	bone mineral density
BMI	body mass index
BMP	bone marrow progenitor
BMT	Boundary Marking Tool
BP	blood pressure
BPD	borderline personality disorder
BPTEACH	Baltimore Partnership to Educate and Achieve Control of Hypertension
BR	breast reconstruction
BRDA	Breast Reconstruction Decision Aid
BRFSS	Behavioral Risk Factor Surveillance System
BRIC	Building Research Infrastructure and Capacity
BRITE	Biomedical and Behavioral Research Innovations to Ensure Equity
BUFS	breast ultrasound fluoroscopy system
BV	bacterial vaginosis
BW	body weight
BWH	Brigham and Women's Hospital
CACTI	Coronary Artery Calcification in Type I Diabetes
CAH	congenital adrenal hyperplasia
CAM	complementary and alternative medicine
CARDIA	Coronary Artery Risk Development in Young Adults
CARDS	Computer Access to Research on Dietary Supplements
CARDS TX	Community-Acquired Respiratory Distress Syndrome Toxin

CARE Contraceptive and Reproductive Experiences

CAREDS Carotenoids in Age-Related Eye Disease Study

CARRA Childhood Arthritis and Rheumatology Research Alliance

CART cocaine and amphetamine regulated transcript

CAT Career Assistance Toolkit

CAT computerized adaptive test

CBPR community-based participatory research

CBT cognitive behavioral therapy

CC cervical cancer

CC Cleveland Clinic

CC coordinating center

CCHMC Cincinnati Children's Hospital Medical Center

CCPC comorbid chronic pain conditions

CCRWH Coordinating Committee on Research on Women's Health

CCSG Cancer Center Support Grant

CCTSI Colorado Clinical Translational Science Institute

CCTST Center for Clinical and Translational Science and Training

CCWH Coordinating Committee on Women's Health

CDC Centers for Disease Control and Prevention

CDDB Contraceptive Discovery and Development Branch

CDE common data elements

CEE conjugated equine estrogen

CFAR Centers for AIDS Research

CFIDS chronic fatigue and immune dysfunction syndrome

CFS chronic fatigue syndrome, also known as myalgic encephalomyelitis (ME/CFS)

CFSAC Chronic Fatigue Syndrome Advisory Committee

CGEMS Cancer Genetic Markers of Susceptibility

CHAMACOS Center for the Health Assessment of Mothers and Children of Salinas

CHARGE Childhood Autism Risks from Genetics and the Environment

CHARM Children's Health and Responsible Mothering

CHD coronary heart disease

CHIS California Health Interview Survey

CIDRZ Center for Infectious Disease Research in Zambia

CIFASD Collaborative Initiative on Fetal Alcohol Spectrum Disorders

CIN cervical intraepithelial neoplasia

CINJ Cancer Institute of New Jersey

CKD chronic kidney disease

CLEK Collaborative Longitudinal Evaluation of Keratoconus

CLHNS Cebu Longitudinal Health and Nutrition Survey

CM cardiac myocyte

CM childhood maltreatment

CMOS complementary metal-oxide semiconductor

CMS Centers for Medicare and Medicaid Services

CMV cytomegalovirus

CNS central nervous system

COBRE Centers of Biomedical Research Excellence

COE Center of Excellence

CoEPE Center of Excellence in Pain Education

COPD chronic obstructive pulmonary disease

COX	cyclooxygenase
CPB	cardiopulmonary bypass
CPDD	College on Problems of Drug Dependence
CPHHD	Centers for Population Health and Health Disparities
CQR	chloroquine resistance
CRC	colorectal cancer
CRECD	Clinical Research Education and Career Development
CREST	Carotid Revascularization Endarterectomy Versus Stenting Trial
CRSRT	China-Rochester Suicide Research Training Program
CRT	Classification and Regression Tree
CRTA	Cancer Research Training Awards
CS	caesarean section
CSA	chondroitin sulfate A
CSC	cancer stem cells
CSD	caveolin scaffolding domain
CSGADP	Cooperative Study Group for Autoimmune Disease Prevention
CSPS	Center for the Study and Prevention of Suicide
CSR	Center for Scientific Review
CST	coping skills training
CT	computed tomography
CTN	Clinical Trials Network
CTS	California Teachers Study
CTSA	Clinical and Translational Science Award
CV	cervicovaginal
CVD	cardiovascular disease
CVS	chorionic villus sampling
CWHR	Center for Women's Health Research
DBT	dialectical behavior therapy
DBT	digital breast tomosynthesis
DC	dendritic cell
DCC	data coordinating center
DCEG/EPB	Division of Cancer Epidemiology and Genetics/Epidemiology and Biostatistics Program
DCE-MRI	dynamic contrast–enhanced MRI
DCIS	ductal carcinoma in situ
DCP	Division of Cancer Prevention
DED	dry-eye disease
DERT	Division of Extramural Research and Training
DEX	dexamethasone
DHEA-S	dehydroepiandrosterone sulfate
DHS	Daily Hormone Study
DHT	dihydrotestosterone
DIL-MIL	daughter-in-law–mother-in-law
DMARD	disease-modifying antirheumatic drug
DMF	U.S. Social Security Administration Death Master File
DMICC	Diabetes Mellitus Interagency Coordinating Committee
DoD	Department of Defense
DOR	Division of Research
DOT	diffuse optical tomography
DPCPSI	Division of Program Coordination, Planning, and Strategic Initiatives
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DREAM	Disparities Research and Education Advancing Mission
DS	Dahl salt-sensitive
DS	degenerative spondylolisthesis

DSHEA	Dietary Supplement Health and Education Act
DSMB	Data and Safety Monitoring Board
DSM-V	Diagnostic and Statistical Manual of the American Psychological Association, Fifth Edition
DTI	diffusion tensor imaging
DUET	Defeating Urinary Incontinence with Exercise Training
DUMC	Duke University Medical Center
DV/SV	dating violence/sexual violence
DW-MRI	diffusion weighted MRI
DXA	dual-energy xray absorptiometry
E+P	estrogen plus progestin
EAE	experimental autoimmune encephalomyelitis
EAWG	Extramural Activities Work Group
EBV	Epstein-Barr virus
ECA	embodied conversational agents
ECG	electrocardiogram
ECHORN	Eastern Caribbean Health Outcomes Research Network
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EDRN	Early Detection Research Network
EEG	electroencephalogram
EFA	essential fatty acid
EG	ethylene glycol
EGFR	epidermal growth factor receptor
EHG	electrohysterography
ELITE	Early Versus Late Intervention Trial with Estradiol
ELS	early life stress
EMBRACE	Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure
EMS	emergency medical services
EMT	epithelial-mesenchymal transition
ENAC	epithelial Na+ channel
ENTRÉE	Enhancing Training, Research Capacity and Expertise in HIV Care
ELP	elastin-like polypeptide nanoparticle
EOC	epithelial ovarian carcinoma
ER+	estrogen receptor-positive
E-SIG	Subcommittee on Inclusion Governance
ESRD	end-stage renal disease
ESTHER	Epidemiologic Study of Health Risk in Women
ETS	environmental tobacco smoke
FACOG	Fellow of American College of Obstetricians and Gynecologists
FACT-B/ES	Functional Assessment of Cancer Therapy—Breast/ Endocrine Subscale
FAES	Foundation for Advanced Education in the Sciences
FAI	femoroacetabular impingement
FAI	Free Androgen Index
FAK	focal adhesion kinase
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorders
FCG	four-core genotype
FCSNI	Female and Culturally Specific Negotiation Intervention
FCTC	WHO Framework Convention on Tobacco Control
FDA	U.S. Food and Drug Administration

FDG-PET	fluorodeoxyglucose positron emission tomography
FEA	finite element analysis
FEMALE-ICD	Female-Specific Education, Management, and Lifestyle Enhancement for Implantable Cardioverter Defibrillator Patients
f-fMRI	fetal functional MRI
FGHF	Fogarty Global Health Fellows Program
FH	fumarate hydratase
FIC	Fogarty International Center
FICRS-F	Fogarty International Clinical Research Scholars and Fellows program
FIRCA-BSS	Fogarty International Research Collaboration Behavioral and Social Sciences
fMRI	functional magnetic resonance imaging
FOA	funding opportunity announcement
FOM	figures-of-merit
FP	family planning
FRC	Family Research Consortium
FRN	feedback-related negativity
FRQ	Fonds de Recherche du Québec
FSH	follicle-stimulating hormone
FSS	Fatigue Severity Score
FX	fragile X
FY	fiscal year
GAO	U.S. Government Accountability Office
GBV	gender-based violence
GDM	gestational diabetes mellitus
GE	gender equality
GEP	Genetic Etiology of POAG
GHDB	Gynecologic Health and Disease Branch
GHESKIO	Haitian Study Group for the Study of Kaposi's Sarcoma and Opportunistic Infections
GHI	global health informatics
GID	Global Infectious Disease Research Training Program
GLAUGEN	Glaucoma Genes and Environment Initiative
GLP-1	glucagon-like peptide 1
GPCMV	guinea pig cytomegalovirus
GRIP	Global Research Initiative Program
GROWH	Gulf Resilience on Women's Health
GWAS	genome-wide association study
GWG	gestational weight gain
HAART	highly active antiretroviral therapy
HAND	HIV-associated neurocognitive disorder
HANDLS	Healthy Aging in Neighborhoods of Diversity across the Life Span
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HC	hormonal contraceptive
HCC	Hollings Cancer Center
hCG	human chorionic gonadotropin
HCW	health care worker
HDL	high-density lipoprotein
HEC	hydroxy ethyl cellulose
H-EPESE	Hispanic Established Populations for Epidemiologic Study of the Elderly
HER2	tyrosine kinase receptor
HERV	human endogenous retrovirus
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma

HLA-G	human leukocyte antigen G
HLRCC	hereditary leiomyomatosis and renal cell cancer
HMHB	Healthy Mothers Healthy Babies
HOPE	Helping to Overcome PTSD through Empowerment
HPA	hypothalamic-pituitary-adrenal
HPFS	Health Professionals Follow-Up Study
HPG	hypothalamic-pituitary-gonadal
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HR-pQCT	high-resolution peripheral quantitative computed tomography
HRSA	Health Resources and Services Administration
HSRIC	Health Services Research Information Center
HSV	herpes simplex virus
HT	hormone therapy
HVTN	HIV Vaccine Trials Network
IAS	internal anal sphincter
IBC	intracellular bacterial community
IBC	invasive breast cancer
IBCERCC	Interagency Breast Cancer and Environmental Research Coordinating Committee
IBD	Identical by Descent
IBIDS	International Bibliographic Information on Dietary Supplements
IBS	irritable bowel syndrome
ICs	Institutes and Centers
ICAM-1	intercellular adhesion molecule-1
ICBP	Integrative Cancer Biology Program
ICD	implantable cardioverter defibrillator
ICOHRTA	International Clinical, Operational and Health Services Research Training Award
IC/PBS	interstitial cystitis/painful bladder syndrome
IDeA	Institutional Development Award
IDL	intermediate density lipoproteins
IDU	injection drug user
IED	intermittent explosive disorder
IeDEA	International Epidemiologic Databases to Evaluate AIDS
IEQ	indoor environmental quality
I-FSCBT	Individual Female Specific Cognitive Behavioral Therapy
IGFBP-3	IGF-binding protein-3
IGF-I	insulin-like growth factor-I
IHDS	India Human Development Survey
IHS	Indian Health Service
IIH	idiopathic intracranial hypertension
IL	interleukin
ILI	intensive lifestyle intervention
IMNCI	integrated management of neonatal and childhood illness
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
IMS	inclusion management system
INBRE	IDeA Networks of Biomedical Research Excellence
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IOM	Institute of Medicine
IOPW	Inclusion Operating Procedures Workgroup
IPAH	idiopathic pulmonary arterial hypertension

IPRWH	Intramural Program on Research on Women's Health
IPV	intimate partner violence
IRB	institutional review board
IR-BU	Interdisciplinary Research in Benign Urology
IRP	Intramural Research Program
IRSDA	International Research Scientist Development Award
IRTA	Intramural Research Training Awards
IRWG	Institute for Research on Women and Gender
ISIS	Women's HIV Seroincidence Study
ITAS	Integrated Time and Attendance System
IUGR	intrauterine growth restriction
IUPC	intrauterine pressure catheter
IVF	in vitro fertilization
IWHR	Interdisciplinary Women's Health Research program
JAMA	Journal of the American Medical Association
JFM	juvenile fibromyalgia
KEEPS	Kronos Early Estrogen Prevention Study
KUMC	University of Kansas Medical Center
LABS	Longitudinal Assessment of Bariatric Surgery
LAIV	Live Attenuated Influenza Vaccine
LAM	lymphangioleiomyomatosis
LC	locus coeruleus
LE	luminal epithelium
LEP	luminal epithelial cell
LGBT	lesbian, gay, bisexual, and transgender
LGBTI	lesbian, gay, bisexual, transgender, and intersex
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LIFE	Longitudinal Investigation of Fertility and the Environment
LMIC	low- and middle-income countries
LOD	logarithm of odds
LOI	loss of imprinting
LONS	Longitudinal Optic Neuritis Study
LPA3	lysophosphatidic acid receptor 3
LRO	lysosome-related organelle
LRP	Loan Repayment Program
LRP-HDR	Loan Repayment Program for Health Disparities Research
LTB	Leiomyoma Tissue Bank
LURN	Lower Urinary Tract Dysfunction Research Network
LUTD	lower urinary tract dysfunction
MAAT	Memory and Attention Adaptation Training
MAF	minor allele frequency
MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
MBD	mammographic breast density
MCAO	middle cerebral artery occlusion
MCI	mild cognitive impairment
MD	mammographic density
MDD	major depressive disorder
ME/CFS	myalgic encephalomyelitis, also known as chronic fatigue syndrome (CFS)
MeCP2	methyl-CpG-binding protein 2
MEP	myoepithelial cell
MEPI	Medical Education Partnership Initiative
MESA	Multi-Ethnic Study of Atherosclerosis

MESAU	Medical Education for Services to All Ugandans
MG	mindfulness group
MGH	Massachusetts General Hospital
MHC	major histocompatibility complex
M**HIRT**	Minority Health and Health Disparities International Research Training
MHN	Men's Health Network
MHT	menopausal hormone therapy
MILES	Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus Trial
MIMIC	Multiparameter Intelligent Monitoring in Intensive Care
MIP	Microbicide Innovation Program
miRNA	microRNA
MIS	Müllerian inhibiting substance
MMHCC	Mouse Models of Human Cancer Consortium
MOMUS	Meeting on Measurement of Urinary Symptoms
MONEAD	Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs
MOON	Multicenter Orthopaedic Outcomes Network
MOST	Multicenter Osteoarthritis Study
MOTHER	Maternal Opioid Treatment: Human Experimental Research
MPIDB	Maternal and Pediatric Infectious Disease Branch
MPP	mucus penetrating nanoparticle
MR	Mendelian Randomization
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopic imaging
MRTC	Malaria Research and Training Center
MS	multiple sclerosis
M-SACRAH	Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands
MsFLASH	Menopause Strategies: Finding Lasting Answers for Symptoms and Health
MSI-FLASH	Menopausal Symptoms Initiative—Finding Lasting Answers to Sweats and Hot Flashes
MSK1	mitogen- and stress-activated protein kinase 1
MSL	male-specific lethal
MSM	men who have sex with men
MSTP	Medical Scientist Training Program
MSU	Michigan State University
MT	menopausal transition
MTCT	mother-to-child transmission
MTD	muscle-tension dysphonia
MTFS	Minnesota Twin Family Study
MTN	Microbicides Trials Network
MTO	Moving to Opportunity for Fair Housing
MTP	microsomal triglyceride transfer protein
MUSC	Medical University of South Carolina
MVC	maraviroc
MVPA	moderate to vigorous physical activity
MWH	Magee-Womens Hospital
MWRI	Magee-Womens Research Institute
NAASP	National Action Alliance for Suicide Prevention
NADA	National Acupuncture Detoxification Association
NAEC	National Advisory Eye Council

NAMS	North American Menopause Society
NARCH	Native American Research Centers for Health
NAS	National Academy of Sciences
NAS	neonatal abstinence syndrome
NBS	newborn screening
NCAA	National Collegiate Athletic Association
NCCAM	National Center for Complementary and Alternative Medicine
NCCU	North Carolina Central University
NCD	noncommunicable disease
NCI	National Cancer Institute
NCIGT	National Center for Image Guided Therapy
NCI-MMHCC	NCI Mouse Models of Human Cancers Consortium
NCNHIR	NIEHS Centers for Nanotechnology Health Implications Research
NCRR	National Center for Research Resources
NDEP	National Diabetes Education Program
NEAD	Neurodevelopmental Effects of Antiepileptic Drugs
NEC	neonatal necrotizing enterocolitis
NECTAR	Novel Education Clinical Trainees and Researchers
NEI	National Eye Institute
NEIGHBOR	NEI Glaucoma Human Genetics Collaboration
NERI	New England Research Institutes
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NEXT PrEP	Novel Exploration of Therapeutics for Pre-Exposure Prophylaxis
NGO	nongovernmental organization
NHANES	National Health and Nutrition Examination Survey
NHGRI	National Human Genome Research Institute
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NHP	non-human primate
NHS	Nurses' Health Study
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health

NIMH National Institute of Mental Health

NIMHD National Institute on Minority Health and Health Disparities

NINDS National Institute of Neurological Disorders and Stroke

NINR National Institute of Nursing Research

NIRS-DOT near-infrared spectroscopy and tomography

NLM National Library of Medicine

NLMS National Longitudinal Mortality Study

NLST National Lung Screening Trial

NM23-H1 human nonmetastatic gene 23

NMA National Medical Association

NMR nuclear magnetic resonance

NMRCD U.S. Naval Medical Research Center Detachment

NMRI Network of Minority Health Research Investigators

NMSM Nelson R Mandela School of Medicine

NNRTI non-nucleoside reverse transcriptase inhibitor

NOD/SCID-hu BLT nonobese diabetic/severe combined immunodeficiency–human bone marrow/liver/thymus

NORDIC Neuro-Ophthalmology Research Disease Investigator Consortium

NPN Nurse Patient Navigation

NPY neuropeptide Y

NR nuclear receptor

NRC National Resource Center

NREM nonrapid eye motion

NRTI nucleoside reverse transcriptase inhibitor

NSAID nonsteroidal anti-inflammatory drug

NSC nonsyndromic craniosynostosis

NSCL/P nonsyndromic cleft lip with or without cleft palate

NSDUH National Survey on Drug Use and Health

NSES neighborhood socioeconomic status

NSF National Science Foundation

NSHAP National Social Life, Health and Aging Project

NTP National Toxicology Program

NU Northwestern University

NUWS NIH Updates on Women in Science

OA osteoarthritis

OAB overactive bladder

OAI Osteoarthritis Initiative

OBSSR Office of Behavioral and Social Sciences Research

OCRPL Office of Constituency Relations and Public Liaison

OCT optical coherence tomography

OD NIH Office of the Director

ODS Office of Dietary Supplements

OECD Organisation for Economic Co-operation and Development

OER Office of Extramural Research

OGTT Oral Glucose Tolerance Test

OHARA Oral HIV/AIDS Research Alliance

OHRC National Maternal and Child Oral Health Resource Center

OHSU Oregon Health & Science University

OIR Office of Intramural Research

OIT oral immunotherapy

OITE Office of Intramural Training and Education

OMB Office of Management and Budget

OMERACT-OARSI	Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International
OMHRC	Office of Minority Health Research Coordination
OMRF	Oklahoma Medical Research Foundation
ONJ	osteonecrosis of the jaw
ONTT	Optic Neuritis Treatment Trial
OPB	oligonucleotide with a phosphorothioate backbone
OPPERA	Orofacial Pain: Prospective Evaluation and Risk Assessment
ORDGMH	Office for Research on Disparities and Global Mental Health
ORS	Office of Research Services
ORWH	Office of Research on Women's Health
OSPA	Office of Science Planning and Assessment
OSPPC	Office of Science Policy, Planning, and Communications
OSUCCC	Ohio State University Comprehensive Cancer Center
OTC	over-the-counter
OUHSC	University of Oklahoma Health Sciences Center
OVX	ovariectomized
PA	program announcement
PACAP	pituitary adenylate cyclase-activating polypeptide
PAEC	pulmonary artery endothelial cell
PAESMEM	Presidential Awards for Excellence in Science, Mathematics, and Engineering Mentoring
PAH	pulmonary arterial hypertension
PARP	poly ADP ribose polymerase
PASS	Prenatal Alcohol in SIDS and Stillbirth
PAT	Parents As Teachers
PBDE	polybrominated diphenyl ether
PBM	probiotic bacterial microbicides
PBMC	peripheral blood mononuclear cell
PBS	painful bladder syndrome
PBV	Preservation by Vaporization
PCB	polychlorinated biphenyl
PCOS	polycystic ovary syndrome
PCT	Present Centered Therapy
PDB	paradichlorobenzene
PDGFR	platelet-derived growth factor receptor
PE	preeclampsia
PE	prolonged exposure
PEARLS	Pregnancy and Early Lifestyle Improvement Study
PEDF	pigment epithelium-derived factor
PEPFAR	President's Emergency Plan for AIDS Relief
PET	positron emission tomography
PFC	prefrontal cortex
PFD	pelvic floor disorder
PFDN	Pelvic Floor Disorders Network
PFP	patellofemoral pain
PGRN	Pharmacogenomics Research Network
PHACS	Pediatric HIV/AIDS Cohort Study
PHAROS	Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma
PI	principal investigator
PI	protease inhibitor
PKC	protein kinase C
PL	phospholipid

PL	Public Law
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PLGA	poly(lactic-co-glycolic acid)
PM	pregnancy malaria
PMDD	premenstrual dysphoric disorder
PMH	postmenopausal hormone
PMS	premenstrual syndrome
PMTCT	prevention of mother-to-child transmission
PN	patient navigator
POAG	primary open angle glaucoma
POI	primary ovarian insufficiency
POP	pelvic organ prolapse
PPRO	Program in Perinatal Research and Obstetrics
PR	progesterone receptor
PrEP	pre-exposure prophylaxis
PRI	Physician-Researcher Initiative
PRO	patient-reported outcomes
PRO	progesterone
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMISE	Promoting Maternal-Infant Survival Everywhere
PROMISSE	Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus
PRR	prorenin receptor
PSA	psoriatic arthritis
PTC	psychosocial telephone counseling
PTEN	phosphatase and tensin homolog
PTH	parathyroid hormone
PTSD	posttraumatic stress disorder
PVD	provoked vestibulodynia
PYD	pyrimidinedione
PYY	peptide tyrosine tyrosine
QOL	quality of life
RA	rheumatoid arthritis
RANKL	receptor activator of nuclear factor kappa-B ligand
RAS	renin angiotensin system
RCA	rolling circle amplification
RCI	reliable change index
RCMI	Research Centers in Minority Institutions
RCT	randomized clinical trial
RCTR	RCMI Infrastructure for Clinical and Translational Research
RCU	Research Coordinating Unit
RD	research director
RDC/TMD	Research Diagnostic Criteria for Temporomandibular Disorders
REAP	Research Enhancement Awards Program
REGARDS	Reasons for Geographic and Racial Differences in Stroke
REM	rapid eye movement
REMAS	Real Men Are Safe
REP	Rochester Epidemiology Project
RES	resveratrol
RFA	radiofrequency ablation
RFA	request for applications
RICE	Rand Interstitial Cystitis Epidemiology
RIMI	Research Infrastructure in Minority Institutions
ROC	receiver operating characteristic
ROCK	Rho kinase
RPG	Research Project Grant
RSDP	Reproductive Scientist Development Program
RSV	respiratory syncytial virus
RT	radiotherapy

RTRN	RCMI Translational Research Network
RTX	repeat-intoxin
RVI	rabbit vaginal irritation
RWEH	Researching Women's Environmental Health
RYGB	Roux-en-Y gastric bypass
SAC	segmental allergen challenge
SAFE	Project Sexual Awareness for Everyone
SAMHSA	Substance Abuse and Mental Health Services Administration
SART	Society for Assisted Reproductive Technology
SBCSS	Shanghai Breast Cancer Survival Study
SBD	sleep disordered breathing
SBIR	Small Business Innovation Research
SCC	sex chromosome complement
SCCPIR	Specialized Cooperative Centers Program in Reproduction and Infertility Research
SCH	Smilow Cancer Hospital
SCOR	Specialized Centers of Research on Sex Differences
SCOT	Scleroderma Cyclophosphamide or Transplantation
SD	spasmodic dysphonia
SD NVP	single-dose nevirapine
SED	socioeconomically disadvantaged
SEEDS	Students Educating and Empowering to Develop Safety
SEER	Surveillance, Epidemiology, and End Results
SELF	Study of Environment, Lifestyle & Fibroids
SES	socioeconomic status
SEVI	semen enhancer of virus infection
SF	saturated fat
SG	support group
SHARE	South Asian Hub for Advocacy, Research, and Education
SHBG	sex-hormone binding globulin
SICCA	Sjögren's International Collaborative Clinical Alliance
SIDS	sudden infant death syndrome
siRNA	small interfering RNA
SIV	simian immunodeficiency virus
SJIA	systemic juvenile idiopathic arthritis
SKM	skeletal muscle
SLE	systemic lupus erythematosus (lupus)
SMR	standardized mortality ratio
SNHL	sensorineural hearing loss
SNM	sacral neuromodulation
SNMA AMEC	Student National Medical Association Annual Medical Education Conference
SNP	single nucleotide polymorphism
SNR	signal-to-noise ratio
sNSC	sagittal nonsyndromic craniosynostosis
SOF	Study of Osteoporotic Fractures
SPIE	Strategic Plan Implementation Evaluation
SPIRES	Scientific Publication Information Retrieval and Evaluation System
SPORE	Specialized Programs of Research Excellence
SRG	scientific review group
SS	Sjögren's syndrome
SSC	Scientific Steering Committee
SSH	sacrospinous hysteropexy
SSRI	selective serotonin reuptake inhibitor

STAR	single-incision trans-axillary robotic-assisted
STARRS	Study to Assess Risk and Resilience in Servicemembers
STRAW	Stages of Reproductive Aging Workshop
STD	sexually transmitted disease
STEM	sciences, technology, engineering, and mathematics
STEMM	science, technology, engineering, mathematics, and medicine
STI	sexually transmitted infection
STTR	Small Business Technology Transfer
SUCCEED	Study to Understand Cervical Cancer Early Endpoints and Determinants
SUI	stress urinary incontinence
SUMC	Stanford University Medical Center
SUNY	State University of New York
SVM	support vector machine
SWAN	Study of Women's Health Across the Nation
TAILORx	Trial Assigning Individualized Options for Treatment
TB	tuberculosis
TBI	traumatic brain injury
TCC	Transdisciplinary Collaborative Centers for Health Disparities Research
TCDD	tetrachlorodibenzo-p-dioxin
TCGA	The Cancer Genome Atlas
TGF	transforming growth factor
TFO	triplex-forming oligonucleotide
Th17	T-helper-producing interleukin 17
TIEG	TGF beta inducible early gene
TIV	trivalent influenza vaccine
TLR	toll-like receptor
TMD	temporomandibular disorders
TMJD	temporomandibular joint disorders
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TOBAC	International Tobacco and Health Research and Capacity Building Program
TOCO	tocodynamometry
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
TOMUS	Trial of Mid-Urethral Slings
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
TrDNA	transrenal DNA
Treg	regulatory T cell
tRNA	transfer RNA
TSC2	tuberous sclerosis complex 2
TSHR	thyroid-stimulating hormone receptor
TSTP	Translational Science Training Program
TT	Teaching Tool
TTP	thrombotic thrombocytopenic purpura
TVH/SSLF	total vaginal hysterectomy with sacrospinous ligament fixation
TVU	transvaginal ultrasound
UAB	University of Alabama at Birmingham
UASB	Universidad Andina Simon Bolivar
UC	University of Cincinnati
UC	usual care
UCA	Universidad del Cauca
UCAMC	University of Colorado Anschutz Medical Campus
UCD	University of California, Davis

UCGHI-PFS University of California Global Health Institute Program for Fellows and Scholars

UCLA University of California, Los Angeles

UCSD University of California, San Diego

UCSF University of California, San Francisco

UEM Universidade Eduardo Mondlane

UI urinary incontinence

UIC University of Illinois, Chicago

UITN Urinary Incontinence Treatment Network

UK University of Kentucky

UL uterine leiomyoma

UMB University of Maryland, Baltimore

UNAIDS United Nations Joint Programme on HIV/AIDS

UNC-CH University of North Carolina, Chapel Hill

UNICEF United Nations Children's Fund

UNM University of New Mexico

UNZA University of Zambia

u-PAR urokinase plasminogen activator receptor

UPCH Universidad Peruana Cayetano Heredia

UPCI University of Pittsburgh Cancer Institute

UPEC uropathogenic *Escherichia coli*

UPMC University of Pittsburgh Medical Center

UPR unfolded protein response

URMC University of Rochester Medical Center

USACAHDR U.S.A.-Caribbean Alliance for Health Disparities Research

USDA U.S. Department of Agriculture

USPSTF U.S. Preventive Services Task Force

UTI urinary tract infection

UTMB University of Texas Medical Branch

UVB ultraviolet B

UW University of Washington

UZCHS University of Zimbabwe College of Health Sciences

VA U.S. Department of Veterans Affairs

VAR varenicline

VAT visceral adipose tissue

VBRT voucher-based reinforcement therapy

VECDor Vanderbilt-Emory-Cornell-Duke Consortium

VEGF vascular endothelial growth factor

VHP village health provider

VIRGO Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients

VITAL Vitamin D and Omega-3 Trial

VL viral load

VLBP Voluntary Leave Bank Program

VLBW very low birth weight

VLP virus-like particle

VLTP Voluntary Leave Transfer Program

VM Virtual Microscope

VMS vasomotor symptoms

VOICE Vaginal and Oral Interventions to Control the Epidemic

VPE Virtual Patient Educator

VT vocal tremor

VTN Vaccine Trials Network

VU IGH Vanderbilt University Institute for Global Health

WGHS	Women's Genome Health Study
WGRG	Women and Sex/Gender Research Group
WHEEL	Women's Health and the Environment over the Entire Lifespan
WHI	Women's Health Initiative
WHIMS	Women's Health Initiative Memory Study
WHISCA	Women's Health Initiative Study of Cognitive Aging
WHO	World Health Organization
WHR	Women's Health Resources
WHS	Women's Health Study
WHSIG	Women's Health Interest Group
WIC	Women, Infants, and Children
WICB	Women in Cell Biology
WIH	Women and Infants Hospital
WIHS	Women's Interagency HIV Study
WIN	Weight-control Information Network
WISE	Women in Science and Engineering
WISE	Women's Ischemia Syndrome Evaluation
WLZ	weight-for-length z-scores
WOMAC	Western Ontario and McMaster Universities Osteoarthritis
WRAPS	Wireless Remote Abdominal Pressure System
WRHR	Women's Reproductive Health Research
WoCRn	Women of Color Research Network
YCC	Yale Cancer Center
ZP	zona pellucida

Index

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

U.S. Department of Health & Human Services

National Institutes of Health

Office of Research on Women's Health
6707 Democracy Blvd. Suite 400
Bethesda, MD 20892-5484
Phone: (301) 402-1770
Fax: (301) 402-1798
http://orwh.od.nih.gov

Publication Number 13-7995