APPENDIX B

ORWH-Cofunded Research Summaries, FY 2013

Contents

Administrative Supplements Program

IC: **National Center for Complementary and Integrative Health**
Title: **Stanford CAM Center for Chronic Back Pain**
PI: **Sean C. Mackey**
Institution: **Stanford University**
Grant No.: **3P01AT006651-03S1**

This project uses real-time functional magnetic resonance imaging (fMRI) neurofeedback techniques to ascertain the relationship between learned control of specific neural processes and chronic pain reduction. The supplement will stratify, based on opioid use and gender, differences in brain morphology determined by fMRI.

IC: **National Cancer Institute**
Title: **Cancer Center Support Grant**
PI: **Michael A. Friedman**
Institution: **City of Hope/Beckman Research Institute**
Grant No.: **3P30CA033572-30S4**

This project is part of a larger NCI-funded Cancer Center Support Grant. The supplement will evaluate outcome differences between men and women with advanced bladder cancer who are treated with a promising new agent, the tubulin inhibitor eribulin. Bladder cancer is more common in men, but bladder-cancer mortality has been reported to be higher in women, and few prospective evaluations have studied this sex-based survival disparity.

IC: **National Cancer Institute**
Title: **Cancer Center Support Grant: University of Hawaii Cancer Center**
PI: **Michele Carbone**
Institution: **University of Hawaii at Manoa**
Grant No.: **3P30CA071789-14S3**

This grant supports the University of Hawaii Cancer Center, which aims to reduce cancer burden through research, education, and service; its location in Hawaii offers access to a distinct environment in terms of ethnic diversity and health disparities. The supplement will examine disparities among women related to screening for tobacco use and nicotine dependence.

IC: **National Cancer Institute**
Title: **Molecular Biomarkers of Airway and Lung Linking COPD and Lung Cancer**
PI: **Avrum E. Spira**
Institution: **Boston University Medical Campus**
Grant No.: **3R01CA164783-03S1**

This project is developing distinct airway biomarkers of chronic obstructive pulmonary disease (COPD), lung cancer, and both diseases, toward development of more effective tools for lung cancer diagnosis, screening, and targeted chemoprevention. The supplement will analyze additional samples from original cohorts to expand descriptions of sex-specific alterations of gene expression that affect disease in lung tissue and the bronchial airway epithelium.

IC: **National Eye Institute**
Title: **Administrative Supplements for Research on Sex/Gender Differences**
PI: **Peter Koulen**
Institution: **University of Missouri–Kansas City**
Grant No.: **3R01EY022774-02S1**

This project is investigating a novel combination pharmacological intervention strategy to control structural and functional degeneration in autoimmune optic neuritis, a leading cause of blindness in the United States and worldwide. The supplement will add a second group of animals of the opposite sex (female) to those in the original study for comparative analyses of gender-mediated effects and treatment outcomes.

IC: **National Human Genome Research Institute**
Title: **Supplement to Anticipating Personalized Genomic Medicine: Impact and Implications**
PI: **Eric T. Juengst**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **3R01HG005277-10S1**

This project is studying the extent to which people who promote, implement, provide, and use "personalized genomic medicine" understand its promises and potential pitfalls. The supplement, focused on interviews with couples considering Fragile X testing, aims to identify sex/gender differences in personal health risks and reproductive genetic risks.

IC: **National Heart, Lung, and Blood Institute**
Title: **Arrhythmogenic Remodeling in Human Heart Failure**
PI: **Igor R. Efimov**
Institution: **Washington University in St. Louis**
Grant No.: **3R01HL114395-02S1**

This project aims to bridge the gap between fundamental discoveries in animal models of human heart failure with validation in clinical trials, using explanted hearts of transplantation patients and rejected donor hearts. The supplement will investigate three important areas of sex/gender differences in heart remodeling: activation, repolarization, and calcium handling.

IC: **National Heart, Lung, and Blood Institute**
Title: **New Approaches for Empowering Studies of Asthma in Populations of African Descent**
PI: **Kathleen C. Barnes**
Institution: **Johns Hopkins University**
Grant No.: **3R01HL104608-03S1**

Using discoveries resulting from the 1000 Genomes Project and select genetic variants that best represent the genome of individuals of African descent, this project is developing a custom DNA-variation chip (the African Power Chip) to complement current, commercially available DNA-sequence chips to study asthma risk in 12,000 individuals. The supplement will identify and replicate genetic variants with sex-specific effects on asthma in 450 African American individuals included in the Consortium on Asthma among African-ancestry Populations in the Americas.

IC: **National Heart, Lung, and Blood Institute**
Title: **Sleep Duration Required To Restore Performance During Chronic Sleep Restriction**
PI: **Elizabeth B. Klerman**
Institution: **Brigham and Women's Hospital**
Grant No.: **3R01HL114088-02S1**

This project is studying short- and long-term consequences of sleep deficiency, which can predispose an individual to attentional lapses, errors, and accidents, especially during the biological (circadian) night—an issue of concern for the 15 percent of Americans who are involved in shift work. The supplement aims to investigate and quantify sex differences in sleep-wake transitions using a large, existing sleep dataset in which sleep was recorded following varying durations of wakefulness.

IC: **National Institute on Aging**
Title: **Johns Hopkins Alzheimer's Disease Research Center**
PI: **Marilyn S. Albert**
Institution: **Johns Hopkins University**
Grant No.: **3P50AG005146-30S1**

The Johns Hopkins Alzheimer's Disease Research Center is conducting dementia research, with a particular focus on the understanding the earliest phases of Alzheimer's disease (AD). Employing a female AD transgenic-mouse model, the supplement will test the hypothesis that cognitive function is more sensitive to the toxic effects of amyloid-beta protein in females than in males.

IC: **National Institute on Aging**
Title: **Noninvasive Treatment of Abdominal Aortic Aneurysm Clinical Trial (N-TA^3CT)**
PI: **Michael L. Terrin**
Institution: **University of Maryland, Baltimore**
Grant No.: **3R01AG037120-03S1**

The N-TA-3CT study is a Phase IIb, randomized clinical trial investigating the effect of doxycycline compared to placebo on the growth of the diameter of abdominal aortic aneurysms. The supplement will enable the investigators to increase the number of women from 50 to 70 in the parent trial to increase the statistical power to detect gender differences in clinical study outcomes and disease mechanisms.

IC: **National Institute on Alcohol Abuse and Alcoholism**
Title: **Integrative Neuroscience Initiative on Alcoholism: Stress and Ethanol Self-Administration in Monkeys**
PI: **Kathleen A. Grant**
Institution: **Oregon Health & Science University**
Grant No.: **3U01AA013510-13S1**

This research in rhesus monkeys (nonhuman primates that are the most valid model of human alcoholics) studies the role of stress in prompting some individuals to drink alcohol excessively, toward understanding alcohol dependency and its interventions in humans. The supplement will measure biological parameters such as changes in hormones and immune-related proteins (from blood samples already collected in the parent study) that indicate the severity of damage due to heavy alcohol consumption.

IC: **National Institute on Alcohol Abuse and Alcoholism**
Title: **Sex Disparities in Overall Response to ART Among HIV-Infected Individuals**
PI: **Amy Caroline Justice**
Institution: **Yale University**
Grant No.: **3U24AA020794-02S2**

The Veterans Aging Cohort Study (VACS) is the largest clinical cohort of HIV-infected individuals in North America and includes in-depth, longitudinal data on alcohol, multi-substance use, and outcomes. This project aims to transform VACS into a new collaboration of research experts, clinicians, patients, and policy makers: the Consortium to improve OutcoMes in HIV/AIDS, Alcohol, Aging, and multi-Substance use (COMpAAAS). The supplement will expand investigation (beyond the VA health care system cohort) of the observed sex disparities in treatment response among HIV-infected individuals that appear to be unrelated to socio-demographic characteristics, health behaviors, and access to care.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Estrogen Receptor a Regulation of Lupus Development and Pathogenesis**
PI: **Karen A. Gould**
Institution: **University of Nebraska Medical Center**
Grant No.: **5R01AI075167-04**

This research employs mouse models to determine the mechanisms through which estrogens promote lupus, a prevalent and life-threatening autoimmune disease that affects women predominantly. The supplement aims to define cellular and molecular pathways through which estrogens enhance lupus susceptibility in women.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Influenza A Virus Infection of Human Nasal Epithelial Cells**
PI: **Andrew S. Pekosz**
Institution: **Johns Hopkins University**
Grant No.: **5R01AI097417-02**

This project is investigating how influenza virus and influenza vaccine strains differ in their ability to replicate in human nasal epithelial cells: In particular, there is growing evidence that females of reproductive age (18–49) are at higher risk for severe disease after influenza infection. The supplement will enable the investigators to acquire additional tissues from male and female donors to identify sex-based differences in viral replication and innate immune response.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Tissue-Specific Borrelia Gene Expression**
PI: **Erol Fikrig**
Institution: **Yale University**
Grant No.: **5R37AI049200-13**

This project focuses on the pathogenesis of and immunity against Lyme disease. Because basic immune responses between men and women are known to differ, and because women have a higher prevalence of autoimmune disorders, this supplement will compare immune responses to infection with the Lyme-inducing Borrelia burgdorferi bacterium in male and female mice.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Tuning Fc-effector Functions of HIV-Specific Antibodies**
PI: **Galit Alter**
Institution: **Massachusetts General Hospital**
Grant No.: **5R01AI102660-02**

This project will define the mechanism of antibody glycosylation in immune (B) cells, toward the design of improved vaccines. Changes in antibody glycosylation can have systemic inflammatory effects, especially in women. The supplement will explore sex differences in this process, including epigenetic changes, in health and during HIV infection.

IC: **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
Title: **Multidisciplinary Clinical Research Center for Rheumatic Diseases in African Americans**
PI: **Gary S. Gilkeson**
Institution: **Medical University of South Carolina**
Grant No.: **3P60AR062755-02S1**

Research conducted by this MCRC grant aims to facilitate research translation, in particular supporting genetic and environmental research studies on scleroderma and lupus, both of which

disproportionately affect women and African Americans. The supplement will test the hypothesis that female sex hormones increase gut permeability, raise levels of microbial translocation and bacterial ligands, and increase monocyte activation—leading to higher susceptibility to autoimmune diseases in females compared to males.

IC: **National Institute of Biomedical Imaging and Bioengineering**
Title: **Patient Motion Detection and Compensation in SPECT**
PI: **Michael A. King**
Institution: **University of Massachusetts Medical School**
Grant No.: **3R01EB001457-09S1**

This project is testing a motion-correction technique to enhance the reliability and utility of single-photon emission-computed tomography (SPECT) imaging used for coronary artery disease risk assessment and stratification. The supplement will determine the clinical value of an additional respiratory-motion correction applied to data from women to increase imaging accuracy.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Host Epigenetic and Mitochondrial Function in HIV-Infected Children**
PI: **Louise Kuhn**
Institution: **Columbia University Medical Center**
Grant No.: **3R01HD073952-02S1**

This prospective study of 500 treated HIV-infected and 250 uninfected children in South Africa is investigating biological pathways for metabolic complications of HIV infection. The supplement aims to increase enrollment in a nested laboratory sub-study to evaluate sex differences in the pathobiology of these pathways that include mitochondrial dysfunction, chronic inflammation, and HIV-related immune senescence.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Integrating Contextual, Proximal, and Individual Risks for Child Conduct Problems**
PI: **S. Alexandra Burt**
Institution: **Michigan State University**
Grant No.: **3R01HD066040-04S1**

Many factors influence development of conduct problems in children, and this project is investigating how neighborhood contextual risk moderates genetic risk—toward the development of individually tailored interventions. The supplement will study 2,000 twin children (aged 6–10 years; half of the population will be girls; the other half, boys) and their parents to examine sex differences in gene-environment interactions underlying child conduct problems.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Understanding the Impact of Antipsychotic Drugs on Recovery After TBI**
PI: **Anthony E. Kline**
Institution: **University of Pittsburgh**
Grant No.: **3R01HD069620-02S1**

Antipsychotic drugs are commonly used to manage agitation and aggression that often follows traumatic brain injury; however, a paucity of research is available on the effect of these medications on subsequent recovery. This project compares three antipsychotic drugs to assess effects on motor and cognitive recovery after traumatic brain injury. The supplement adds a study of female animals to compare to preliminary results obtained with a male-only sample.

IC: **National Institute on Drug Abuse**
Title: **Assess the Effects of ETS on Neurodevelopment**
PI: **Virginia A. Rauh**
Institution: **Columbia University Medical Center**
Grant No.: **3R01DA027100-04S1**

This project is assessing the effects of environmental tobacco smoke exposure on brain development and neurobehavioral functioning in inner-city children. Toward identifying biological and behavioral trajectories associated with environmental tobacco smoke exposure, the supplement will combine male and female subjects from two ongoing prospective studies to obtain adequate statistical power for sex-specific analyses of preexisting data.

IC: **National Institute on Drug Abuse**
Title: **Drug Abuse Vulnerability: Mechanisms and Manifestations**
PI: **Ralph E. Tarter**
Institution: **University of Pittsburgh**
Grant No.: **3P50DA005605-22S1**

This grant funds the Center for Education and Drug Abuse Research, which was established in 1989 as part of a larger research effort to understand the etiology of substance use disorder, toward development of methods and instruments to identify at-risk youth. The supplement will derive and validate six age-specific versions of a transmissible liability index for girls and young women, akin to a similar transmissible liability index developed for boys and young men.

IC: National Institute on Drug Abuse
Title: Mechanisms of nicotine reinforcement
PI: Paul J. Kenny
Institution: Scripps Florida
Grant No.: 3R01DA020686-07S1

This project first identified nicotinic acetylcholine receptor subtypes in the midbrain and thalamus that limit nicotine consumption, and its ongoing studies are looking for other therapeutic targets for smoking cessation. The supplement will expand studies investigating sex-specific differences in nicotine consumption using transgenic rats, including follow-up analyses of a genetic variant associated with schizophrenia and results suggesting a correlation between nicotine response and sexual behavior.

IC: National Institute on Drug Abuse
Title: Neuronal Substrates of Cocaine Reward
PI: George F. Koob
Institution: The Scripps Research Institute
Grant No.: 3R01DA004398-26S2

This project is studying the role of stress in the compulsivity that is associated with cocaine dependence, vulnerability, and potential treatments. Both clinical human and preclinical animal studies indicate that compared to males, females exhibit enhanced cocaine-seeking within all stages of addiction. The supplement will expand a male-only study by adding female rats to investigate sex differences in stress-system neuroadaptations underlying addiction.

IC: National Institute on Deafness and Other Communication Disorders
Title: Vestibular Thresholds, Including Psychophysical Response Dynamics
PI: Daniel M. Merfeld
Institution: Massachusetts Eye and Ear Infirmary
Grant No.: 3R01DC004158-12S1

The vestibular system of the inner ear detects head/body motion and tilting relative to gravity. This project measures human vestibular perceptual thresholds for tilt, linear, and rotational motion using four new precise and efficient quantitative tests. The supplement adds threshold testing for 50 male and 50 female age-matched normal subjects, paired to determine whether there is a statistically significant sex/gender difference in vestibular perception thresholds over a wide age range.

IC: **National Institute of Dental and Craniofacial Research**
Title: **Cortico-striatal Plasticity in the Transition to Chronic Pain**
PI: **Apkar Vania Apkarian**
Institution: **Northwestern University at Chicago**
Grant No.: **3R01DE022746-02S1**

This project, which combines brain imaging with cellular, molecular, and electrophysiological assays in mice and rats and then in humans with back pain, is based on the idea that brain emotional and motivational learning circuitry is an integral part of the transition from acute to chronic pain. The supplement increases statistical power to test for gender dependence of both analgesic efficacy and transition from acute to chronic low-back pain.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Discovery and fine mapping of susceptibility loci for IgA nephropathy**
PI: **Ali G. Gharavi**
Institution: **Columbia University Health Sciences**
Grant No.: **3R01DK095510-02S1**

This project is conducting genetic studies related to immunoglobulin A nephropathy, an understudied disease that is a major cause of kidney failure in the United States and worldwide. The supplement will analyze genome-wide association data stratified by gender to look for clues to help explain the striking gender disparity in this condition.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Lactation and Incidence of Diabetes Mellitus in CARDIA Women**
PI: **Erica Pauline Gunderson**
Institution: **Kaiser Foundation Research Institute**
Grant No.: **3R01DK090047-03S1**

As part of the larger Coronary Artery Risk Development in Young Adults Study (CARDIA) population-based study, this project investigates effects of breastfeeding on prevention of type 2 diabetes. The supplement enables contrast of biological and lifestyle effects to determine sex differences in cardiometabolic risk, in men and women, by assessing the impact of childbearing (as a "lifestyle" effect) on both sexes.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Localization of Saturated Diacylglycerol and Insulin Sensitivity in Humans**
PI: **Bryan C. Bergman**
Institution: **University of Colorado Denver**
Grant No.: **3R01DK089170-04S1**

This project is investigating fundamental mechanisms that underlie insulin resistance, which is often less prevalent in women than men of the same age, body mass index (BMI), and ethnicity.

The supplement will expand on preliminary observations showing that women have a lower saturated-to-unsaturated-fatty-acid ratio in skeletal muscle by increasing the number of obese subjects to permit a statistically relevant gender-specific data analysis.

IC: **National Institute of Environmental Health Sciences**
Title: **Mechanisms of Asthma-Dietary Interventions Against Environmental Triggers**
PI: **Gregory B. Diette**
Institution: **Johns Hopkins University**
Grant No.: **3P01ES018176-05S1**

Using well-controlled mouse-model studies, this research aims to better understand the relationship between dietary intake and asthma. The supplement will allow sex differences to be examined for all parameters of the project's population-based study and will compare the effects of air pollution and diet on asthma in female and male mice.

IC: **National Institute of General Medical Sciences**
Title: **An Intercross Between the Circadian and NF-κB Pathways**
PI: **Marina Antoch**
Institution: **Roswell Park Cancer Institute**
Grant No.: **3R01GM095874-03S1**

This research explores how biological clocks and the immune system interact at the molecular level. The supplement will look for sex-specific differences in an organismal response (male or female mice) to acute stressors using a key immune regulatory system, the NF-κB signaling pathway.

IC: **National Institute of General Medical Sciences**
Title: **Receptor Selective Spinal Analgesia**
PI: **James Eisenach**
Institution: **Wake Forest University Health Sciences**
Grant No.: **3R37GM048085-21S1**

This project explores the clinical observation that trauma during childbirth very rarely causes chronic pain, in an effort to understand this protective effect and apply it to other settings. The supplement will investigate sex differences in spinal astrocyte activation after injury, and it will assess the relevance of sex differences on spinal astrocyte activation to hypersensitivity.

IC: **National Institute of Mental Health**
Title: **Characterization of Leptins Antidepressant Activity**
PI: **Xin-Yun Lu**
Institution: **University of Texas Health Science Center at San Antonio**
Grant No.: **3R01MH076929-06A1S1**

This project aims to understand the causes and disease progression of depression-related behaviors and to explore the role of the adipocyte hormone leptin in mood regulation. Since the parent grant only employed male subjects, the supplement will add sufficient numbers of females to investigate sex differences in mood and difficulty experiencing pleasure.

IC: **National Institute of Mental Health**
Title: **HIV Prevention Intervention for Young Transgender Women**
PI: **Robert Garofalo**
Institution: **Ann & Robert H. Lurie Children's Hospital of Chicago**
Grant No.: **3R01MH094323-03S1**

This project tests the efficacy of a uniquely targeted HIV risk-reduction intervention for young transgender women (16–24) who are at risk for HIV acquisition or transmission. The supplement will compare sexual risk behaviors and psychosocial risk and resilience factors between transgender women and transgender men who have sex with men. This approach enables separation of sex (biological) and gender (behavioral/cultural) factors.

IC: **National Institute of Mental Health**
Title: **In Utero Programming of the Dopamine System: Behavior, Neuroanatomy, and Epigenetics**
PI: **Teresa M. Reyes**
Institution: **University of Pennsylvania**
Grant No.: **3R01MH087978-04S1**

Intrauterine growth retardation can lead to neurobehavioral disabilities, including an increased risk for attention deficit hyperactivity disorder (ADHD). This project employs an animal model to explore potential causes and interventions. The supplement may shed light on gender differences in ADHD by examining the effect of restricted maternal dietary intake on behavior in male and female offspring, as well as on patterns of DNA methylation and gene expression in male and female offspring.

IC: National Institute on Minority Health and Health Disparities
Title: Addressing Disparities in Chronic Disease with a Teen and Young-Adult Focus
PI: Kirsten Bibbins-Domingo
Institution: University of California, San Francisco
Grant No.: 3P60MD006902-02S1

This project funds the Center for Health And Risk in Minority youth and adults (CHARM), which is dedicated to chronic disease prevention in racial/ethnic minority communities in the San Francisco Bay area, focusing in particular on youth and young adults. The supplement will extend a current study of childhood asthma and obesity in Latino Americans to identify sex-specific differences in the obese asthma phenotype and to uncover the contributions of genetics, socio-demographics, and early-life events in the development of these conditions in Latino and African American girls and boys.

IC: National Institute on Minority Health and Health Disparities
Title: Retrospective Cohort Study of Racial Disparities in HIV Survival, Florida
PI: Mary Jo Trepka
Institution: Florida International University
Grant No.: 3R01MD004002-05S1

This study examines the role of various factors such as socioeconomic status, segregation, and rural residence in causing a survival disadvantage for HIV-infected African Americans, and it includes a focus on sex/gender differences in HIV morbidity and mortality. The supplement expands this focus to include transgender individuals with HIV. This approach enables a unique examination of sex (biological) and gender (behavioral/cultural) influences, providing an opportunity to disentangle biological and non-biological factors related to HIV/AIDS.

IC: National Institute of Neurological Disorders and Stroke
Title: Estrogen-Induced Hippocampal Seizure Susceptibility
PI: Catherine S. Woolley
Institution: Northwestern University
Grant No.: 3R01NS037324-15S1

This research is defining novel mechanisms by which estrogen affects levels of neurotransmitters and neuropeptides in the hippocampus, a key brain region involved in epilepsy. The supplement will look for sex-based effects of brain-synthesized estrogens on limbic seizures, and it will also test for sex differences in estrogen function in the hippocampus.

IC: National Institute of Neurological Disorders and Stroke
Title: Failure of Metabolite Clearance in a Model of Multi-lacunar Infarcts
PI: Maiken Nedergaard
Institution: University of Rochester
Grant No.: 3R01NS078167-02S1

This research tests the hypothesis that accumulation of metabolic waste products contributes to impairment of cognitive functions in a mouse model of multi-infarct dementia. The supplement will evaluate the effect of age and tissue injury on the clearance of waste fluid in the brains of male and female mice.

IC: National Institute of Neurological Disorders and Stroke
Title: Inflammasome Activation in Complex Regional Pain Syndrome
PI: David J. Clark
Institution: Palo Alto Veterans Institute for Research
Grant No.: 3R01NS072143-02S1

This project investigates complex regional pain syndrome (CRPS), a common neurological condition causing chronic pain and disability that has been recently linked to innate-immunity triggered inflammation. Women are affected by CRPS four times more frequently than are men and may respond differently to treatment, but experiments to date have been conducted exclusively on male animals. The supplement adds a study of female animals to ascertain the sex-dependence of CRPS severity and duration using multidimensional experimental outcomes mirroring those experienced by humans.

IC: National Institute of Neurological Disorders and Stroke
Title: MECP2 Modulation of BDNF Signaling Shared Mechanism of Rett and Autism
PI: Lucas D. Pozzo-Miller
Institution: University of Alabama at Birmingham
Grant No.: 3R01NS065027-04S1

This project studies Rett syndrome, an X-linked neurodevelopmental disorder associated with autism and mental retardation, which is more common in girls and is known to be caused by a genetic mutation that affects production of a neuronal growth factor. The supplement will extend the project's reach by including an analysis of hippocampal function in female transgenic mice; the original project included only male animals.

IC: National Institute of Nursing Research
Title: The Influence of Gender on Symptom Characteristics During Acute Coronary Syndrome
PI: Holli A. Devon
Institution: University of Illinois at Chicago
Grant No.: 3R01NR012012-05S1

This project explores gender differences in the symptoms of acute coronary syndrome. The supplement adds a sample of Mexican-American women and men to the parent study. This addition will permit subgroup analyses by gender and also includes an ethnic minority underrepresented in acute coronary syndrome research.

Advancing Novel Science in Women's Health Research

IC: National Cancer Institute
Title: Effects of Continuous Versus Cyclic Oral Contraceptives on Mammary Tumor Growth
PI: Patricia Ann Masso-Welch
Institution: State University of New York at Buffalo
Grant No.: 1R21CA170056-01A1

There is no question that breast cancer susceptibility is strongly correlated with lifelong exposure to estrogen and progesterone (E+P). Extension of E+P exposure using a widely employed hormone replacement therapy (HRT) increased breast cancer risk in postmenopausal women. Oral contraceptive (OC) use, in a manner similar to HRT, is an example of a widely used hormonal regimen with the potential to impact breast cancer chemoprevention in a huge population. Unlike HRT, OC are used over a large expanse of a lifetime, sometimes initiated as early as puberty, to control fertility and menstrual side effects. With the recent advent of the continuous dosing regimen, in which the hormone withdrawal period is eliminated, women have the option to undergo months or years of continuous hormonal exposure with no remodeling of the breast or uterus that normally accompanies cyclic dosing regimens. Based on the ability of OC to eliminate menstruation and accompanying side effects, it is not surprising that many of the ~ 21% of adult women in the US who are current users of OC have begun to shift to a continuous regimen. It is critical, therefore, to determine whether continuous exposure to OC carries a significant risk to increase breast cancer. Although we might predict an increased risk (based on the risks from HRT), cycling women experience two types of tissue responses that do not occur in menopausal women: (i) cycles of epithelial and stromal vascular (angiogenic) proliferation in response to hormones, and (ii) cycles of apoptosis and glandular and stromal vascular regression. These two observations suggest two alternate potential outcomes of continuous OC dosing: (i) If hormone-dependent epithelial and angiogenic proliferation is critical to breast cancer risk, we predict that continuos OC use will increase breast cancer risk; (ii) Alternately, if the glandular and stromal vascular regression and remodeling in response to hormone withdrawal contribute to breast cancer risk (as has been proposed for hormone withdrawal during post-lactational involution), then continuous dosing may decrease breast cancer risk. This proposal is designed to test these two alternate hypotheses. Aim 1 will compare the ability of cyclic (3 days on, 1 day off) versus continuous dosing +/- OC to alter spontaneous tumor development, progression, and metastases in the FVB-MMTV-Her-2/Neu model of spontaneous mammary tumorigenesis. Aim 2 will compare the ability of cyclic versus continuous dosing +/- OC to alter the mammary tumor growth using the TM2H transplantable mouse mammary tumor cell line. Mammary tumors from different treatment groups will be compared for alterations in expression of ER, PR, and Her2/Neu, vascularity and proliferative and apoptotic indices. The primary outcome of these studies is to define the effects of continuous dosing of OC on primary and metastatic mammary tumor growth in two distinct mouse mammary tumor models, relative to no OC or cyclic dosing of OC.

IC: National Cancer Institute
Title: Validation of a Risk Assessment Decision Rule for Epithelial Ovarian Cancer
PI: Nicole Denise Urban
Institution: Fred Hutchinson Cancer Research Center
Grant No.: 1R21CA179443-01

Our goal is to develop a risk-classification tool to identify post-menopausal women who are at high or elevated risk for epithelial ovarian cancer (EOC). We will develop and validate a risk-assessment decision rule based on serum markers CA125 and HE4, as well as epidemiologic risk factors, using a split-sample design and data from the Women's Health Initiative (WHI) Observational Study (OS), the WHI Clinical Trial (CT), and the Prostate, Lung, Colon and Ovary (PLCO) trial. A decision rule developed as preliminary work identified 10%–13% of all post-menopausal women as elevated risk and predicted 26%–58% of cases. Surgical prevention consisting of prophylactic removal of fallopian tubes (FTs) and ovaries is recognized as the best approach to prevent epithelial ovarian cancer (EOC) and especially high-grade serous cancer (HGSC) in high-risk women. We will develop a tool to categorize women into risk classifications that have clear clinical implications including recommendations for surgical prevention, imaging, surveillance, and routine care. In the first 2 aims, we will focus on development of the epidemiologic portion of the model because the serum marker portion of the decision rule has already been developed based on extensive published work. In Aim 3, we will validate the final decision rule that combines epidemiologic risk factors with serum markers. We operationally define high risk as relative risk (RR) of at least 6, and elevated risk as RR of at least 2. Aim 1: Using a randomly selected fraction of women participating in the WHI OS, WHI CT, and the PLCO trial, develop decision rules to identify women at elevated risk for EOC and HGSC using epidemiologic variables alone. Using the remaining women from each study, validate each decision rule within each population. Decision rules developed in this aim will be specific to each study population in order to take advantage of all of the epidemiologic data collected by each study. Aim 2: Cross-validate the decision rules developed in Aim 1 to identify the rule that best identifies women at elevated risk for EOC and HGSC across the 3 different populations. This will require refinement of the decision rules to accommodate differences in data collection across the cohorts. The study fraction used for development will be used to identify the best common rule, and cross-validation will employ the remaining validation fraction of women participating in the WHI OS, WHI CT, and the PLCO trial. This aim will identify the best epidemiologic decision rule for use in the overall decision rule to be validated in Aim 3. Aim 3: Using nested case-control study serum marker data as well as epidemiologic data from each study, validate the best decision rule from Aim 2 in combination with the serum marker component of the rule to identify women at elevated- and high-risk for EOC and HGSC in each of those populations. In this aim, we will validate the final decision rule that incorporates both epidemiologic risk factors and serum markers.

IC: National Heart, Lung, and Blood Institute
Title: Pregnancy Complications, Future Cardiovascular Disease Risk Factors, and Cardiovascular Disease Risk Prediction in Women
PI: Nisha Indravadan Parikh
Institution: The Queen's Medical Center
Grant No.: 1R21HL115398-01A1

Currently available cardiovascular disease (CVD) risk scores in women usually include risk factors, which are gender-neutral and often lead to an underestimate of CVD risk. There are factors in the life course of women that are unique and gender-specific, which relate to long-term CVD risk. Pregnancy is considered a "cardiometabolic stress test" such that adverse pregnancy factors/outcomes in a woman predict future CVD risk factors and incident CVD. The American Heart Association's and American College of Cardiology's Effectiveness-Based Guidelines for CVD Prevention in Women recommend taking a pregnancy history for CVD risk stratification; however, it is unclear which pregnancy factors are independently related to CVD when taken together. Specific pregnancy factors that have been demonstrated to predict CVD risk factors and CVD include pregnancy-induced hypertension or pre-eclampsia, gestational diabetes, having a small for gestational age infant, a low or very high number of pregnancies, pre-term delivery, stillbirth, and a history of subfertility. We believe that a pregnancy risk score derived from these candidate pregnancy factors will help medical caregivers determine which specific factors in a woman's pregnancy history are most important as far as predicting future CVD risk factors and future CVD. A pregnancy risk score may help providers with personalized, earlier referral for upstream risk factor modification and may also allow a woman to assess her own CVD risk. In this proposal, we have the following three research goals: (1) To determine which subset of pregnancy-related factors is related to blood pressure, oral glucose tolerance test, and lipid profile in the Västerbotten Intervention Programme (VIP) when linked to the Swedish population registers (estimated n = 16,041); (2) Utilize a multiple-marker approach to develop and validate a pregnancy factor risk index in the Swedish population registers (estimated n = 800,000); and (3) To determine whether the pregnancy factor risk score (developed in specific Aim 2) improves CVD risk stratification (discrimination, calibration, and net reclassification) above and beyond established CVD risk factors among women using the VIP dataset linked to Swedish population register.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Magnetic Resonance Imaging of Bound and Free Water in Cortical Bone
PI: Jiang Du
Institution: University of California, San Diego
Grant No.: 1R21AR063894-01A1

Routine clinical evaluation of osteoporosis (OP) has been limited to the assessment of bone mineral density (BMD) using dual energy x-ray absorptiometry (DEXA) and/or CT. The majority of bone, the organic matrix, and water, which together represent ~ 57% of bone by volume, are not accessible with these techniques. BMD alone predicts fractures with only a 30%–50% success rate. The missing factor may be the contribution of bone organic matrix and water. Bone water occurs at various locations and in different states. It is bound to the organic matrix or in "free" form in the Haversian and the lacunar-canalicular systems. The bound water

content reflects organic matrix density. The free water content can potentially provide a surrogate measure of bone porosity. However, neither DEXA nor CT can detect either bound or free water in cortical bone. We have developed Ultrashort Time-to-Echo (UTE) magnetic resonance imaging (MRI) sequences with minimum TEs of 8 μs, and this makes it possible to detect water signal from bone. Total bone water can be quantified by comparing UTE signal from bone and a water phantom. Bound water can be selectively imaged with SIR-UTE sequences, which use a single adiabatic inversion pulse to invert and null the free water magnetization. Free water can be selectively imaged with DIR-UTE sequences, which saturate bound water while leaving free water magnetization unaffected. Bound water has ~ 10 times shorter T2* than free water. The two components may be separated with bi-component fitting. Free water has a short T2* but long T2, and may be imaged with FSE sequences. The UTE approach may detect the effect of Gadolinium chelates within cortical bone and study its perfusion at high resolution. This provides a new way to characterize cortical bone. In this proposal we hypothesize that bone water content and bone perfusion can be non-invasively assessed by novel MRI techniques and can serve as sensitive biomarkers of bone quality. We aim to develop novel UTE, SIR-UTE, DIR-UTE, and FSE techniques to measure total, bound, and free water in cortical bone (Aim 1); to evaluate the accuracy of MR measures of two groups of women cadaveric human tibia specimens, the younger group (< 60 years old) and the older group (> 80 years old), and correlate the results with cortical porosity determined by mCT and organic matrix content determined by ashing, as well as elastic properties (modulus, yield stress, and strain) and failure properties (ultimate stress, failure strain, and energy) determined by 4-point bending test (Aim 2); and to develop translational MR techniques to quantify total, bound, and free water as well as bone perfusion in two groups of postmenopausal women: i.e., below 60 without OP and above 80 with OP (Aim 3). The intention is to develop and validate these techniques in tissue studies and a small number of patients to provide preliminary data for an RO1 grant application on the use of MR in diffuse bone disease including OP, renal osteodystrophy, Paget's disease, and osteomalacia. The comprehensive characterization of bone in these conditions could have a profound impact in their diagnosis and treatment.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Role of MicroRNA-29 in Uterine Leiomyoma Pathogenesis**
PI: **Erica E. Marsh**
Institution: **Northwestern University**
Grant No.: **1R21HD077479-01**

Leiomyomas are highly pervasive benign tumors of the uterus that have an overall prevalence of 70% in women by the age of 50. They are the leading cause of hysterectomy in the United States, accounting for almost 50% of the 600,000 hysterectomies performed annually and $34 billion in annual health care costs. Despite their prevalence and public health impact, the cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Phenotypically, these tumors are distinct from the adjacent normal tissue largely due to the overproduction of extracellular matrix component, especially the major fibrillar collagens (I, II, and III). We, and others, have demonstrated that in addition to differentially expressed genes between LEIO and MYO, there is differential expression of microRNAs, suggesting that they play a role in gene regulation of these tumors. MicroRNAs are a class of small non-coding RNAs that negatively regulate gene expression. While several studies have documented

hormonal and growth factor regulation of miRNAs in leiomyomata, none have demonstrated a functional role for them in terms of their main distinguishing pathological finding: excessive collagen deposition. Our lab has found that all of the members of the miR-29 family (29a, 29b, 29c) are downregulated in leiomyoma versus normal myometrial tissue. Based on recent studies in other fibrotic diseases and preliminary data included in this application, we hypothesize that this dysregulation of the miRNA-29 family plays a functional role in the aberrant extracellular matrix components found in leiomyomata. To address this hypothesis, we propose the following two specific aims: In Specific Aim 1, we seek to determine the mechanism by which TGF-β regulates miR-29 levels in uterine leiomyomas. TGF-β is known to be present in higher concentrations in leiomyoma versus adjacent normal myometrial tissue. To determine its role in the regulation of miRNA-29, we will perform SMAD2/3 knockdown and chromatin immunoprecipitation studies. In Specific Aim 2, we will determine the contribution of the miR-29 family (a/b/c) to the excess major fibrillar collagen production in uterine leiomyoma. The role of miRNA-29 will be assessed using knockdown and overexpression studies. The results from these studies will not only provide mechanistic information on the excess extracellular matrix seen in leiomyomas but will also lay the foundation for future preclinical studies as our understanding of both miRNAs in human disease and oligonucleotide based therapeutics continues to expand.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **STI Risk Among Adolescent Females: Activity Spaces and Spatial Mobility**
PI: **Elizabeth Ann Reed**
Institution: **University of California, San Diego**
Grant No.: **1R21HD073610-01A1**

The goal of this study is to determine the role of social spaces (locations where social interactions occur) and spatial mobility on risk for chlamydia and gonorrhea among adolescent girls living near the US–Mexico border. Adolescent girls have the highest burden of chlamydia (CT) and gonorrhea (GC) compared to any other age-sex group in the United States. Several studies have begun to examine how neighborhood or community-level structural factors may influence health risks, including sexual risk and sexual violence; however, these studies don't account for mobility of individuals across arbitrary neighborhood boundaries. The exposures and experiences that occur in adolescents' different social spaces shape their own behaviors, including those that put them at higher risk for STI and sexual violence. Mobility may impact not only exposure to different community-level structural factors, but also the number and type of social spaces frequented. Additionally, the rapid increase in the number and type of accessible technologies for communication has greatly impacted the manner in which socialization occurs. Understanding how adolescents incorporate this technology into identification of social spaces and attendance of social activities may help identify novel targets for sexual health interventions. In this study, we aim to (1) develop categories and measures to describe the types and characteristics of adolescents social spaces, including locations where adolescents may be exposed to sexual violence, and adolescents' patterns of mobility; (2) compare types of social spaces, including the geographic location of these spaces, and patterns of mobility between adolescents testing positive for CT and/or GC and those testing negative; and (3) to use qualitative methods to provide a deeper understanding of the role of communication technology

in adolescents' identification of activity spaces and engagement in social activities and related sexual and substance use risk behaviors. To meet these aims, we will conduct a case-control study among adolescent girls (age 15–19 years) in collaboration with a youth center and clinic in a culturally diverse neighborhood with a high proportion of ethnic minorities. Fifty cases (positive test for CT and/or GC) will be referred from the clinic, and 150 controls will be recruited from those seeking family planning/reproductive health services from the youth center. Participants will be asked to complete an interviewer-administered survey including questions about demographics, sexual/reproductive health, sexual and substance use behavior, and exposure to sexual violence, as well as a mapping component to identify social spaces using Google Earth. A sample of cases will be asked to participate in a second, in-depth interview about the use of technology in social activity decision making. This study is consistent with the goals of the NIH ANSWHR PAS (PAS-10-226), offering an interdisciplinary study combining concepts of spatial mobility with a gendered perspective on STI risk among sexually active adolescent girls and will provide a framework to explore innovative structural-level interventions to reduce STI risk among this population.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Exploring Disparities: Urinary Incontinence Treatment Seeking in Mid-life Women**
PI: **L. Elaine Waetjen**
Institution: **University of California, Davis**
Grant No.: **5R21DK092864-02**

Urinary incontinence (UI) is a frequent midlife problem that disproportionately affects women. While a number of effective treatments exist for UI, women can be inhibited in seeking care for this problem. This study proposes to explore racial/ethnic, socioeconomic, and educational level disparities in treatment seeking behavior for UI 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/ethnic, community-based, prospective cohort study of women transitioning through menopause. With longitudinal logistic regression and discrete proportional hazards statistical modeling, we will analyze the complex interplay between demographic characteristics and longitudinal changes in UI characteristics, economic, social psychological, and health factors that may affect: (1) not seeking UI treatment and reported reasons for not seeking treatment from health care providers, and (2) the types of treatments prescribed for and tried by community-dwelling midlife women who do seek UI care. With information from this study, public health educators can target messages to specific groups with bothersome UI symptoms at risk for not accessing UI care. For health care providers, a better understanding of what factors make a woman more or less likely to report UI to them and try their recommended treatments will allow them to improve and individualize assessment of and treatment plans for their incontinent patients.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Role of GBS Capsule in Ascending E. Coli UTI and Urosepsis in Aged Multiparous Mice
PI: Amanda L. Lewis
Institution: Washington University in St. Louis
Grant No.: 5R21DK092586-02

Pathogenesis of mucosal infections is often studied in monomicrobial settings that ignore the possible influence of other potentially pathogenic microbial flora present at the time of exposure. Urinary tract infection (UTI) is a common and sometimes persistent disease that can have life-threatening outcomes in susceptible populations. Women are at much higher risk of UTI than men and are more likely to experience complications of infection during particular stages of the reproductive lifespan—in pregnancy and after menopause. Abundant and diverse microbial populations exist in periurethral and nearby mucosal sites; therefore, there is a high likelihood that bacterial exposures of the urinary tract are often polymicrobial. Uropathogenic E. coli (UPEC) is the most common cause of UTI but often co-occurs with low levels of Gram-positive bacteria in urine in a polymicrobial context. The presence of sub-diagnostic levels of Gram positives in urine is usually considered clinically insignificant; however, this assumption has never been tested experimentally. Group B Streptococcus (GBS) in a common commensal of the lower gastrointestinal and vaginal tracts and is commonly isolated from women with UPEC UTI or asymptomatic bacteriuria. This proposal describes the development of a novel murine model to study polymicrobial-host interactions in the urinary tract in mice. Proposed experiments use this model to investigate the impact of GBS on UPEC UTI outcomes. Preliminary data show that GBS has a striking impact on UPEC infection, altering the course, severity, and outcome of UTI. Ongoing cellular and molecular studies are defining specific host and bacterial factors involved in the polymicrobial dialogue. In this proposal, we aim to more fully understand the mechanisms driving alterations to the UPEC pathogenic cascade upon polymicrobial inoculation with GBS. In addition to paradigm-shifting implications for urinary pathogenesis, the proposed studies may uncover valuable predictors of risk in particular clinical settings.

IC: National Institute of Environmental Health Sciences
Title: Arsenic Repression of GADD153 and Breast Cancer
PI: Keshav K. Singh
Institution: University of Alabama at Birmingham
Grant No.: 1R21ES023091-01

Arsenic is a well-known human carcinogen. Previous studies including human population studies provide an extensive and important link between the arsenic exposure and development of breast cancer. These studies suggest that arsenic accumulates in breast tissues and acts as an endocrine disruptor to promote development of breast cancer. Arsenic is one of the few human carcinogens that do not induce tumors in laboratory animals. Therefore, development of models for arsenic-induced breast cancer is critical for understanding the mechanism(s) underlying the tumorigenic process. We have developed a mammary epithelial cell model for arsenic-induced cancer. To replicate normal field exposure conditions, we exposed mammary epithelial cells to a low dose of arsenic for several months. We discovered that a five month continuous exposure of mammary epithelial cells results in increased cell proliferation, increased wound healing, increased anchorage independent growth, as well as increased matrigel invasion. These studies

suggest a tumorigenic transformation of mammary epithelial cells by exposure to arsenic. Mitochondria control cell growth and cell death. Mitochondria also perform other cellular functions including ATP production via mitochondrial oxidative phosphorylation (mtOXPHOS). Consistent with this finding, arsenic-transformed cells show (1) altered mtOXPHOS Complex I and IV activities, (2) an altered expression of subunit NDUFB8 comprising mtOXPHOS Complex I, and (3) altered expression of COXII subunit comprising mtOXPHOS complex IV. Interestingly, our study suggests that arsenic-treatment did not induce changes in mtOXPHOS Complex II and III activities. These preliminary studies revealed that arsenic targets mitochondria and induces mitochondrial stress. Recent studies suggest that human cells contain mitochondria specific stress response pathway in which transcription factor GADD153 (also known as CHOP or DDIT3) plays a key role. We measured the expression of GADD153 and found that arsenic represses GADD153 expression. GADD153 is described to play a critical role in cell death, and suppression of GADD153 expression is known to protect cells from cell death. However, GADD153's role in arsenic induced carcinogenesis is unknown. We hypothesize that arsenic represses expression of GADD153/CHOP/DDIT3 to protect cells from arsenic induced cell death, which contributes to tumorigenic transformation of mammary epithelial cells induced by arsenic. To address this hypothesis, we will: Aim 1: Determine a role for GADD153 in protection against cell death and mitochondrial stress induced by arsenic. Aim 2: Determine whether arsenic repression of GADD153 expression contributes to tumorigenic transformation of breast epithelial cells in vitro and in vivo in mouse xenograft model. The proposed studies should provide insight into the mechanism involved in arsenic induced breast tumorigenesis.

IC: **National Institute of General Medical Sciences**
Title: **Macrophage Phenotype as a Determinant of Outcome in Pelvic Organ Prolapse Repair**
PI: **Bryan Nicklaus Brown**
Institution: **University of Pittsburgh**
Grant No.: **1R21GM107882-01**

Pelvic organ prolapse (POP) results in 225,000–300,000 surgical procedures per annum and with costs exceeding $1 billion in the United States. Native tissue repair of POP is associated with high recurrence rates. Therefore, synthetic mesh, originally intended for abdominal wall hernias, has been increasingly used in repair of pelvic organ prolapse to improve anatomic success. However, surgeries which include mesh, such as the "gold standard" abdominal sacrocolpopexy and the newer vaginal mesh procedures, are associated with high rates of patient morbidity, including higher rates of fistula formation, erosion, infection, and pain. The rates of these complications are significant enough to warrant FDA warnings in 2008 and 2011. Many of these complications have been directly attributed to the immune response of the host to the synthetic mesh. There is a lack of rigorous scientific studies characterizing the effects of this host response in the vagina and the design of mesh materials largely relies on data generated in abdominal hernia repair. As a result, clinicians may select products based upon the recommendations of a vendor or institution, leading to the use of mesh in women on a trial and error basis. Macrophages have recently been classified as having diverse and plastic phenotypes between M1 (classically activated; pro-inflammatory) and M2 (alternatively activated; regulatory, homeostatic) extremes. Increasingly, macrophage polarization and plasticity are being shown to play important, and determinant, roles in disease pathogenesis and tissue remodeling. The timely modulation of macrophage phenotype appears to be a crucial event in the tissue remodeling

process. An increasing number of studies in the field of biomaterials have begun to apply these paradigms and concepts, and have shown that macrophage phenotype is a predictor of integration following placement. Briefly, the early macrophage response following implantation of biomaterials is a necessary and essential component of a beneficial response and that strategies which incorporate and modulate the host macrophage response rather than seek to avoid it result in improved tissue incorporation and long-term functional outcomes as a result. We, therefore, propose to investigate the role of macrophage polarization following placement of synthetic mesh in an in vivo transvaginal model to further elucidate how both individual mesh characteristics and modulation of macrophage phenotype in the immediate postoperative period can determine long-term incorporation or complications related to synthetic mesh placement. Completion of these studies on the evaluation and modulation of the host tissue response to synthetic mesh used in pelvic organ prolapse has the potential to inform the selection of mesh materials and to significantly affect the design of next generation mesh materials leading to improved patient outcomes.

Building Interdisciplinary Research Careers in Women's Health

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Careers in Women's Health**
PI: **Clay F. Semenkovich**
Institution: **Washington University in St. Louis**
Grant No.: **5K12HD001459-14**

Gender has complex and poorly understood effects on health throughout the different phases of life. The mechanisms underlying the unique course of several diseases affecting women remain unclear in part because of longstanding impediments to research efforts involving different disciplines. The long-term objective of this application, supporting the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program at Washington University, is to produce independent investigators conducting interdisciplinary research in women's health. The application 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. During the past 10 years, the Washington University BIRCWH Program has successfully achieved this aim through a combination of a mentored research experience (utilizing outstanding mentors representing a broad research base encompassing most of the diseases that differentially affect women), didactic training, interaction with scientists from other disciplines pursuing problems in women's health, establishing a visiting scientist program, and formalizing interdisciplinary research links with a substantial number of clinical programs in women's health. The Program now proposes to extend this 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 Infectious Disease Research (CWIDR) 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Careers in Women's Health at UC Davis**
PI: **Ellen B. Gold**
Institution: **University of California, Davis**
Grant No.: **5K12HD051958-09**

Over the past 4 years, the 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 crosscutting 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. The guiding values of our BIRCWH program include collaboration and celebration of diversity, traditions at UC Davis reflecting the demographics of our community. A formal evaluation program will drive continuous improvement to ensure that we nimbly respond to new research directions and techniques and the needs of our scholars and the women we serve.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Career in Women's Health Scholars**
PI: **Elizabeth S. Burnside**
Institution: **University of Wisconsin–Madison**
Grant No.: **5K12HD055894-07**

The goals of the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholars Program at the University of Wisconsin (UW) are (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 (WH). 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. We believe that integrating biomedical sciences, public health sciences, and sociocultural and behavioral sciences is a prerequisite to addressing the linkages of macro-societal issues with pathogenesis of disease, so important in addressing health disparities. Thus, the UW BIRCWH provides interdisciplinary and 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. To address not only the broad array of research areas outlined above but also the interdisciplinary nature of the possible candidates, the faculty is interdisciplinary and consists of physician scientists, perinatal researchers, sociologists, nurse scientists, nutritional scientists, epidemiologists, and economists. The outstanding research mentors selected for the BIRCWH

are enthusiastic about the opportunity to mentor more advanced scholars through the BIRCWH. A major strength of the UW proposal is the integration of the BIRCWH scholars into a thriving interdisciplinary WH and health equity and health disparities research network. 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. These future leaders in academic medicine will play a major role in improving the health and health care of all women, pushing forward the frontiers of WH research, bringing new knowledge to beneficial application, and framing the WH research agenda of the future.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Careers in Women's Health**
PI: **Katherine E. Hartmann**
Institution: **Vanderbilt University**
Grant No.: **5K12HD043483-12**

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. Scholars are selected by competitive review of applications from among early career faculty. Training is tailored to the individual investigator, in the context of structured interdisciplinary mentorship, and is overseen by the PI, Program Director and Assistant Program Director (each a former BIRCWH Scholar). BIRCWH program resources are further enhanced by myriad institutional resources that ensure our researchers thrive. Scholars form a mentoring panel, participate in regular BIRCWH work-in-progress presentations and seminars, receive formal evaluation each year, attend twice-monthly career development seminar series with other K-awardees, and are regularly exposed to case

studies on responsible conduct of research. They have access to: (1) an array of core labs and resources; (2) biostatistics consultations; (3) manuscript preparation work groups; (4) technical editing of completed products; (5) studios with experts to vet scientific ideas, research designs, and aims; (6) robust intramural pilot and feasibility funding; and (7) grant writing support including grant workshops, a funded grant library, and mock study sections. Tools are in place to evaluate both mentees and mentors and to continuously enhance our program. Further oversight is provided by an Advisory Committee and biennial external reviews. Combined, these efforts assure we carefully foster excellence in the next generation of women's health researchers.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Careers in Women's Health at Michigan State**
PI: **Claudia B. Holzman**
Institution: **Michigan State University**
Grant No.: **5K12HD065879-04**

The ultimate goal of the Building Interdisciplinary Research in Women's Health (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. The Advisory Committee includes distinguished researchers and leaders, including the leaders of two NSF-funded initiatives to enhance faculty development at MSU. The proposed program will sponsor approximately eight BIRCWH scholars over the life of the grant. Each scholar will each receive two to four years of support, with a fifth year available with the recommendation of the Advisory Committee. Scholars will have at least 75% protected time (50% for surgeons). The MSU BIRCWH program includes a core curriculum and a curriculum tailored to the stage of development of the scholar and emphasizing responsible conduct in research. 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. The University and the participating centers, colleges, and programs are fully committed to the success of the BIRCWH program. The program will help ensure that promising junior researchers have the protected time, mentorship, and training to become successful women's health researchers.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Careers in Women's Health in Pittsburgh**
PI: **Yoel Sadovsky**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **5K12HD043441-12**

The goal of this competitive renewal of our career development program, entitled Building Interdisciplinary Research Careers in Women's Health in Pittsburgh (BIRCWH@Pitt), is to build on our past programmatic success to train, nurture, and support talented University of Pittsburgh faculty scholars in interdisciplinary research across a woman's lifespan. Our objectives build on our unparalleled strength in reproductive sciences and women's health research, emanating from Magee-Womens Research Institute (MWRI) at the geographical center of the main campus of the University of Pittsburgh. MWRI is also adjacent to Magee-Womens 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, 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 in 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, attraction of new trainees through intellectual stimulation, motivation of new collaborative synergies, and implementation of sustainable women's health research. Cognizant of the fact that our scholars enter our program with diverse academic backgrounds and investigative skills, we have crafted individually tailored career development plans of 2–4 years, depending on each scholar's training and expertise. 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. We plan to train seven scholars with diverse research interests, each guided by an interdisciplinary group of three mentors, and overseen by an Advisory Committee comprised of researchers with heterogeneous scientific backgrounds. Resources garnered through our program are shared with other reproductive sciences trainees in the Departments of OB/GYN, MWRI, and elsewhere in the University. Together, BIRCWH@Pitt emphasizes imaginative thinking, cross-fertilization, and collaboration that bridges basic sciences and clinical medicine, and serves to propel our scholars to successful careers in women's health.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Women's Health at MUSC**
PI: **Kathleen T. Brady**
Institution: **Medical University of South Carolina**
Grant No.: **5K12HD055885-07**

This application from the Medical University of South Carolina (MUSC) requests support for renewal of the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program initially funded in 2007. 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 U.S. Since its inception, the MUSC BIRCWH has supported 9 Scholars, including 4 PhDs, 4 MDs, and 1 MD/PhD. 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 two and maximum of four years, depending on their level of training and experience at entry. We plan to have 5 Scholars in the program at any point in time: 4 supported by the BIRWCH program and 1 under-represented minority Scholar supported by an institutional commitment from the Dean of the College of Medicine. While each Scholar will have an individual career development plan, all will participate in core components, such as a seminar series focused on sex and gender issues in neuroscience research, MUSC's Sex and Gender Studies Research Day, and training in responsible conduct of research, providing ample opportunity for interaction and the development of interdisciplinary collaborations. 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 four 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. Their research interests are congruent with the special emphasis areas of prevention and treatment, and biological and behavioral basis of sex and gender differences, identified as high-priority areas in the new BIRCWH RFA-OD-11-002.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Career Development in Women's Health**
PI: **Andrea Dunaif**
Institution: **Northwestern University at Chicago**
Grant No.: **5K12HD055884-07**

The Northwestern University (NU) Building Interdisciplinary Careers in Women's Health (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 the Feinberg School of Medicine (Medicine, Neurology, Obstetrics & Gynecology, Preventive Medicine, and Psychiatry & Behavioral Sciences) and the 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. It should be noted that many of the NU BIRCWH CDWH Mentors have longstanding programs that are interdisciplinary in nature, which means that they could fit well within more than one of our research categories. NU BIRCWH CDWH Scholars will be assigned Mentors from at least two different disciplines and training backgrounds for interdisciplinary research and career development. Each Scholar's Mentors will interact closely with the Scholar and provide guidance to develop a tailored career development plan as part of an interdisciplinary mentoring team. The Mentors are all committed to continuing their involvement throughout the award period. The Program will continue to be monitored by the external advisory committee whose members are all BIRCWH PIs at other institutions as well as by the oversight committee. Formal program evaluation has already been implemented by the NU Searle Center for Teaching Excellence.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Career Development Program in Women's Health Research at Penn State**
PI: **Carol S. Weisman**
Institution: **Pennsylvania State University Hershey Medical Center**
Grant No.: **5K12HD055882-07**

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 8 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 BIRCWH Program is overseen by an Advisory Committee including 11 senior administrators and faculty members from the three participating colleges. The 8 BIRCWH Scholars funded during the Program's first 5 years represented the fields of general internal medicine, endocrinology, infectious disease, kinesiology, physiology, psychology, and sociology/demography, and were recruited from a large, diverse applicant pool. 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Cincinnati Interdisciplinary Women's Health Research Career Training Grant**
PI: **Joel Tsevat**
Institution: **University of Cincinnati**
Grant No.: **5K12HD051953-09**

The overall objective of this competitive renewal application is to sustain an effective Interdisciplinary Research Careers in Women's Health Research (BIRCWH) Scholars Program, whose mission is to identify and train junior faculty members within the University of Cincinnati (UC) College of Medicine (COM) and the Cincinnati Children's Hospital Medical Center (CCHMC). The 2 institutions are located across the street from each other and share faculty, with all CCHMC faculty having appointments at UC. The 2 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. Our BIRCWH program has established a track record of developing junior faculty in the area of women's health. The first 3 Scholars who graduated were recruited to full-

time faculty positions: 1 at University of Texas - Southwestern, 1 at UCLA, and 1 at UC's Department of Environmental Health; all 3 are independently funded. The BIRCWH renewal application focuses in 6 main areas: cancer, developmental biology, pharmacology/pharmacogenetics, reproductive health, adolescent gynecology, and behavioral medicine. As with the first BIRCWH, we plan to train 4 scholars at a time: 2 MDs and 2 PhDs. Scholars will have 3 years of protected time for mentored research and career development. We have assembled a cadre of mentors who have at least $250,000 of funding, 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Hormones and Genes in Women's Health: Bench to Bedside**
PI: **Jill M. Goldstein**
Institution: **Brigham and Women's Hospital**
Grant No.: **5K12HD051959-09**

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 our Harvard 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 competing renewal application seeks to continue to support an integrated interdisciplinary training program that is based on a translational approach to understanding differential 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 Brigham & Women's Hospital (BWH) is and will continue to be the home site for this endeavor, in the broader context of a Harvard-wide training program. The program capitalizes on the long tradition of interdisciplinary research in women's health with Mentors who already collaborate across institutions at BWH, Massachusetts General Hospital, Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute, McLean Hospital, Harvard School of Public Health, Harvard Medical School and the Eli & Edythe Broad Institute. Each of four Scholars is assigned a team of Mentors in order to operationalize the concept of training Scholars to think in a translational manner. Primary Mentors are in clinical or basic research and provide the site at which the Scholar works. Secondary Mentors are in basic or clinical research (as a counterpart to the Primary) and help to guide thinking, suggest coursework, and readings, depending on the Scholar's interest. Career Mentors advise Scholars in the relevant departmental and academic structures for career advancement. Mentors in health disparities expose Scholars to thinking about how the roles of hormones and genes in predicting morbidity are influenced by socioenvironmental factors. The Harvard BIRCWH program focuses on the following disorders, given either the known higher incidence in women than 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, uterine). By capitalizing on the vast resources and faculty at Harvard, we would argue that Harvard is an ideal site for continuing to offer an integrated, interdisciplinary and truly translational program that is training the next generation of leaders in women's health.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Kansas BIRCWH Career Development Program in Women's Health**
PI: **Patricia A. Thomas**
Institution: **University of Kansas Medical Center**
Grant No.: **5K12HD052027-09**

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 a successful application for a 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 five 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 12 and 31 in the nation for NIH funding, respectively. Mentors are in five thematic areas related to women's health: (i) women's reproductive health; (ii) maternal health; (iii) pathogenesis of diseases prevalent in women; (iv) drug design, drug delivery, and pharmacogenomics; and (v) prevention, intervention, and health disparities. After the grant was funded, the KUMC BIRCWH K12 program provided advanced training and career guidance for 10 junior faculty members pursuing interdisciplinary research in women's health. Four years into the funded project, 7 IWHR scholars have received extramural funding and at least 11 junior level (assistant professor) faculty members have been hired in tenure-track positions pursuing women's health research at the University of Kansas. 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. Successful renewal of the KUMC BIRCWH K12 Program will continue to positively impact the pursuit of women's health research in Kansas.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Maryland's Organized Research Effort in Women's Health**
PI: **Patricia Langenberg**
Institution: **University of Maryland, Baltimore**
Grant No.: **5K12HD043489-12**

The primary goal of the University of Maryland's proposed 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 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. The objectives of the program are (1) to continue to identify and recruit outstanding new investigators who are either already on the faculty of one of the professional schools at UMB or who would be excellent external candidates for faculty positions (special attention will be given to the recruitment and training of underrepresented minorities, those with disabilities, and women); (2) to continue to provide mentored interdisciplinary training in women's health research by developing individualized teams of mentors for each Scholar, taking advantage of the strong existing basic science, genomic and genetic, translational, clinical, behavioral, epidemiological, and health services research based at UMB, the institutional research infrastructure, and formal didactic training opportunities in design and conduct of research; (3) to provide junior investigators with training in the academic and professional skills needed to become successful independent scientific investigators; (4) to continue to evaluate the ''MORE-WH program by tracking the career progress of its Scholars, by responding to the advice and critiques of our Internal and External Advisory Committees, and by continuing to employ feedback mechanisms for program modification.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Mayo Clinic Interdisciplinary Women's Health Research Program**
PI: **Rebecca S. Bahn**
Institution: **Mayo Clinic, Rochester**
Grant No.: **5K12HD065987-04**

The Mayo Clinic Interdisciplinary Women's Health Research (IWHR) Program is designed to be highly responsive to the "Building Interdisciplinary Careers in Women's Health" RFA-OD-09-006. Embedded in the design of our program are each of the overarching themes of the RFA,

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, which 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 cross 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 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. IWHR scholars will benefit from a structured, mentored research training experience, including a didactic program appropriate to their background and career goals. The broad scope and interdisciplinary nature of our IWHR Program reflects the intra- and interdisciplinary opportunities at Mayo and extends research in women's health beyond that which is currently represented at the other funded BIRCWH programs. Thus, the Mayo Clinic IWHR Program will help to sustain diversity and depth in women's health research for the Nation.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Michigan BIRCWH Career Development Program**
PI: **Timothy R. Johnson**
Institution: **University of Michigan**
Grant No.: **5K12HD001438-14**

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 4 scholars with a minimum of two clinician scientists and one or two non-clinical postdoctoral scientists per year for a minimum of two 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. The scholars will have 75 percent protected time for research and research career development. 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. Each plan will include an intensive supervised research experience,

instruction and assistance in grant writing/submission, experience in scientific writing, ongoing mentor feedback, formal annual evaluation, and instruction in the responsible conduct of research. 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. A senior Advisory Committee will oversee the program with emphasis on recruitment, selection, assessment of progress, and post-completion tracking of scholars. Support provided by the grant will help assure continued success in our efforts to promote the transition of women's health researchers to scientific independence. Of the 17 scholars trained by the Michigan BIRCWH since 2000, 5 are currently associate professors in schools of medicine, public health, and literature and science; 11 are assistant professors in schools of medicine, nursing, social work, and literature and science; and one is a research investigator in social research, each conducting interdisciplinary research in women's health.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan**
PI: **Jeanne-Marie Guise**
Institution: **Oregon Health & Science University**
Grant No.: **5K12HD043488-12**

This competing renewal application seeks to continue and enhance the OHSU BIRCWH program entitled Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan. Our 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/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 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. The institution is deeply committed to the BIRCWH, providing each scholar up to 50 hours of statistical support, tuition-free education through the Human Investigations Program, and direct financial contributions to support their research. We will continue the existing best practices that have made our program highly successful. In this renewal, we expand the centers, institutes, and mentors affiliated with the BIRCWH to address all 6 high-priority NIH ORWH research goals and propose the following innovative expansions to: (I) 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) disseminating best practices (lessons and tools) for mentoring nationally; and (II) 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. The Oregon BIRCWH is dedicated to training the next generation of leaders in women's health research whose discoveries improve the health of girls, women, and populations. We are pleased with our program's and scholars' successes and are excited about the opportunities in this renewal to increasingly contribute at a national and programmatic level.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **The Colorado Building Interdisciplinary Research Careers in Women's Health Program**
PI: **Judith G. Regensteiner**
Institution: **University of Colorado Denver**
Grant No.: **5K12HD057022-07**

University of Colorado Anschutz Medical Campus (UCAMC) Building Interdisciplinary Research Careers in Women's Health (Colorado 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 the BIRCWH, exemplified by strong financial support from the Dean of the School of Medicine for the BIRCWH. The Leadership Team for the Colorado BIRCWH will be headed by Judith Regensteiner, Ph.D., who will continue as Principal Investigator/Program Director (PI/PD) with Nanette Santoro as co-PI/PD. Both have extensive mentoring and research experience. 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 3 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. Scholars will also have access to UCAMC's rich base of

institutional research resources, including interdisciplinary programs and coursework, as well as substantial core facilities. Because of the complexity of most current research, interdisciplinary research teams are the wave of the future, and our BIRCWH Scholars should become extraordinarily well positioned to be the next generation of leaders in biomedical science. Given the success of our BIRCWH Scholars in the current program, we are eager to continue developing and improving our program through this renewal.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Tulane Building Interdisciplinary Research Careers in Women's Health (BIRCWH)**
PI: **Marie A. Krousel-Wood**
Institution: **Tulane University**
Grant No.: **5K12HD043451-12**

This is a competing renewal application for the Tulane BIRCWH Program, which has successfully trained a racially/ethnically and professionally diverse group of interdisciplinary researchers in women's health and increased awareness of women's health research at Tulane over the last 4 years. We propose now 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 2 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 to 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 address 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). We propose to train 8 faculty Scholars for a minimum of 2–3 years (3 years minimum for physician-scientists). Ongoing and

comprehensive evaluation will guide improvements to the program's demonstrated effectiveness in bridging research training and research independence for junior investigators focused on sex differences and CVD.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UCSF/Kaiser Permanente DOR Program for Developing Independent Women's Health Researchers**
PI: **Bernard J. Guglielmo**
Institution: **University of California, San Francisco**
Grant No.: **5K12HD052163-14**

This competing renewal application proposes continuation of the UCSF–Kaiser Department of Research (DOR) Bridging Interdisciplinary Research Careers in Women's Health (BIRCWH) K-12 Program. The program's aims are to: (1) recruit a superb and diverse group of early career women's health researchers, (2) provide them fiscal and individually tailored training and mentoring, (3) build upon our existing program by broadening it to specifically target important women's health topics that are understudied, (4) strengthen and integrate models of multidisciplinary research and develop researchers who foster linkages across disciplines and institutions, and (5) promote the prominence of and resources allocated to women's health research by mentoring BIRCWH scholars and alumni in academic process and leadership. The 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 Advisor 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 in UCSF CTSI career development and training programs. The career development path for each scholar is tailored to the specific types of experience and mentoring that will most effectively support her or his transition to an independent clinical scientist. 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 program overall will continue to be a unique resource for the continuation and expansion of women's health science in the San Francisco Bay area.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UIC Program for Interdisciplinary Careers in Women's Health Research**
PI: **Stacie E. Geller**
Institution: **University of Illinois at Chicago**
Grant No.: **5K12HD055892-07**

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 four 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 PI or Co-I, published over 70 peer-reviewed manuscripts, and given more than 70 oral and poster presentations at national or international scientific conferences. We build on the strengths of our current program, particularly the integration of the BIRCWH with UIC's institutional and programmatic excellence in women's health research, UIC's proven institutional dedication to and success in mentoring new investigators, especially women, and our focus on and alignment with ORWH's 2020 Strategic Plan. 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); (3) to recruit and train at least 8 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UNC BIRCWH Career Development Program**
PI: **Eugene P. Orringer**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **5K12HD001441-14**

This application represents the competitive renewal of UNC's BIRCWH Award. 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 BIRWCH Program are to: (1) facilitate the mentored career development of junior investigators pursuing 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. In our application, we have focused on 8 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 UNC. In addition, each has theme has numerous, nationally recognized mentors who are willing and available to work with our BIRCWH Scholars. During our first 2 cycles of funding, the UNC BIRCWH Program has proven to be remarkably successful. Thus far, we have chosen and supported a total of 27 junior faculty members who exhibit broad diversity in terms of discipline, academic home, gender, ethnicity, and type of research. Finally, it is of note that each of the 20 graduates of our BIRCWH Program is the Principal Investigator on at least one NIH grant, grants that alone total over $33 million. Thus, the UNC BIRCWH Program has added a great deal to the UNC women's health research community, and we are convinced that it will continue to do so for many years to come. Relevance: 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **University of Minnesota Building Interdisciplinary Research Careers in Women's Health**
PI: **Nancy Cox Raymond**
Institution: **University of Minnesota**
Grant No.: **5K12HD055887-07**

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. To accomplish this goal, we will offer a program that ensures our UMN BIRCWH Scholars become premier interdisciplinary scientists. 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 address 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. Our career development program is

organized around broad themes and includes increasing knowledge regarding: (1) research knowledge and skill development; (2) women's health and sex/gender difference research issues, methodologies, and emerging topics; (3) scientific dissemination; (4) interdisciplinary leadership development; (5) advocacy (e.g., translating research into policy); and (6) academic career development. The career development program will consist of required and individualized components, which will be delivered through didactic and experiential training methods designed to achieve the program goals. Scholar research projects that will be funded reflect (but are not 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, including sex-specific basic mechanisms and disease presentation. Rationale and design of the program: We will make progress toward 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. Planned duration and projected number of scholars: The UMN BIRCWH program will fund four women's health researchers who are assistant professors in year one through four of their tenure track or clinical track appointment for up to three years. As Scholars complete the program, additional Scholars will be added.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UTMB Women's Health Research Scholars Program**
PI: **Abbey B. Berenson**
Institution: **University of Texas Medical Branch at Galveston**
Grant No.: **5K12HD052023-09**

In response to RFA-OD-09-006, The University of Texas Medical Branch (UTMB) proposes a renewal of our successful BIRCWH Program to develop independent researchers in women's health. The Program includes 17 experienced senior investigators as Mentors from 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. The Candidate Pool is fed by a multilevel pipeline, including local departments, centers, and T32 programs, followed by applicants from UT System campuses designated as Hispanic-serving institutions. Additional efforts to obtain diverse applicants extend to the national level through advertisements and solicitations made with leading historically black colleges and universities. During the first cycle of funding, we trained 10 Scholars who received 12 awards from private and federal sponsors, including NIH. For our second cycle of funding, our Program will continue to use the mentored research experience as the core of Scholars' tailored career development plans. 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. In addition, we will add a Resource Laboratory for individual assistance with methods development and statistical guidance. Our proposed renewal is supported by a significant institutional commitment assured by the Executive Vice President & Provost. A renewal will further strengthen women's health research at UTMB and will ensure that more of our Scholars become

independently supported investigators in the many areas of health that affect women over the lifespan.

IC: **National Institute on Drug Abuse**
Title: **Kentucky BIRCWH Program: Training the Next Generation of Women's Health Scholars**
PI: **Thomas E. Curry**
Institution: **University of Kentucky**
Grant No.: **5K12DA035150-02**

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. This approach will continue to provide our BIRCWH scholars with state-of-the-art multidisciplinary training, leading to their development as faculty with independent NIH funding. The focused areas targeted toward 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 positioned 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. Key aspects of training will include: (a) pairing the BIRCWH scholar with senior level scientists and former BIRCWH scholars, forming a research team and thus modeling interdisciplinary collaboration; (b) providing these teams with access to cutting-edge technologies; and (c) providing scholars with training in concepts relevant to women's health. A strength of our BIRCWH program is its multidisciplinary, cross-departmental, and interactive nature positioned in an area with unique health needs. As evident by the success of our former BIRCWH scholars, we are well positioned to continue the tradition of excellence in mentoring our scholars to become independent researchers in women's health.

IC: National Institute on Drug Abuse
Title: Yale BIRCWH Scholar Program on Women's Health and Addictive Behaviors
PI: Carolyn M. Mazure
Institution: Yale University
Grant No.: 5K12DA031050-04

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 U.S. 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. Yale's interdisciplinary research program on women's health, in collaboration with our internationally renowned research program on addictions, requests funding through the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholar Program (RFA-OD-09-006) for four BIRCWH Scholar positions. We have assembled an outstanding team of 25 experienced, productive, and dedicated Mentors 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, 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. Ultimately, the purpose of our program is to ensure the development of scientists who make enduring contributions to the prevention and treatment of addictive behaviors, which result in direct practical benefit for women and their families.

NCI–ORWH Supplements

IC: National Cancer Institute
Title: Capitalizing on NSAID Enantiomer Selectivity for Cancer Prevention and Therapy (PQ)
PI: Laurie G. Hudson
Institution: University of New Mexico Health Sciences Center
Grant No.: 3R21CA170375-02S1

Provocative question (PQ) 5 challenges us to determine the mechanism whereby "drugs commonly used for other indications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), can protect against cancer incidence and mortality." Strong preliminary data lead us to propose that for certain chemical entities the chemopreventive and/or anti-tumor activity is attributable to interaction of the R-enantiomer of select NSAIDs with novel cancer-relevant targets. There are many examples of stereoselective differences in drug activity. The R-forms of NSAIDs are essentially inactive against cyclooxygenases, and there is mounting evidence that R-enantiomers are distinct chemical entities with independent pharmacologic activities. We find that the R-enantiomers of naproxen and ketorolac inhibit the small GTPases Rac1 and Cdc42. More than 20 other NSAIDs were inactive against these proteins, suggesting novel target selectivity by R-naproxen and R-ketorolac. Rac1 and Cdc42 regulate cytoskeletal dynamics in addition to other functions and have been recognized as attractive cancer therapeutic targets, although no specific inhibitors are currently in clinical trials. In keeping with the known functions of Rac1/Cdc42 in regulating actin-based functions, we find enantiomer-selective inhibition of ovarian tumor cell migration and adhesion. Furthermore, R-naproxen, but not S-naproxen or the structurally related 6-methoxynaphthalene acetic acid (6-MNA), reduced implantation of ovarian tumors by ~ 75% in an intraperitoneal xenograft model. The objective of this application is to define the mechanism of action for the observed biologic activities of R-naproxen and R-ketorolac. This will provide the foundations for reconsideration of potential anti-tumor activities of other NSAID R-enantiomers based on interaction with novel targets. We hypothesize that R-ketorolac and R-naproxen inhibit Rac1 and/or Cdc42 and associated cellular responses through a novel mechanism based on drug binding to the GDP-bound (inactive) form of the enzymes. We will test this hypothesis by using biochemical and cellular approaches coupled with structure-activity analyses; we will test whether there is R-enantiomer-selective interaction with the GDP-bound forms of the GTPases as predicted by cheminformatics, leading to blockade of GTP binding, enzyme activation and downstream cellular responses. The work is significant because the novel pharmacologic and tumor-relevant functional activities of NSAID R-enantiomers have not been previously described, and successful completion of the project will offer new mechanistic insights into the anti-cancer benefit of NSAIDS. The studies will also yield additional and critical information on the benefits of targeting Rac1 and Cdc42 in ovarian and other cancers.

IC: National Cancer Institute
Title: Fatigue, Depression, and Inflammation in Cancer Survivors: A Prospective Study
PI: Janice K. Kiecolt-Glaser
Institution: Ohio State University
Grant No.: 3R01CA131029-06S1

Fatigue is the most common post-treatment problem among cancer survivors, affecting a third or more of long-term survivors. Persistent fatigue in survivors may be related in part to over activation of the inflammatory network; the immune activation that is secondary to the tissue destruction and associated inflammation from many cancer therapies may leave patients vulnerable to the behavioral consequences of proinflammatory cytokines, including fatigue. What is more, a cancer diagnosis and cancer treatments can be quite stressful, and stress and depression can directly enhance the production of proinflammatory cytokines. Fatigue has been well studied in breast cancer survivors, but far less is known about fatigue in other cancer survivor populations. Furthermore, although several lines of evidence suggest that inflammation plays a significant role in cancer-related fatigue, the data are limited, and longitudinal data in survivors are almost nonexistent. Moreover, the extent to which the incidence and prevalence of fatigue among cancer survivors differs from comparable adults without a cancer history remains an important question; similarly, whether there are differences in inflammation between cancer survivors and adults without a cancer history is unknown. This project provides the opportunity to examine mechanistic connections among fatigue, depression, NF-κB activation, health behaviors, and proinflammatory cytokines both cross-sectionally and longitudinally, with initial data on each of these key dimensions collected before cancer treatment, as well as 6 months, 18 months, and 30 months after completion of primary treatment. Subjects will be stage I–IIIA breast cancer survivors, stage I–IIIC colon cancer survivors, and men and women who had a benign diagnosis following an initial abnormal test for breast or colon cancer. The proposed project would provide the first prospective study of inflammation, depression, and fatigue from pretreatment through survivorship in two groups of cancer survivors, as well as a noncancer comparison group. Specific Aims: (1) To assess the association between inflammation and fatigue cross-sectionally at each of the time points, as well as the extent to which higher levels of inflammatory markers at baseline predict subsequent fatigue; to evaluate these relationships in breast and colon cancer patients, as well as noncancer controls; and to compare the magnitude of both cross-sectional and longitudinal associations across the three groups. (2) To evaluate relationships between past or current syndromal depression and/or depressive symptoms with inflammatory markers, NF-κB activation, and fatigue, as well as their association with subsequent inflammation and fatigue. (3) To appraise the relative impact of health-related behaviors (sleep, pain, physical activity, n-6/n-3 dietary fatty acids, central adiposity, and chronic health conditions) as correlates and predictors of syndromal depression and depressive symptoms, inflammatory markers, and fatigue.

IC: National Cancer Institute
Title: MR Diffusion Tensor Imaging for Detection and Characterization of Breast Lesions
PI: Savannah Corrina Partridge
Institution: University of Washington
Grant No.: 5R01CA151326-04

Breast cancer is extremely common, striking 1 in 8 American women, and is the second leading cause of cancer death among women in the U.S. Earlier detection through screening is a fundamental way to improve survival. Dynamic contrast-enhanced MRI (DCE-MRI) of the breast has a high sensitivity for breast cancer detection and is the most sensitive technique for screening high-risk women and detecting contralateral or multifocal disease in patients with recently diagnosed breast cancer. However, overlap in the appearance of benign and malignant breast lesions on DCE-MRI can produce many false positives. Particularly in light of recent American Cancer Society guidelines recommending annual MRI screening for high-risk women, estimated to affect up to 1.8 million women in the U.S., there is a clear and quickly growing need to improve the specificity of breast MRI in order to limit the number of unnecessary biopsies that will result from expanded use of this highly sensitive screening tool. Furthermore, the high costs and safety concerns of gadolinium-based contrast agents limit the accessibility of breast MRI screening for many women, so identifying a non-contrast alternative to DCE-MRI for detecting breast cancer would have strong clinical impact. A promising adjunct MRI technique is diffusion tensor imaging (DTI), which indirectly assesses tissue microstructure and can provide complementary information to DCE-MRI for lesion characterization. Our group and others have demonstrated notable differences in apparent diffusion coefficient (ADC) values between benign and malignant lesions. Moreover, we have promising preliminary data suggesting apparent diffusion coefficient (ADC) measures can increase the positive predictive value of conventional breast MRI assessment, and that DTI fractional anisotropy (FA) adds complementary information to ADC measures in discriminating malignancies. We have also observed that many mammographically and clinically occult cancers are visible on diffusion-weighted images and can be detected on MRI without using a contrast agent. The aims of this work are: (1) to validate DTI as a valuable adjunct to improve lesion characterization on breast MRI and determine the optimal way to incorporate DTI measures into the clinical breast MRI assessment, (2) to better understand the effects of tumor histology on DTI measures, and (3) to evaluate the potential role of DTI as an alternative non-contrast breast screening technique. The outcomes of this study are potentially significant because DTI could provide a quickly translatable solution to improve the specificity of conventional breast MRI and reduce the number of unnecessary biopsies, and alternatively, DTI could provide a faster, less expensive, and safer screening option than DCE-MRI.

IC: National Cancer Institute
Title: Re-replication of Chromosomes and Cancer
PI: Anindya Dutta
Institution: University of Virginia
Grant No.: 3R01CA060499-19S1

In the last cycle of this project, we discovered how easy it is for mammalian cells to bypass the regulatory pathways that ensure that origins of replication are licensed only once per cell cycle

and that the chromosomes are replicated once and only once per cell cycle. Different manipulations that increased the ratio of the replication initiator, Cdt1, relative to its inhibitor, geminin, led to re-replication. Intriguingly, the extensive re-replication was accompanied by DNA damage and activation of checkpoint pathways that led to cell-cycle arrest and eventually cell death. The checkpoint pathways used several genes whose mutations predispose individuals to genomic instability and cancer: p53, BrCa1, and the Fanconi anemia proteins. These results lead us to the hypothesis that will be tested in the first Aim: small degrees of re-replication that are tolerated and are compatible with cancer cell viability lead to the deletions and gene amplifications that are the hallmark of cancer cell chromosomes. This will be the first model linking disorders in replication initiation in mammalian cells to chromosomal structural variation and the genomic instability of cancer. A "first-in-its-class" new drug has been developed by a pharmaceutical company and will be given to us. This drug, MLN4924, inhibits the ubiquitin ligases that help degrade Cdt1 in S phase, and as a result stabilizes Cdt1 and causes extensive re-replication, DNA damage, and cytotoxicity. Aim 2 will test the hypothesis that the cytotoxic effect of this drug is through the re-replication and activation of checkpoint pathways. If this hypothesis is true, we will provide a rationale for the development of other anti-cancer drugs that produce extensive re-replication and successfully predict whether the clinical trial of MLN4924 will benefit from a measurement of the status of p53, BrCa1, or Fanconi anemia proteins in the tumors being treated. Although we have discovered two independent ubiquitin ligases that promote the polyubiquitinylation of Cdt1 and its degradation, preliminary results indicate that a third ubiquitin ligase of an entirely different class from the ones already implicated has a critical role in destabilizing Cdt1. In the third Aim we will test the hypothesis that inhibition of this third ubiquitin ligases will also cause re-replication and cytotoxicity, determine the mechanism by which this ligase destabilizes Cdt1, and assess whether inhibition of this ligase will synergize with MLN4924 in cancer chemotherapy.

IC: **National Cancer Institute**
Title: **Role of Phospho-Progesterone Receptors (PR) in Hormone Refractory Breast Cancer**
PI: **Carol A. Lange**
Institution: **University of Minnesota**
Grant No.: **3R01CA159712-02S1**

The mechanism(s) of breast cancer progression to steroid receptor (SR)–positive but hormone refractory breast cancer remain elusive. Much of the research in this field is focused on the linkage of estrogen receptor-? (ER) to signal transduction, as mediated by peptide growth factor activation of tyrosine kinase receptors; these molecules are important clinical targets. However, progesterone receptors (PR) may also play a key role as mediators of early breast cancer progression. Recently, we uncovered a novel mechanism of hormone-independent hyperactivation of PR transcriptional activity that is mediated by membrane-initiated phosphorylation events. In response to mitogenic protein kinases (c-Src, MAPKs, CDK2) often elevated in breast cancer, persistent phosphorylation of PR Ser294 blocks ligand-induced SUMOylation at K388 (a repressive modification). Abundant total PR is a marker of "good tumor" behavior. However, we hypothesize that de-repressed phospho-PR acts on genes whose products mediate early breast cancer progression or "bad tumor" behavior. One check on PR hyperactivity includes rapid ligand-dependent degradation by the ubiquitin-proteasome pathway. Indeed, in the presence of hormone, phospho-PR undergoes rapid turnover, often rendering the

low abundance protein undetectable by standard antibody-binding assays (i.e., clinically used IHC). Clinical observations of PR "loss" have led to the incorrect conclusion that PR transcriptional activity is unimportant in "PR-low" breast cancers. However, our studies reveal that phospho-PR is transcriptionally hyperactive and remarkably targets genes that are not sensitive to progesterone or progestins; IRS-1 is an example of a ligand-independent phospho-PR gene. Furthermore, under conditions of high kinase activities, Ser294-phosphorylated PRs are not SUMOylated, and thus fail to transrepress ER but may instead cooperate with ER at non-classical (non-PRE containing) gene targets in the complete absence of steroid hormones; STC-1 is an example of an ER-gene that is de-repressed by phospho-PR. Notably, the proliferation of breast cancer cell models expressing mutant PRs that cannot be SUMOylated (K388R) is very sensitive to estrogen, but resistant to anti-estrogen. Similarly, we predict that phospho-PR signaling drives the growth of some hormone-refractory breast cancers that can be identified by a unique PR gene signature. Herein, we will define the phospho-PR gene signature using unique cell line models engineered for inducible PR expression. The role of the PR SUMOylation/phosphorylation "switch" in the regulation of hormone responsiveness at endogenous genes will be defined (Mechanisms; Aim 1). Our unique phospho-PR gene signature will be validated in in vitro models of tam- and AI (aromatase inhibitor)- resistance and in human tumors (Validation; Aim 2). Finally, our innovative hypothesis will be tested in AIB1-transgenic mice, an in vivo model of SR-driven (ER+/PR+) and tam-resistant breast cancer (Biology; Aim 3). Little is known about how PR and ER/PR interactions contribute to hormone resistance in breast tumors. Our studies on phospho-PR signaling will provide valuable insight into the coordinated regulation of PR and ER function by pathways that can be easily targeted for therapeutic intervention.

IC: **National Cancer Institute**
Title: **The University of Texas M. D. Anderson Cancer Center SPORE in Ovarian Cancer**
PI: **Robert C. Bast**
Institution: **University of Texas M. D. Anderson Cancer Center**
Grant No.: **3P50CA083639-14S1**

The overall goal of the University of Texas M. D. Anderson Cancer Center (MDACC) SPORE is to reduce the morbidity and mortality of ovarian cancer through innovative translational research in the detection and treatment of ovarian cancer based upon the molecular, cellular, and clinical biology of the disease. MDACC contains a unique community of >35 talented investigators who are dedicated to translational, clinical, fundamental, and population-based ovarian cancer research, 20 of whom participate directly in the SPORE. Collaborators include 25 investigators from 9 universities and 4 companies. Over the last 4 years, MDACC has cared for 1,055 new patients with ovarian and peritoneal cancer and has placed 241 on clinical trials. MDACC has given high priority to ovarian cancer research through recruitment, salary support, clinical facilities, laboratory space, and philanthropic funds. MDACC with the help of the SPORE has recruited 5 outstanding faculty members with an interest in ovarian cancer research, strengthened the research infrastructure, funded 13 developmental research projects (DRP), and supported 4 career development program (CDP) awardees. Over the last 5 years, SPORE investigators have contributed 381 peer-reviewed publications regarding ovarian cancer. Achievements include: (1) development of a two-stage screening strategy for early ovarian cancer that has provided a 30% positive predictive value for detecting early stage disease; (2) identification of a panel of

biomarkers that detect 87% of early stage ovarian cancers; (3) discovery of pericytes as targets for anti-angiogenic therapy; (4) observation of a 39% response rate with aflibercept (VEGF-Trap) and docetaxel against platinum-resistant disease; (5) detection of response to the AKT inhibitor perifosine in ovarian cancers with PTEN mutations; (6) discovery that as many as 30% of ovarian cancer patients have BRCA dysfunction; and (7) identification of PVT-1 and PFDN4 as targets for siRNA therapy. Five projects proposed for the next grant period will: (1) evaluate a multi-marker algorithm for early detection of ovarian cancer; (2) target Dll4/Notch signaling to reverse resistance and synergize with anti-VEGF therapy; (3) test personalized therapy of low-grade cancer with MEK, AKT, and IGFR inhibition; (4) personalize treatment for high-grade ovarian cancers with activated PI3K signaling or BRCA dysfunction; and (5) develop mesenchymal stem cells as vehicles for tumor tropic delivery of IFN-B in preclinical and clinical studies. This work will be supported by three cores: Administrative; Biostatistics, Bioinformatics and Systems Biology; and Pathology. Support will be provided for DRP and CDP recipients to attain peer-reviewed funding. Valuable advice will continue to be provided by internal, external, and advocate advisors.

Other Cofunding

IC: **Fogarty International Center**
Title: **AIDS International Training and Research Program**
PI: **Adaora A. Adimora**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **5D43TW001039-15**

This is the second competitive renewal application for the UNC AIDS International Training and Research Program (AITRP). We propose to continue to provide training in three countries: The People's 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.

IC: **Fogarty International Center**
Title: **Emory AIDS International Training and Research Program**
PI: **Carlos Del Rio**
Institution: **Emory University**
Grant No.: **5D43TW001042-15**

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 such as PEPFAR that are currently occurring in our collaborating countries.

IC: **Fogarty International Center**
Title: **Fogarty Global Health Fellows Coordinating Center**
PI: **Charles Michael Van Der Horst**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **5R25TW009340-02**

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, and multilayered mentoring. Each primary training site has a lengthy history of NIH and U.S. government research funding, training of U.S. 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 as 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 U.S. 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 longstanding 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.

IC: Fogarty International Center
Title: Global Health Fellows and Scholars Research Training
PI: Lee W. Riley
Institution: University of California, Berkeley
Grant No.: 5R25TW009338-02

We propose to establish a Support Center (Consortium) involving the University of California, Berkeley; Yale University; Stanford University; and Florida International University to train postdoctoral fellows, Ph.D. 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, non-communicable, 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 U.S. 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 underrepresented 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.

IC: Fogarty International Center
Title: Haiti AIDS Research Training: Models to Implementation
PI: Jean William Pape
Institution: GHESKIO Center
Grant No.: 4U2RTW006896-10

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 (100xU.S. 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 (HVTN), 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 master's in public health degree program, established with ICOHRTA support, will continue to be offered in Haiti by Université Quisqueya, in partnership with GHESKIO and Cornell University.

IC: **Fogarty International Center**
Title: **Northern/Pacific Universities Global Health Research Training Consortium**
PI: **Joseph Raymond Zunt**
Institution: **University of Washington**
Grant No.: **5R25TW009345-02**

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; and bimonthly Internet-based research-in-progress sessions involving all Global Health Research 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 co-mentors 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 and a potential second year of fellowship funding for the most promising trainees; to assistance in 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 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 Research 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.

IC: **Fogarty International Center**
Title: **Tobacco Control Network Among Women in Parana, Brazil - II**
PI: **Isabel C. Scarinci**
Institution: **University of Alabama at Birmingham**
Grant No.: **5R01TW009272-02**

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 fewer 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 threefold: (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.

IC: **Fogarty International Center**
Title: **University of California Global Health Institute Program for Fellows and Scholars**
PI: **Craig R. Cohen**
Institution: **University of California, San Francisco**
Grant No.: **5R25TW009343-02**

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 all 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 online 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.

IC: **Fogarty International Center**
Title: **Vanderbilt University's CIDRZ AIDS International Training and Research Program (AITRP)**
PI: **Sten H. Vermund**
Institution: **Vanderbilt University**
Grant No.: **5D43TW001035-15**

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: 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.

IC: **Fogarty International Center**
Title: **Vanderbilt-Emory-Cornell-Duke Consortium for Global Health Fellows (VECDor)**
PI: **Sten H. Vermund**
Institution: **Vanderbilt University**
Grant No.: **5R25TW009337-02**

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 U.S. 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 U.S. 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.

IC: National Eye Institute
Title: Broad Spectrum Molecular Therapy for Blinding Retina Disorders
PI: Jean Bennett
Institution: University of Pennsylvania
Grant No.: 5DP1EY023177-03

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; and (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. Successful application of optogenetic therapy will expand the number of disease targets that are potentially treatable by gene therapy dramatically. It will change the number of retinal gene therapy targets from the realm of isolated orphan diseases to conditions that are epidemic in nature. In addition, the reagents, strategies, and technical advances developed in this project will be useful for many other ocular and extra-ocular applications. Finally, not only could the results from this project lead to a significant improvement in the quality of life for millions of individuals, but they could also pave the way for development of novel gene therapy approaches for the treatment of other devastating sensorineural diseases.

IC: National Human Genome Research Institute
Title: African Collaborative Center for Microbiome and Genomics Research
PI: Clement Adebayo Adebamowo
Institution: Institute of Human Virology
Grant No.: 1U54HG006947-01A1

The African Collaborative Center for Microbiome and Genomics Research (ACCME) is a multi-country, multi-institutional collaborative research initiative involving the Institutes of Human Virology and Genome Sciences at the University of Maryland; the Department of Epidemiology and Public Health at the School of Medicine, University of Maryland, Baltimore; University of Abuja Teaching Hospital, Abuja, Nigeria; and the Centre National d'Appui à la lutte contre la

Maladie (CNAM) Mali. The objectives of the Center are to collaborate and implement high-impact research programs characterizing the human microbiome and its role in health and disease. Specifically, ACCME links and leverages existing funded research and program activities at the collaborating institutions to study the interaction between vaginal microbiome, host genetic factors, and molecular variants of human papilloma virus (HPV) to determine correlates of viral persistence in the causal pathway of cervical cancer, a major cause of preventable mortality on the African continent. Recent studies by the investigative team, employing a bacterial culture-independent, "clone and sequence approach" employing 16S ribosomal RNA (rRNA) gene technologies, have documented the complexity of vaginal microbiome and classified consistent microbial groupings termed "community state types" that open a new window to understanding the role that the vaginal microbiome plays in cervical cancer pathogenesis. In addition to contributing to knowledge about vaginal microbiome, HPV persistence and cervical carcinogenesis, ACCME also develops capacity by training postdoctoral students to become the new generation of African scientific leaders, while empowering hundreds of African scientists to conduct research in microbiome and genomics.

IC: **National Heart, Lung, and Blood Institute**
Title: **A Formative Examination of the Health and Safety of Female Firefighters**
PI: **Sara Anne Jahnke**
Institution: **National Development and Research Institutes**
Grant No.: **5R21HL119024-02**

Firefighters/EMS personnel are vital for public health safety, representing over 2 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 information 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 U.S. 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 U.S. fire service and identifying areas of intervention and prevention for this understudied occupational group.

IC: **National Heart, Lung, and Blood Institute**
Title: **Avoiding Toxicity Associated with MTP Ablation**
PI: **M. Mahmood Hussain**
Institution: **SUNY Downstate Medical Center**
Grant No.: **5R01HL095924-04**

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 avoid 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 PPAR1 agonist to enhance 2-oxidation of fatty acids, for 3 or 24 weeks. In another group, ω-3 fatty acids, PPAR1/4 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 ω-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; and 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.

IC: **National Heart, Lung, and Blood Institute**
Title: **Molecular Mechanism of Platelet Dense Granule Biogenesis**
PI: **Santiago Mauro Di Pietro**
Institution: **Colorado State University**
Grant No.: **5R01HL106186-02**

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.

IC: National Institute on Aging
Title: Creation of the Einstein Aging Study Data Warehouse
PI: Mindy Katz
Institution: Albert Einstein College of Medicine
Grant No.: 1R03AG045474-01

The Einstein Aging Study (EAS) program project (NIH NIA: P01 AG03949) is a longitudinal study of the natural history of aging and the onset of dementia in a diverse community-based sample in Bronx, New York. We propose to archive the EAS dataset at the National Archive of Computerized Data on Aging (NACDA), in order to make this rich and unique data set available for public use. This will facilitate investigations into the aging process that are beyond the scope of our funded studies. The EAS has systematically recruited and followed a community-based, multiracial cohort (n = 2014, ages > = 70) for more than 20 years. EAS participants have been comprehensively characterized via extensive evaluations at baseline and annually thereafter, with an average follow-up time of 4.0 years (range, 1–17 years). Data from the EAS have demonstrated strong links among cognitive, locomotor, and mortality outcomes in the elderly and have been used to identify novel biological and psychosocial risk factors that contribute to these outcomes. The EAS cohort is broadly representative of the elderly population of the Bronx, one of the most demographically diverse counties in the United States. Since 2003, the EAS has complied with the NIH data-sharing mandate. Many of the data-sharing requests have been part of multiple NIH collaborative studies. To date, however, the analytic focus of these pooled analyses has been limited to the discreet subset of EAS variables related to Alzheimer's disease and cognitive decline, with the result that much of the extensive EAS data resource remains underexploited. The proposed data archiving project will permit us to build on the extant database in two essential ways: (1) to capture and preserve the wide range of variables assessed in our cohort during the years 1993–2003 (prior to the date of the Mandatory Data Sharing Policy put forth by the NIH (October 1, 2003)). This includes harmonizing previously un-archived data with the current EAS database; and (2) to expand the database to include the host of behavioral, biological, and psychosocial measures, not part of the primary EAS program project, that have been funded from pilot projects, foundation grants, and affiliated NIH R01s. Creating and documenting new summary measures and standard formats will be part of the process. The central aims of this proposal are to archive and preserve an expanded EAS database in order to facilitate efficient and cost effective use of the extensive scientific resources from our longstanding and well-characterized cohort. The proposed collaboration with NACDA will ensure our capacity for widespread dissemination of high quality data to the national and international aging research communities.

IC: National Institute on Aging
Title: Family Transitions, Marital Functioning, and Health: Longitudinal and Dyadic Links
PI: Lauren M. Papp
Institution: University of Wisconsin–Madison
Grant No.: 1R03AG042984-01A1

Experiencing the empty nest during marriage is highly normative in middle adulthood in the United States, yet scant longitudinal marital research has been conducted during this period. Establishing how spouses and marriages fare during the empty nest is important because marital

functioning predicts an extensive set of older adults' outcomes in the later years of life, including physical, psychological, and financial health, and mortality. As well, midlife health and well-being reliably predict the developmental transition to old age. In this proposal, I set forth two specific aims to address gaps in our understanding of the role of the empty nest in middle adulthood marital functioning and health. First, I propose to examine empty nest status as a predictor of both marital functioning (quality and course) and health (mental and physical) for men and women over time, and to then test moderators of the longitudinal associations. Second, I propose to use dyadic data obtained from participants and their spouses to test within-couple associations between concurrent empty nest status and husbands' and wives' marital quality and health, respectively, and to again test moderators of these linkages. This proposal seeks to conduct these aims with value-added secondary analysis of the Wisconsin Longitudinal Study (WLS). The WLS is uniquely suited to accomplish the proposed aims for several reasons. First, detailed interviews that spanned middle adulthood tracked participants' empty nest status, relationship functioning, and health over time. Here, sophisticated quantitative methods will appropriately handle longitudinal data. Additionally, the WLS incorporates marital functioning indicators of quality and course in a single study, offering the potential to reconcile disparate findings in the existing empty nest literature. Second, the WLS includes a spousal sub-sample, which will facilitate direct statistical tests comparing effects of the empty nest on marital quality and health for husbands versus wives. Again, appropriate dyadic quantitative modeling will be employed. Third, a broad array of theoretically informed spouse and marriage characteristics will be tested as covariates and potential moderators, thereby elucidating protective and risk factors. Thus, the proposed research holds important implications for translational efforts designed to prevent and alleviate distress in partners and relationships. Identifying protective factors that encourage some spouses and marriages to thrive and endure in middle adulthood is critical to understanding the determinants of healthy aging and promoting public health.

IC: **National Institute on Aging**
Title: **Gene-by-Environment Interactions, Social Stress, and Depression in Older Adults**
PI: **Mark A. Whisman**
Institution: **University of Colorado Boulder**
Grant No.: **1R03AG045301-01**

Depression is one of the most widespread and debilitating psychiatric disorders. Among older individuals, depression is the most frequent cause of emotional suffering, and the detrimental effects of late-life depression are well documented. One common theoretical model for understanding depression is the perspective that genetic characteristics interact with environmental influences in predicting the onset, severity, and course of depression. There has been considerable interest in evaluating such gene-by-environment interactions, including twin studies that have examined latent genetic influences and candidate gene studies that have evaluated the potential moderating role of specific genes. In the proposed research, we seek to build on prior gene-by-environment research through conducting a reanalysis of existing data from a large, population-based sample of older adults (i.e., the Health and Retirement Study) to provide a test of a novel gene-by-environment model for depression that integrates genetic and social perspectives. Specifically, the proposed research seeks to build on prior gene-by-environment research through (a) expanding the assessment of genetic influences by using a gene-environment-wide interaction study (GEWIS) approach; (b) focusing the assessment of

environmental influences on a stressor that has been consistently associated with depression (i.e., social stress); (c) disaggregating the assessment of social stress to evaluate whether stress in certain relationships (e.g., one's relationship with one's spouse or partner) is more strongly associated with depression than is stress in other relationships (e.g., one's relationships with one's children, relatives, and friends); and (d) evaluating both vulnerability and differential susceptibility gene-by-environment models. There are no published GEWIS studies on depression, and so the proposed research will be an important scientific advance as it will be among the first studies to use this methodology in examining the genetic vulnerability to environmental influences on depression. Furthermore, there are few studies that have evaluated the differential susceptibility model with respect to depression, particularly among older individuals, and so the study will be among the first studies to compare vulnerability and differential susceptibility gene-by-environment models of depression in older adults. Finally, by examining social stress across several types of social relationships, the results from the proposed research will provide important advances in identifying particular social relationships for which stress is most strongly associated with depression that can be targeted in preventing and treating depression in at-risk older adults.

IC: **National Institute on Aging**
Title: **Novel Integration of Multidimensional Data from an Emerging Model of Aging**
PI: **Jenny Tung**
Institution: **Duke University**
Grant No.: **1R03AG045459-01**

Advancing our understanding of social and behavioral effects in aging will increasingly require the integration of complex and often disparate data sets. To measure such effects, investigators must manage demographic data on mortality and fertility, behavioral or survey data on social relationships, and, increasingly, biomarker data that capture genetic and physiological variation. Currently, extant databases are designed to facilitate analysis of complex demographic and sociobehavioral data or complex genetic and genomic data: Databases that meet the challenge of integrating all of these data types do not yet exist. Consequently, the research community is not reaping the full benefits of these datasets for understanding aging. Further, we lack models for how to house these data types together in a cohesive and accessible fashion. We propose to develop such a model by building on an existing database on wild primates that houses individual-based multidimensional, longitudinal phenotypic data that have already proved valuable for studies of social and behavioral effects on aging. We also have a growing set of complementary genetic and genomic data on the same individuals, including candidate gene and whole genome resequencing, gene expression, and epigenetic data sets that promise to capture physiological changes across the life course. In the proposed work, we will provide centralized, integrated archival storage for these multidimensional datasets, create a seamless integration of genetic and phenotypic information at the individual level, and provide a much needed, well documented model of such an integration. We will also work with the National Archive of Computerized Data on Aging (NACDA) to build mechanisms for sharing these data with other researchers in the field. Specifically, we propose to (1) build database modules to house our expanding multidimensional genetic and genomic datasets; (2) link these new genetics and genomics modules to our existing database (BABASE) and to each other to integrate our genetic and phenotypic information; and (3) create a public portal to BABASE that will allow open

access to all components of the genetics/genomics modules of the database, as well as open access to key aging-related components of the phenotypic data; this portal will be accessible through NACDA. Our new genetic modules will draw on database module designs pioneered by Chado, a branch of the Generic Model Organism Database project (GMOD). Together, these efforts will provide important archival storage for these valuable data sets, increase the efficiency of data analysis, and promote new, synergistic research directions, including collaborations with outside investigators that will allow us to gain deeper insights into aging in natural mammal populations. In addition, because all the code underlying BABASE and its new extensions will be open source, the proposed work will produce models for how other population studies focused on aging can achieve similar goals.

IC: **National Institute on Aging**
Title: **Study of Women's Health Across the Nation - Coordinating Center**
PI: **Maria Mori Brooks**
Institution: **University of Pittsburgh**
Grant No.: **5U01AG012553-19**

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 midlife and the menopausal transition to the development of both positive and adverse health states in early old age. The primary objectives of SWAN IV are to: (1) Characterize the endocrinology and symptomatology 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 midlife; and (3) Understand the relations between the midlife 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 subclinical disease measures and hard outcomes. This may lead to improved strategies for the primary prevention of disease in women.

IC: National Institute on Aging
Title: SWAN: Study of Women's Health Across the Nation
PI: Joel S. Finkelstein
Institution: Massachusetts General Hospital
Grant No.: 5U01AG012531-20

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. 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, 3,302 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 3,302 women enrolled, 1,550 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.

IC: National Institute of Allergy and Infectious Diseases
Title: A Systems Biology Approach for Pediatric and Adult Autoimmune Diseases
PI: Maria Virginia Pascual
Institution: Baylor Research Institute
Grant No.: 5U19AI082715-05

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; and (5) Development of a unique microarray database of human autoimmune diseases. Clinical Component (Cush, J). Clinical Component Description: 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 dermatomyositis (JDM). 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Airway Inflammation and Airway Remodeling**
PI: **David H. Broide**
Institution: **University of California, San Diego**
Grant No.: **5U19AI070535-08**

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 noninvasive 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 will 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 IOFM Core is also proposed as requested by the RFA.

IC: National Institute of Allergy and Infectious Diseases
Title: Airway Inflammation and HLA-G in Asthma
PI: Steven R. White
Institution: University of Chicago
Grant No.: 5U19AI095230-03

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.

IC: National Institute of Allergy and Infectious Diseases
Title: Autoimmunity Center of Excellence (ACE) at Stanford
PI: Charles Garrison Fathman
Institution: Stanford University
Grant No.: 5U19AI082719-05

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 biomarkers 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Epithelial Barrier Programs in Asthma and Allergic Disease**
PI: **Michael J. Holtzman**
Institution: **Washington University**
Grant No.: **5U19AI070489-08**

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 toward 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.

IC: National Institute of Allergy and Infectious Diseases
Title: Epithelial Genes in Allergic Inflammation
PI: Gurjit K. Khurana Hershey
Institution: Cincinnati Children's Hospital Medical Center
Grant No.: 5U19AI070235-08

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.

IC: National Institute of Allergy and Infectious Diseases
Title: Host and Viral Determinants of Infant and Childhood Allergy and Asthma
PI: Ray Stokes Peebles
Institution: Vanderbilt University
Grant No.: 5U19AI095227-03

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 2,000 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Mechanisms of B Cell Responses in Autoimmune Disease**
PI: **Eugene William St. Clair**
Institution: **Duke University**
Grant No.: **5U19AI056363-10**

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 unique 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 elucidating 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Oklahoma Autoimmunity Center of Excellence**
PI: **Judith A. James**
Institution: **Oklahoma Medical Research Foundation**
Grant No.: **5U19AI082714-05**

The Oklahoma Medical Research Foundation (OMRF) 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 (TTP), systemic lupus erythematosus (SLE), 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 complementary, 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 complementary 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 multidisciplinary 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, M.D., 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, multisite 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 preclinical SLE, Sjögren's syndrome, and potentially TTP, our first trial examines the efficacy and biologic impact of anti-IFN-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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Pathophysiologic and Therapeutic Mechanisms of Aspirin-Exacerbated Respiratory Disease**
PI: **Joshua A. Boyce**
Institution: **Brigham and Women's Hospital**
Grant No.: **5U19AI095219-03**

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 hyper-responsiveness 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Role of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin in Asthma**
PI: **Joel Barry Baseman**
Institution: **University of Texas Health Science Center at San Antonio**
Grant No.: **5U19AI070412-08**

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 histopathological 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy**
PI: **Andrew D. Luster**
Institution: **Massachusetts General Hospital**
Grant No.: **5U19AI095261-03**

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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Washington Women's Interagency HIV/AIDS Study (WIHS)**
PI: **Mary A. Young**
Institution: **Georgetown University**
Grant No.: **2U01AI034994-20**

Since 1993, the Washington Metropolitan WIHS (WMW) Consortium has enrolled and retained a representative community cohort of HIV-infected and uninfected women with the purpose of supporting NIAID in understanding the current epidemiology of HIV, risk behaviors, disease progression, treatment uptake and outcomes, and related co-morbidities. The early cohort of infected women is aging, and the effects of age and menopausal status on disease outcomes and co-morbidities is yet to be elucidated. The WMW has joined with centers around the country and with sites across metropolitan Washington, D.C., to address these issues. This is particularly pertinent as Washington, D.C., has the highest prevalence of HIV of any urban center in the U.S., and the WMW has enrolled and retained a cohort that represents women both ethnically and psychosocially. The WMW has successfully participated in all elements of the WIHS protocol and has actively supported the infrastructure of the national WIHS. WMW investigators have participated in all of the major WIHS scientific initiatives. Additionally, with its rich database and local and national specimen repository, the WMW has supported local and national initiatives designed to understand the pathophysiology underlying co-morbidities. The WMW proposes to continue this work and to expand its research portfolio by continuing its strong collaborative relationship with the national WIHS in the area of protocol development, implementation, sub-study participation, and identification of new initiatives. Additionally, for the next cycle of funding, we have proposed new initiatives that include a telephone-based intervention for depression that will positively impact adherence and health behaviors with the goal of reducing community viral load. This intervention can easily be implemented in the larger D.C. community. We are expanding our local initiatives on HIV- and HCV-associated liver disease by engaging a team of researchers in exploring the host response, epigenetic factors, and protein glycosylation in liver disease and cancer. We will also continue and expand our investigations in organ specific morbidities associated with long-term survival in an aging population with the goal of reducing or preventing morbidity in the areas of vascular health, neurocognitive decline, and the vaginal immunologic response in aging. We will accomplish this by engaging with national and local investigators with proven expertise in these areas to further leverage the NIH investment in this important cohort of women. This will allow us to better define the status of women with HIV and bring to fruition the goals of an AIDS-free generation and effective and sustainable treatment for those already infected.

IC: **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
Title: **Sex-Specific Movement Differences in Young Adults with and Without Hip Pain**
PI: **Cara L. Lewis**
Institution: **Boston University**
Grant No.: **5R21AR061690-02**

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 noninvasive 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 noninvasive therapeutic interventions. It also could be used to develop prevention programs focused on neuromuscular retraining.

IC: **National Institute of Biomedical Imaging and Bioengineering**
Title: **Ultrasound-Induced Tissue Damage Assessment**
PI: **William D. O'Brien**
Institution: **University of Illinois at Urbana-Champaign**
Grant No.: **3R37EB002641-16S1**

The proposed research program is a basic science (non-clinical) investigation of a potentially significant ultrasound (US)-induced biological effect, that is, whether the application of ultrasound contrast agents (UCAs) in humans adversely affects the vasculature. The medical profession benefits from these studies if it is shown that diagnostic US is a significant medical risk to the patient by advising clinicians about this risk and by suggesting how the clinician can monitor the degree of risk. Likewise, the medical profession benefits from these studies if it is shown that diagnostic US is not a significant medical risk to the patient by eliminating vascular injury as a clinical concern. In either case, there is clear medical significance. The data necessary to decide this issue are not currently available. Today, we are faced with a significant challenge about the use of UCAs in humans, that is, the lack of knowledge as to whether the interaction of US with UCAs is a significant medical problem in humans. The FDA is also uncertain about UCAs' safety and/or effectiveness and is waiting until more is known about the risk of these agents before approving new UCAs, thus denying their well-known benefits to the patient.

Studies have been designed to address directly this "safe-use" issue by an interdisciplinary group of investigators who have considerable experience with US-induced tissue damage studies, as well as considerable experimental and theoretical experience with US biophysics and related physics areas. Using our continued proactive approach, we propose to utilize our extensive US bioeffects/biophysics expertise, along with our pathological, nutritional, biostatistical modeling, and animal model expertise, to determine whether the interaction of US with UCAs is a significant medical problem in humans. The experimental (animal-based) and theoretical (mechanism-development) research program has four specific aims, viz., (1) to determine the US thresholds for arterial damage in normal, healthy New Zealand white (NZW) rabbits when US interacts with UCAs in vivo; (2) to determine the US thresholds for arterial damage in post-exposure atherogenic diet-fed NZW rabbits when US interacts with UCAs in vivo; (3) to determine the US thresholds for arterial damage in pre-exposure atherogenic diet-fed NZW rabbits when US interacts with UCAs in vivo; and (4) to determine UCA thresholds in vitro. We are proposing 7 in vivo studies and a set of in vitro studies to accomplish our experimental and theoretical objectives.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response**
PI: **Candace S. Brown**
Institution: **University of Tennessee Health Science Center**
Grant No.: **5R01HD065740-03**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **A Longitudinal Study: The Influence of Sex and Puberty on Neurodevelopment**
PI: **Megan Marie Herting**
Institution: **Children's Hospital of Los Angeles**
Grant No.: **1F32HD078084-01**

Adolescence is a time period of significant neurodevelopment and is also a time when psychopathology begins to emerge in a sex-specific fashion. It is essential for us to understand what factors influence typical brain development and vulnerability for psychopathology. To date, research on brain organization and structure has been primarily studied in the developmental context of age. Recent research, however, suggests that puberty may uniquely contribute to the timing of neuromaturation differently in girls and boys, and may potentially contribute to the development of mental health problems that materialize during adolescence. However, the conclusions from the majority of these studies are limited due to their cross-sectional study design. The goal of the current project is to more fully characterize the influence of pubertal maturation, as measured by physical and hormonal assessments, on brain and mental health behaviors in typically developing girls and boys. Utilizing two independent longitudinal design datasets, the proposed study will use a multimodal approach, including structural and functional magnetic resonance imaging (MRI) and diffusion tensor imaging, to quantify the contributions of pubertal maturation in predicting changes in neurodevelopment within the same adolescents over an average of 2 years. Furthermore, the current study will examine if pubertal-related changes are distinct or similar depending on sex and, using behavioral self-reports, determine if individual differences in rates of pubertal-related brain maturation influence internalizing and externalizing behavior in typically developing adolescents. By improving our understanding of what role puberty plays in neurodevelopment, these experiments act as a novel and necessary first step toward determining if puberty's impact on neurodevelopment may help to explain the emergence of psychopathology in a sex-specific manner during adolescence.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Brown/WIH Pelvic Floor Disorders Network (PFDN) Site**
PI: **Vivian W. Sung**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **5U10HD069013-03**

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 and expertise of our multidisciplinary 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 multisite, collaborative surgical, pharmaceutical and nonsurgical 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 longstanding, formal relationship with multidisciplinary 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 1,211 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 nonsurgical 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 longstanding 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Brown/WIH Women's Reproductive Health Research (WRHR) Career Development Program**
PI: **Maureen G. Phipps**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **5K12HD050108-09**

The purpose of the Brown/Women & Infants Hospital WRHR Program is to train a new cadre of women's health translational researchers with expertise and research skills to develop innovative research in women's reproductive health from basic science to clinical applications relevant to public health. Scholars for the Brown/WIH WRHR Program will be recruited from local and national fellowship programs and junior faculty positions. The overarching goal for the program is to provide a supportive and stimulating research environment that enables well-qualified,

junior faculty physician-scientists to develop into leaders in women's reproductive health research with expertise in clinical translational research. Translational research areas include: fetal development, reproductive toxicology, perinatal genetics, pregnancy epidemiology and outcomes, gestational diabetes, postpartum depression, women's cancer epidemiology, environmental health, biomarkers and treatment development, ovarian preservation, HIV, infectious diseases, incontinence, adolescent decision-making, substance abuse, nutrition, obesity, cardiovascular disease, and aging. The training program involves a tailored research and career development plan that works by incorporating intensive multidisciplinary mentoring, didactic seminars, and practical hands-on research investigation. The immediate objective for the Program is to identify and train scholars who have the potential to develop as independent women's reproductive health investigators. The objective will be pursued by identifying promising scholars, training them in multidisciplinary translational research methods to pursue women's reproductive health research investigations, and mentoring scholars to become independent researchers. The long-term objective of the Program is to have an established, robust model training program for talented junior women's reproductive health researchers to develop into academic leaders who are capable of assuring what is discovered at the basic science bench is translated into outcomes that improve women's health. The long-term career objective for each scholar includes establishing an independent research career that involves training the next generation of women's reproductive health scholars.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Cleveland Clinic Clinical Site**
PI: **Matthew Barber**
Institution: **Cleveland Clinic Lerner College of Medicine of Case Western Reserve University**
Grant No.: **5U10HD054215-08**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Colorado WRHR Career Development Center**
PI: **Nanette F. Santoro**
Institution: **University of Colorado Denver**
Grant No.: **5K12HD001271-14**

The CU Denver Women's Reproductive Health Research (WRHR) Career Development Center provides a rich environment for the development of creative programs of research related to women's reproductive health while enhancing the pool of highly qualified obstetricians and gynecologists who pursue independent research careers. In this application, we request funds to support three scholars who will be faculty members of Obstetrics and Gynecology and who will utilize 75% of their time to train in a mentored position that will foster their development as independent clinician-scientists. Scholars will be recruited from a national pool of candidates who have completed a residency in obstetrics and gynecology, as well as a subspecialty fellowship, and show evidence of an intense desire to pursue the career of a clinician-scientist. The candidate may select any area of science relevant to obstetrics and gynecology, from a pool of outstanding mentors in obstetrics and gynecology, endocrinology, immunology, epidemiology, pediatrics, and psychiatry who are willing to supervise scholars. For example, specific training programs can be designed in a basic science such as immunology or molecular endocrinology, in translational science such as oncology or the endocrinology of diabetes, or in clinical science including outcomes research. Suitable mentors will be senior scientists with a track record of funding and training scholars. The scholar's progress will be tracked by an Advisory Committee of senior scientists and clinicians with interests similar to those of the scholar. The environment in the Department of Obstetrics and Gynecology includes a strong Basic Reproductive Science research program, an interdisciplinary graduate program in Reproductive Science, an excellent program of seminar and journal clubs, and a clinical faculty with strong research interests who collaborate with members of other departments in the school.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team**
PI: **Pamela A. Moalli**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **5R01HD061811-05**

Each year, roughly 200,000 U.S. women undergo a surgery to repair pelvic organ prolapse. 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, to 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Detroit Reproductive Career Development Research Center**
PI: **Elizabeth Puscheck**
Institution: **Wayne State University**
Grant No.: **5K12HD001254-15**

The overall objective of the proposed career development program is to develop independent OB/GYN physician-researchers in basic, translational, and/or clinical areas related to women's reproductive health. Institutional commitment to doing so is historically strong at Wayne State University (WSU), which has resulted in a strong research and training environment that includes the 75,000 sq. ft. C.S. Mott Center for Human Growth & Development and NIH's Perinatology Research Branch. WSU is a minority-serving institution (African & Arab Americans). Women's Reproductive Health Research Scholars will be appointed, based on

recommendations of an Advisory Committee, from a pool of candidates (local and national) who have demonstrated interest and prior experience in research. Members of underrepresented groups will be recruited in proactive partnerships with Meharry Medical College and the University of Puerto Rico in San Juan. Selection criteria have been sharpened by experience gained during the previous two periods of support. Training of Scholars will be individualized based on their past experiences and competences. Three individuals will be enrolled at any one time, with the expectation that a total of six Scholars will be trained. The proposed PI and Research Director are well experienced in research, training, and administration. Mentors will be experienced investigators with training track records who have research programs that are broadly relevant to women's reproductive health. These investigators will be complemented by a wide range of contemporary, sophisticated, clinical, and research resources. There will be six training aims: (1) Provide individualized coursework/lectures/seminars; (2) Provide essential ancillary skills and support resources to meet unique needs of each Scholar; (3) Provide a critical, mentored research experience that is relevant to each Scholar's long-term research interest; (4) Teach each Scholar to write a competitive grant application; (5) Proactively network each Scholar with prominent, disciplinarily relevant senior investigators; and (6) Assure that each Scholar is well grounded in the responsible conduct of research. Annual evaluation of the program by an outside evaluator will include objective analysis of both process and outcome. Advisory Committee members will provide oversight and also assess programmatic effectiveness. Scholars will complete their training when they have demonstrably reached research independence, objectively measured by such criteria as ability to compete successfully for independent grant support. Scholars will be tracked after leaving the program. Overall, the training is expected to contribute substantively to the nation's capacity for future conduct of women's health research.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Development of Wireless Abdominal Pressure Senor for Pelvic Floor Research**
PI: **Ingrid E. Nygaard**
Institution: **University of Utah**
Grant No.: **5R01HD061787-05**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Effect of Feeding Buddies on Adherence to WHO PMTCT Guidelines in South Africa**
PI: **Kiersten Ann Israel-Ballard**
Institution: **PATH**
Grant No.: **5R01HD075090-02**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women**
PI: **Brahim Aissani**
Institution: **University of Alabama at Birmingham**
Grant No.: **5R01HD064398-04**

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 tricarboxylic 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Identification of Genes Predisposing to Pelvic Floor Disorders**
PI: **Lisa Cannon Albright**
Institution: **University of Utah**
Grant No.: **5R01HD061821-05**

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 health care 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **KUMC Women's Reproductive Health Research Career Development Program (K12)**
PI: **Carl P. Weiner**
Institution: **University of Kansas Medical Center**
Grant No.: **5K12HD065260-04**

Described herein is a training program in Women's Reproductive Health Research (WRHR) designed to develop 3 physician-scientists in the Department of Obstetrics and Gynecology at the Kansas University Medical Center (KUMC) over the next 5 years. We will take full advantage of the scientific wealth and infrastructure of the entire University of Kansas system. Among its faculty are more than 30 extramurally funded scientists pursuing basic and translational research in women's reproductive health, and it is these scientists that form the pool of potential mentors for the KU WRHR Scholars. Indeed, reproductive biology is among the top 3 institutional research missions at KUMC, and the Chair of Obstetrics and Gynecology has superb University support for Scholar development. The proposed program will add junior faculty with state-of-the-art research training in women's reproductive health to the region's main academic health center, stimulate women's reproductive health research in a collaborative fashion among disciplines, and secure an outstanding research experience for the Scholar leading to a successful, independent research career. The training and mentoring program encourages both basic and clinical science careers and is divided into two flexible but defined phases. In Phase I (years 1–2), basic science Scholars who have not done graduate-level work will complete the core doctoral curriculum of the KU Interdisciplinary Graduate Program in the Biomedical Sciences. Clinical science Scholars will complete the KU Clinical Research Program designed to increase the number of funded clinical scholars committed to patient-oriented research. Phase I completion brings Phase II, where the Scholar spends 3 years conducting research and writing grants/manuscripts. Throughout, they are mentored by a primary mentor selected at program application and a mentoring team that includes a member of the Internal Advisory Committee. Program success is defined by progression of Scholars through academic ranks, the achievement of independently funded research and program feedback after graduation. We will be successful if our Scholars are published, funded, promoted, tenured, establish an independent research program, and make significant contributions to women's health research.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Magee-Womens Basic and Translational Reproductive Health Training Program**
PI: **William Allen Hogge**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **5K12HD063087-05**

The specific aim of the Women's Reproductive Health Research (WRHR) Career Development Program at Magee-Womens Research Institute, the University of Pittsburgh, is to prepare outstanding junior faculty in the field of obstetrics and gynecology for a productive and exciting investigative career in reproductive biology and medicine. This specific aim, along with the

pursuit of knowledge in reproductive sciences and the translation of discoveries into improved health of women and their infants, constitute the mission of Magee Womens Research Institute's Department of Obstetrics, Gynecology and Reproductive Sciences. Our program will support three scholars in a well-structured curriculum of two to three years of basic or translational laboratory-based training. The scholars will be selected among either graduates of an OBGYN residency or among OBGYN sub-specialty fellows in the final research year of postdoctoral fellowship. Our ability to selectively target trainees in basic or translational reproductive biology is supported by the rich and comprehensive fundamental research programs at Magee-Womens Research Institute. The institute includes a recently renovated laboratory research building of 125,000 sq. ft., furnished with state-of-the-art technology and equipment items that are housed in individual laboratories or integrated core facilities. Among a community of more than 50 reproductive biology researchers, we selected a group of 14 exceptional mentors who will guide the WRHR scholars throughout their training. The mentors were selected based on their intelligent, imaginative scientific pursuits, productivity, well-established laboratories, and a strong dedication to research education and mentorship. Furthermore, all mentors, who represent a diverse and rich portfolio of reproductive biology research, have a proven ability to secure extramural funding. An Internal Advisory Committee, monitored by an External Review Board, will oversee and monitor the program's quality and the progress of individual scholars along well-defined milestones. A comprehensive evaluation system, which is based on a set of sophisticated tools, will provide feedback to the PI, Research Director, and Advisory Committee, allowing the program to maintain excellence. Using these strategies, our Magee-Womens WRHR program will constitute a research incubator that will advance the investigative career of a cohort of basic or translational reproduction biologists. We will propel the career of junior scholars into research independence, and thereby enrich our field with well-qualified reproductive biology physician-scientists and mentors of high stature, both nationally and internationally.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **OB/GYN Faculty Research Career Development Program**
PI: **William Walton Andrews**
Institution: **University of Alabama at Birmingham**
Grant No.: **5K12HD001258-14**

We propose to renew the UAB Women's Reproductive Health Research (WRHR) Career Development Program, which has been dedicated to providing junior OB/GYN faculty with the research skills that can be applied to the study of important reproductive health problems in women. The primary objectives of the Program will be: (1) To recruit junior faculty (scholars) to the UAB Department of OB/GYN who are motivated to develop an independent research career; (2) To promote the career development of these scholars by providing degree-oriented (master of science in public health in clinical and translational science) or other advanced training in the principles and techniques of biomedical research; and (3) To integrate the career development of these scholars within research projects in scientific areas of emphasis with important relevance to women's reproductive health. We anticipate attracting trainees of diverse backgrounds involved in basic biomedical, translational, and clinical research, covering the disciplines of gynecologic oncology, urogynecology, reproductive endocrinology and infertility, genetics, and maternal-fetal medicine. The Program will utilize specifically selected NIH-funded senior UAB Program

mentors, the resources of the UAB Center for Women's Reproductive Health (CWRH), the newly established UAB Center for Clinical and Translational Science (CCTS), and other UAB campus resources to guide the research career development of these scholars. The Principal Investigator and the Program Director, with the assistance of an Advisory Committee and Minority Recruitment consultants, will be responsible for managing all aspects of the Program and for formally tracking the performance of the Program and scholars. The UAB Department of OB/GYN and the Program have a broad range of funded research interests in which the scholars could be mentored. This Program model was successfully implemented during the past decade and has a proven track record of developing OB/GYN physician-scientists.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Partner Violence and Reproductive Coercion Among Native American Women**
PI: **Elizabeth Miller**
Institution: **University of Pittsburgh**
Grant No.: **1R21HD077101-01**

Unintended pregnancy confers significant adverse consequences for women, their children, and society, and is closely associated with intimate partner violence (IPV) and sexual assault (SA). Native American (NA) women are at particularly high risk for experiencing unintended pregnancy and IPV/SA. IPV confers risk for unintended pregnancy through multiple mechanisms including forced unprotected sex and compromised decision-making regarding contraceptive use, as well as through reproductive coercion—male partners promote pregnancy through threats and contraceptive sabotage. Studies have not included sufficient numbers of NA women to understand how IPV, reproductive coercion, pregnancy intentions, and contraceptive behaviors may differ from non-NA women. A family planning clinic-based, brief safety-card intervention has been shown to reduce reproductive coercion, and is being tested in a large cluster-randomized controlled trial to assess the impact on IPV and unintended pregnancy (1R01HD064407-01A1, PI Miller). However, in a pilot demonstration project funded by the Office on Women's Health with the Hoopa tribe in Northern California, health care providers and victim advocates identified limitations with this safety card for use with NA women on reservations including limited access to clinical and victim services, low levels of contraceptive use, and ambivalence around pregnancy. We propose to conduct a qualitative study with NA adolescent and adult women in three diverse tribal communities: the Hoopa tribe in Northern California, the tribal nations and pueblos of New Mexico, and the Maliseets and surrounding tribes in Maine. We propose to conduct one-on-one semi-structured interviews with NA adolescent and adult women ages 16 to 35 in these communities (N = 60) to identify pathways connecting IPV, reproductive coercion, pregnancy intentions, contraceptive behaviors, and reproductive histories among NA women (Aim 1); to explore how cultural, structural, and relationship factors shape NA women's experiences with IPV, pregnancy, contraceptive use, and care seeking behaviors (Aim 2); and to test face and construct validity of existing survey items for assessing IPV, reproductive coercion, and unintended pregnancy with NA adolescent and young adult women (Aim 3). To date, no studies have examined NA women's experiences with reproductive coercion, IPV/SA, and unintended pregnancy. This study will help clarify how NA adolescent and adult women describe pregnancy intention and contraceptive behavior, and the cultural, structural, and relationship factors including violence, which affect their intentions and

behaviors. This study will advance our understanding of the relationships among unintended pregnancy, violence, race, and contraceptive decision-making while simultaneously pinpointing targets for intervention. This study will lay the groundwork for an R01 to adapt and test a brief intervention designed to help NA women connect their relationship experiences with pregnancy intentions, promote effective contraceptive use, and reduce IPV and unintended pregnancy.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pediatric CFS in a Community-Based Sample**
PI: **Leonard A. Jason**
Institution: **De Paul University**
Grant No.: **1R01HD072208-01A1**

Existing published pediatric epidemiologic CFS studies are similar to the first generation of adult CFS prevalence studies in that they have had either poor sampling plans (e.g., recruitment at medical centers; Nijhof et al., 2011), or systematic biases that excluded certain people such as youth of lower socioeconomic status and those of color who were less likely to have access to health care (Dobbins et al., 1997), or failed to include a medical examination (Jones et al., 2004). We will determine the prevalence of pediatric CFS in a demographically diverse sample of participants unbiased by illness, help-seeking behaviors, or differential access to the health care system. In addition, we will assess orthostatic intolerance (OI) symptoms in a community-based sample of children with pediatric CFS, who are unbiased by help-seeking behaviors or differential access to the health care system. In the proposed study, the quantifiable response to a mental task undertaken during orthostatic stress (a) will operationally define central fatigue and neurocognitive impairment, and (b) will be applied as a biomarker for community-based CFS when compared to a community-based control group. We believe that cognitive fatigue, cognitive loss, and dizziness are a function of abnormalities in cerebral blood flow as it relates to total cardiac output, total blood volume, regional blood flow, and blood volume distribution during the orthostatic stressor. In addition, we will be able to resolve discrepant findings regarding cerebral blood flow, which, we believe, are due to the differing ways of measuring the response of cerebral blood flow velocity to arterial pressure. In summary, this proposed study will determine the prevalence of pediatric CFS in a community-based sample, as well as the relative frequency of CFS among various groups (e.g., different age groups, genders). This study will also identify the prevalence of orthostatic abnormalities among youth with CFS and controls and will examine its relationship with neurocognitive functioning.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pelvic Floor Disorders Network**
PI: **Charles William Nager**
Institution: **University of California, San Diego**
Grant No.: **5U10HD054214-08**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pelvic Floor Disorders Network: Duke University Clinical Site**
PI: **Anthony G. Visco**
Institution: **Duke University**
Grant No.: **5U10HD041267-14**

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 nonsurgical management of urinary incontinence (Ul), pelvic organ prolapse (POP), fecal incontinence, and defecatory dysfunction. Last year, our Division cared for more than 1,550 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: multichannel 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), (2) InterStim vs. Botox RCT (ROSETTA, Dr. Amundsen, full protocol), and (3) 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 nonsurgical 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pelvic Floor Disorders Network Clinical Sites (U10)**
PI: **Lily A. Arya**
Institution: **University of Pennsylvania**
Grant No.: **5U10HD069010-03**

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 M.D., M.S., (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 multicenter 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 nonsurgical 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 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Perioperative Pelvic Floor Rehab: A Randomized Trial**
PI: **Holly E. Richter**
Institution: **University of Alabama at Birmingham**
Grant No.: **5U10HD041261-13**

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 (FI) 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 FI, 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 FI (although it is not yet FDA approved for this indication). We propose a randomized trial to credibly characterize the effect of SNM on FI 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pittsburgh Pelvic Floor Research Program**
PI: **Halina M. Zyczynski**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **5U10HD069006-03**

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 and compare clinical outcomes of meshes whilst providing specimens for translational studies.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **RCT of Hypnotherapy vs. Tpolterodine for OAB: Voiding and Brain Activation Changes**
PI: **Rebecca Glenn Rogers**
Institution: **University of New Mexico Health Sciences Center**
Grant No.: **5U10HD069025-03**

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, multicenter 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 multicenter randomized trials and proven leadership and productivity. The UNM PFDN site brings to the Network a busy clinical service with large numbers of underrepresented 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Reproductive Sciences Research Career Development Center**
PI: **Thomas Richard Moore**
Institution: **University of California, San Diego**
Grant No.: **5K12HD001259-14**

The goal of this application is to build upon and enhance the outstanding academic training currently provided in the UCSD Women's Reproductive Health Research (WRHR) Career Development Center. WRHR Scholars are selected through nationwide searches by an Advisory Committee, comprised of internationally recognized researchers, that identifies high-performing OB/GYN physicians who aspire to scientific excellence in women's health and are committed to academic careers as physician-scientists. Scholars are matched with an established senior-scientist Mentor from a broad range of women's health interest areas including epidemiology, perinatal physiology and genetics, obesity and metabolism, urogynecology, reproductive endocrinology, and cancer. The program is flexibly organized into two phases: in the first 1 to 2 years, the Scholar works toward research competency; in the final 3 to 4 years, efforts are directed to achieving research independence and academic expertise. During Phase 1, didactic and practical instruction supplements intensive laboratory work, and clinical work is minimized. First phase Scholars participate in the two-year CREST program in epidemiology, biostatistics, data management, and informatics. During a third optional year, an M.P.H. degree can be achieved. In Phase 2, Scholars join the UCSD NCLAM Leadership Program, which teaches academic development, leadership, and organizational effectiveness and prepares the Scholar to function as an accomplished Associate Professor. Individualized instruction in grant writing, ethics, and medical enterprise is conducted regularly. Throughout, the Center's Mentoring Committee closely monitors Scholars' progress in monthly meetings and an Individual Mentoring Committee (similar to a Ph.D. thesis committee), appointed specifically for each Scholar, meets twice yearly, ensuring that both the research environment and clinical demands are optimized and balanced. The Advisory Committee reviews Mentoring Committee reports annually and assesses each Scholar's advancement and reappointment to the program yearly. The well-established success of the Center over the last ten years will be enhanced and extended as a new a cadre of outstanding Scholars is recruited, trained, and transitioned into mature clinician-scientists.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Research Career Development in Obstetrics and Gynecology**
PI: **Serdar E. Bulun**
Institution: **Northwestern University**
Grant No.: **5K12HD050121-09**

The long-term goal of the 'WRHRCDC at Northwestern University is to continue to foster and develop an outstanding mentored, research training program for obstetrician-gynecologists, and to prepare our WRHR trainees (Scholars) to become independent investigators in women's health research. Since it has been first funded in 2005, our WRHRCDC has made major progress in reaching this goal. We have successfully trained 4 Scholars, who published 27 papers and received 18 grant awards, including 6 from NIH, and have met all our WRHRCDC benchmarks.

The Department of Ob/Gyn will continue to coordinate and administer the WRHRCDC Program and make full use of the scientific wealth and reproductive research infrastructure at Northwestern in its entirety. The key leadership at Northwestern made strong institutional commitments to the WRHRCDC Program. Sherman Elias, M.D., Chair of Ob/Gyn, and Serdar Bulun, M.D., the Division Director of Reproductive Biology Research will continue to serve as the PI and WRHR Research Director, respectively. The Department of Ob/Gyn at Northwestern has traditionally recruited high-quality residents, subspecialty fellows, and junior faculty; currently 16% of this group are underrepresented minorities (URM). One of our current WRHR Scholars is an URM. Thus, we have a large and active pool of candidates for WRHR Scholar selection. These Scholars will have an opportunity to choose between highly competitive clinical research teams or laboratories conducting research in the areas of reproductive endocrinology and infertility, maternal-fetal medicine, gynecologic oncology, and reproductive genetics, and covering the reproductive portion of hypothalamic-pituitary axis, ovary, uterus, placenta, and the fetus. The WRHR Scholars will interact with existing two P01, two U54, and one SCOR Center grants and one T32 training grant specifically in the area of obstetrics and gynecology. As the Northwestern WRHRCDC Program, we are fully equipped to continue to recruit top-quality obstetrician-gynecologists and train them to conduct research and compete for federal grants and retain them as they become independent investigators. Our excellent track record during the past funding period strongly supports our application.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Short-Term Outcomes of Interventions for Reproductive Dysfunction**
PI: **Amy B. Wisniewski**
Institution: **University of Oklahoma Health Sciences Center**
Grant No.: **1R01HD074579-01A1**

Whether or not to surgically correct ambiguous genitalia to be more female- or male-typical with genitoplasty is an area of pediatric medicine that is highly controversial. Suboptimal outcomes such as poor post-surgical cosmesis and sexual dysfunction following outdated surgical procedures have driven intense controversy in the medical community over how, or if, genitoplasty should be used in the treatment of young children with ambiguous genitalia. To resolve this debate, a prospective study of outcomes of current genitoplasty procedures, including complication rates associated with these procedures, is needed of individuals who receive masculinizing or feminizing surgery during early childhood. Additionally, studies of parents who decide to proceed, or not, with genitoplasty for their young child are necessary to understand how these controversial decisions impact parents' reactions to surgical outcomes for their child. The overall goal of this proposal is to assess the outcomes of modern genitoplasty techniques with a consideration of the psychological outcome of parents who make the decisions to proceed with genital surgery for their child. This information is crucial for physicians to provide guidance to parents regarding the optimal approach for the management of ambiguous genitalia in young children, including the possibility that no surgery is best. The interdisciplinary group of clinicians and researchers included in the proposed studies spans the fields of psychology, statistics, pediatric endocrinology, and pediatric urology. The collective experience of our group optimizes our ability to translate findings from the proposed studies to a clinical setting in a timely manner.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **The Iowa Women's Reproductive Health Research Career Development Center**
PI: **Kimberly K. Leslie**
Institution: **University of Iowa**
Grant No.: **5K12HD063117-05**

The Iowa Women's Reproductive Health Research Career Development Center, the Department of Obstetrics and Gynecology at the Carver College of Medicine, the University of Iowa, is an outstanding site to house a Women's Reproductive Health Research (WRHR) Career Development Center. This application draws upon the following specific strengths: (1) the exceptional research milieu and infrastructure as well as the national prominence of the University of Iowa Carver College of Medicine in research and education; (2) a successful model of research career development for young faculty that is already in place; (3) established and successful research themes in women's health in the department of obstetrics and gynecology and throughout the college of medicine; (4) an already existing strategic research plan that will be integrated into the WRHR Center; (5) an experienced and highly qualified Principal Investigator, Kimberly Leslie, M.D. (former WRHR Program Director at the University of Colorado and an AAOGF and RSDP scholar), and an acclaimed scientist and teacher, Mario Ascoli, Ph.D., who will serve as the Research Director; (6) an impressive cadre of senior scientists and leaders from the department and throughout the college who will serve as mentors and advisors; (7) a broad-based applicant pool from which to recruit with an emphasis on an innovative mini-sabbatical program to recruit scholars from underrepresented groups; and (8) very strong institutional support that will contribute to our success. Two research tracts (basic and clinical) and six programmatic themes, chosen because Iowa has world-class research in these fields, are supported by the University of Iowa WRHR. The research themes are (1) cancer and hormones, (2) epidemiology of reproductive disorders, (3) genetics and genomics, (4) hormones and signaling, (5) host defense, and (6) hypertension and the vasculature. A well-integrated WRHR Program that supports both basic and clinical-epidemiologic investigation is in place. Scholars will benefit from pertinent didactic coursework along with intensive training in the finest basic and clinical laboratories throughout the institution. The University of Iowa proposed WRHR has all of the components to meet the ultimate goal of the program, to develop a successful cadre of academic investigators who will excel in research and expand the frontiers of knowledge in women's reproductive health going into the future.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **The Penn Center for Career Development in Women's Health Research**
PI: **Deborah Anne Driscoll**
Institution: **University of Pennsylvania**
Grant No.: **5K12HD001265-15**

This competing renewal application for the Penn Women's Reproductive Health Research (WRHR) Career Development Center seeks continued support for training and mentorship for

obstetrician-gynecologists with the goal of cultivating a cadre of independent scholars in women's health, emphasizing multidisciplinary approaches. The program will continue to have a steady state of 3 WRHR Scholars. The Penn WRHR Center builds on a tradition of multifaceted investigation and training in reproductive and women's health at the University of Pennsylvania, dating back to 1966. It is an integral part of Penn's exceptional biomedical research enterprise, ranking among the top in the nation in terms of NIH grant awards to medical schools. The short term goals of the WRHR Center are to identify especially talented physicians who have demonstrated potential for successful careers in research, to place them in an exciting and supportive research environment under the guidance of an experienced mentor(s), and to advance their skill sets in research to the point that they can establish a productive, independent line of investigation. Based on successes in the previous funding periods, the Penn WRHR Center will continue to formulate individualized curricula and career development plans. This may include enrollment in a master of science or Ph.D. degree program. Academic enrichment including seminars and specialized workshops has been established to enhance research skills, as well as publication and grant writing. Continued support for a Biostatistician (instead of a Biostatistics Core) is requested based on its significant contributions to the research career development of Scholars during the past periods of support. The long-term goals of the Center are to insure that Scholars who graduate from the Penn WRHR Center establish sustainable research programs and develop expertise in mentorship that will allow them to guide future Scholars. A novel feature of the present proposal is that we have incorporated the joint recruitment of WRHR Scholars with Temple University (non-research intensive department of Ob/Gyn) and Howard University (minority institution) in order to start building the Women's Health Research manpower at those institutions. Overall success of the Penn WRHR Center will be measured in terms of the quality and importance of work published by the Scholars, their ability to win and retain extramural research funding, professional recognition for their research activities, effectiveness in mentoring trainees under their direction, academic promotion, and assumption of leadership roles in the specialty of obstetrics and gynecology.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **The Yale WRHR Career Development Center**
PI: **Hugh S. Taylor**
Institution: **Yale University**
Grant No.: **5K12HD047018-10**

The Department of Obstetrics, Gynecology, and Reproductive Sciences proposes to continue the Yale Women's Reproductive Health Research (WRHR) Career Development Center with the goal of selecting outstanding novice or more experienced physician-scientists for advanced training in basic, translational, or clinical science under the guidance of skilled scientific mentors. The Principal Investigator/Program Director (PD/PI) and Research Director (RD) will monitor the Scholars' academic progress toward research independence. We identify prospective scholars from our residents, subspecialty fellows, and junior faculty, as well as national networking by the PD/PI and RD and advertisements in professional journals, letters to program directors and Chairs, and postings at national meetings. Our selection committee chooses WRHR Scholars who exhibit exceptional promise and commitment to a career in women's health research. The PD/PI, RD, and Advisory Committee are directly involved in the training, evaluation, and academic development of each WRHR Scholar. Mentors are experienced in

career development and are outstanding scientists in fields related to women's reproductive health. Core training in basic lab techniques and molecular biology, along with a didactic program, are required for all WRHR Scholars and include instruction in the responsible and ethical conduct of research. There are three WRHR Scholars in the Department at any given time, with each Scholar assigned departmental laboratory space with access to shared teaching and training cores. In addition to having 75% time directly covered by the Center, in order to pursue career development, Scholars will receive research support for 2–5 years to underwrite costs while they obtain preliminary data and develop grant applications. Scholars enter the Department of Ob/Gyn as Assistant Professors, with appropriate office and support staff. Clinical duties and responsibilities relate directly to research interests. Career development will span two to five years, depending on the individual Scholar's initial level of experience and particular training goals as a Scholar. The Yale WRHR Center aims to foster Scholars' development into established, independent investigators. Yale seeks to retain as faculty Scholars who successfully complete the individualized training program at Yale and who have made significant progress toward independent funding.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **University of Michigan WRHR Career Development Program**
PI: **Timothy R. Johnson**
Institution: **University of Michigan**
Grant No.: **5K12HD065257-04**

The goal of the University of Michigan WRHR Program is to increase the number and effectiveness of obstetrician/gynecologist scientists through a departmental-based, multidisciplinary, junior faculty development program. We propose to recruit physician faculty to develop their women's reproductive health research careers for a minimum of two and up to five years. Recruitment of scholars with outstanding potential will be primarily from obstetric/gynecology fellowship programs. During the past ten years, we have developed a track record of training a number of outstanding obstetrician/gynecologists in our department for careers in academic medicine. It is our goal to select the most promising candidates for appointment from three-year ABOG-approved subspecialty fellowships as well as minimally invasive surgery, family planning, genetics, breast and women's health fellowships, AGOS fellows, and Robert Wood Johnson Clinical Scholar programs to participate in the WRHR. Special medical school-wide programs are in place to recruit and support under-represented minority scholars. From among the potential mentors in the department's Reproductive Sciences Program and related Initiative for Women's Health Researchers, we have chosen those with proven records of accomplishment in fostering research career development. The research programs of these mentors span cutting-edge cellular and molecular aspects of reproductive biology to translational and clinical research. We aim to target programmatic content in specific areas of pelvic floor and urogynecology research, reproductive science biology, and reproductive and perinatal genetics, where institutional strengths support development of junior faculty. A Career Development Program and Center Advisory Committee will assure that the scholars have the best possible environment for success. The program will be measured by the success of WRHR scholars achieving research independence and in receiving extramural funding. The University of Michigan has a current BIRCWH program. We request support for a WRHR program to focus specifically on developing careers of multidisciplinary trained

obstetrician/gynecologists. The WRHR program will complement the BIRCWH program since only obstetrician/gynecologists will be candidates for the WRHR program, and it will offer a distinct opportunity for these scholars to develop their research programs in areas of specialty-focused relevance and interest with excellent mentors, while at the same time providing an opportunity to interact with a different cadre of women's health scholars with many opportunities for cross-training and peer-support.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Uterine Leiomyoma Research Center Program**
PI: **Serdar E. Bulun**
Institution: **Northwestern University**
Grant No.: **5P01HD057877-05**

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 profibrotic factor TGF-beta. Project I (Bulun) will be pursued to understand the mechanisms as to how anti-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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UTMB WRHR Career Development Center of Excellence**
PI: **Gary D. Hankins**
Institution: **University of Texas Medical Branch at Galveston**
Grant No.: **5K12HD001269-15**

UTMB-Galveston and the Ob/Gyn Department respectively submit this competing application to continue our WRHR Career Development Center. We have trained 9 Scholars: 4 women and 5 men, including 1 underrepresented minority investigator and 1 disabled investigator; all scholars were drawn from diverse clinical specialties; 4 initially had virtually no research experience; and 1 earned her Ph.D. as a Scholar. We commit to achieving all goals as set forth by the RFA: The Department has broad-based, basic research in important women's reproductive health problems and has greatly increased both translational research and clinical research (ranks 3rd in number of NIH grants awarded to Ob/Gyn departments, FY 2007). The Mentors for the WRHR Scholars, both from within the Ob/Gyn Department and from other departments, have experience training physicians who want to become independent investigators. This effect is further enhanced by Ob/Gyn Mentors' having a dual appointment in the following: neurosciences and cell biology, microbiology, pediatrics, biochemistry and molecular biology, pharmacology and biology, surgery, and psychiatry. We have a group of excellent WRHR scholar candidates, and our fellowship programs, all of which require 18 months of basic research and a master of science degree, will continue to produce well-qualified candidates. The research laboratories of the Ob/Gyn Mentors (20,000 sq. ft.) are modern and well equipped as are the laboratories of the Mentors from other departments. The environment both in the Department and at UTMB is supportive of developing young physicians who want research careers. Research has been of the highest priority for the past two department chairmen, Drs. Anderson and Hankins, and some of the key personnel in this grant developed their research careers in our own Department. UTMB has demonstrated its support of this grant by pledging money, research space within the Department, and adherence to the 75% protected research time. Both the Department and UTMB have demonstrated their commitment to recruitment and promotion of women physicians and underrepresented minority physicians. (Black Issues in Higher Education magazine has consistently identified UTMB among the nation's top granting institutions of medical degrees for underrepresented minorities.) We have the necessary infrastructure to successfully train young physicians to become independent investigators in areas that address important women's reproductive health concerns. The scholars we have trained in the last two cycles have been very productive, obtained several extramural grants, published extensively, and remain in academic institutions and are now establishing their careers as clinician-scientists. In this application we request funding to continue this productive activity.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Women's Reproductive Health Research**
PI: **Linda C. Giudice**
Institution: **University of California, San Francisco**
Grant No.: **5K12HD001262-15**

The principal mission of the University of California, San Francisco (UCSF), Women's Reproductive Health Research (WRHR) Career Development Center is to promote health and prevent disease in women by expanding the pool of well-trained, imaginative, productive investigators in the field of women's reproductive health. It is our purpose to recruit, mentor, and prepare outstanding candidates to acquire and refine the skills needed to reach this goal. As one of the original institutions awarded a WRHR Center, we have established an infrastructure, curriculum, and Scholar mentoring system to meet the challenge of training the next generation of academic obstetrician-gynecologists. Based on the successes of two cohorts of Scholars over the past 10 years, we propose a structured Scholar program of sufficient duration, relevant didactic education, and immersion into a vibrant, intellectually challenging, research community, leading to academic independence. The education of our Scholars will be further enriched by our collaboration with the UCSF Clinical & Translational Science Institute (CTSI), which provides ongoing infrastructure, resource, training, and research opportunities. We have learned that appropriate scientific and academic mentoring is mandatory during the initial years of a junior faculty appointment, helping the individual to overcome hurdles that impede a rewarding, successful, and productive academic career. Scholars will be recruited to pursue two general areas, biomedical (laboratory-based) research and clinical research, in reproductive science. In addition, two general pathways (I and II) have been established to guide relatively inexperienced (Track I) and more senior Scholars (Track II), respectively. Translational research, a burgeoning focus within our department that has benefited from longstanding multidisciplinary partnerships, will be gained through participation in studies bridging the biomedically and clinically oriented projects. We are committed to nurturing a cadre of UCSF WRHR Scholars who will improve the health status of women by conducting important discovery, expanding knowledge, and testing innovations for the prevention, diagnosis, and treatment of reproductive disorders. Through our proposed mentoring program, we anticipate that our Scholars will be independent investigators and future leaders of women's reproductive health research nationally and internationally.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Women's Reproductive Health Research at the University of Washington**
PI: **David Eschenbach**
Institution: **University of Washington**
Grant No.: **5K12HD001264-15**

The Women's Reproductive Health Research (WRHR) Center, a career development program for obstetrician gynecologists, was established at the University of Washington in 1998. The aim of the WRHR program at the University of Washington (UW WRHR) is to foster the education, training, and scientific development of obstetrician gynecologists who demonstrate clear research potential and are committed to a career in academic medicine. Our long-term goal is to

improve women's health. The program has successfully trained 6 individuals, with 3 additional scholars in training. This proposal describes a plan for continuation of the UW WRHR program. The goal remains a commitment to bridge the gap between clinical and research training to enable young physicians to establish research careers tailored to their specific interests and to become independent investigators. Proposed training is a multidisciplinary mentored experience for 2–5 years. During this period, a scholar devotes 80% of his/her time to research. The program aims to recruit individuals from other institutions and to recruit individuals from underserved backgrounds. The UW WRHR is unique in offering a broad menu of scientific disciplines and training environments designed to create the best opportunities for trainees. We have a distinguished group of 18 mentors with expertise in a diverse spectrum of specialties ranging from genomics to global health—with investigation in obstetrics, gynecology, and women's reproductive health research as the core activity. Particular strengths include: reproductive immunology, infectious disease, medical genetics, global health (e.g., HIV/AIDS, malaria), prematurity, behavioral medicine, cancer epidemiology, and placental pharmacokinetics. We believe that through partnerships with outstanding scientists in disciplines that lie outside of the traditional boundaries of obstetrics and gynecology (e.g., gynecologic oncology, perinatal medicine, and reproductive endocrinology), our scholars have the greatest opportunity to achieve their scientific potential, build unique and successful interdisciplinary careers, and advance the cause to improve the health and well-being of women and their families. The Ob/Gyn Department and the School of Medicine at UW are prepared to make major commitments to support continuation of the UW WRHR program.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Women's Reproductive Health Research Career Development Program at Washington University, St Louis**
PI: **George A. Macones**
Institution: **Washington University in St. Louis**
Grant No.: **5K12HD063086-05**

The goal of the Washington University School of Medicine WRHR program is to promote the performance of research and transfer of findings that will benefit the health of women through the development of well-qualified, new physician-scientists. The program will achieve this goal by providing each scholar with a core seminar series essential for his/her development as an independent investigator in women's health, a suitable mentor who can provide the guidance and expertise to assure successful academic development and skills as an independent investigator, and the research infrastructure and adequate protected time to create an environment conducive to investigation into women's health. This program is unique in that both basic and clinical science tracks separately are available to scholars; however, they train with mentors who cross disciplines and are exposed to both, in order to be able to interact and translate their own training into cooperative research. The leadership, Dr. George Macones as the PI and Dr. Kelle Moley as the PD, reflects this interactive and cooperative approach to career development in reproductive sciences. Their distinct backgrounds and different career pathways, Dr. Macones in the area of clinical research and Dr. Moley in the area of basic translational research, create a unique juxtaposition of leadership styles, which complement each other. Their combined efforts and vision represent the necessary melding of academic backgrounds necessary to perform outstanding investigative science in the area of reproductive health research. In addition, such a

multidisciplinary program, emphasizing both clinical and basic research equally, will attract the best and brightest scholars to the WUSM WRHR program. This quality sets this Career Development Program apart from those preceding it at other locations. WUSM is ranked the third best medical school in the USA as reported in US News & World Report, and it has a rich scientific history in basic and clinical science research. Given our existing strengths, we believe the theme which unites the mentors involved in the WUSM WRHR Program is the translation of basic research into patient-oriented, clinical research to improve women's health. This uniting concept is shared by our specific focus areas of expertise including: (1) Women's Infectious Diseases (Drs. Hultgen, Gordon, and Peipert); (2) Endometrial Cancer: Genetics and Cancer Disparities (Drs. Goodfellow, Milbrandt, Colditz, Rader, and Mutch); (3) Developmental Biology: Stem Cells and Origins of Adult Disease (Drs. Moley, Schedl, Gottleib, Schaffer, and Semenkovich); (4) Behavioral Health, Health Disparities, and Contraception (Drs. Peipert, Cottler, and Gelbart); (5) Developmental Neurology and Maternal Fetal Physiology (Drs. Inder, VanEssen, and Holtzman; and (6) Placental Biology and Maternal Fetal Interaction (Drs. Nelson, Atkinson and Yokoyama).

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **WRHR—A Mentoring Program in Women's Reproductive Health Research at the University of Vermont**
PI: **Ira Mark Bernstein**
Institution: **University of Vermont & State Agricultural College**
Grant No.: **5K12HD063082-05**

The Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Vermont is committed to the career development of physician-scientists with an emphasis on women's health. To this end, we have assembled a multidisciplinary group of 20 experienced investigators, who will serve as mentors, and a nine-member Advisory Committee, and are applying for the WRHR Career Development Program grant to formalize and facilitate the training process. Each mentor has an active, funded research program in one of five scientific themes that reflects the research strengths of our Institution, and around which our training efforts will be structured—female vascular diseases, genital tract smooth muscle contractility, reproductive immunology and infectious disease, genetics and developmental biology, and endocrine signaling related to metabolism and aging. WRHR scholars will include women and underrepresented minorities and be recruited from our Department and from OB/GYN training programs in our region and throughout the country. The training process will include instruction in grant and manuscript preparation and review, experimental design and statistical analysis, and the responsible and ethical conduct of research. The University of Vermont Center for Clinical and Translational Science and the Graduate College will provide a foundation of elective courses required for performing successful research. Direct experience in the process of research will be obtained under the guidance of the primary mentor. We have created a two-track plan for individuals with little vs. substantial previous research experience. Defined benchmarks for progress, including early formalization of specific aims, seminar presentation, and a formal review process will help monitor and assure each individual's progress. Each scholar will have the opportunity to attend and present their work. We anticipate enrollment of three WRHR Scholars at any one time, and completion of training in 3–5 years with the end point for each

scholar being the development of his/her own scientific ideas and submission of grant applications for extramural funding.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Xenograft Study on Growth-Control of Human Uterine Leiomyomata**
PI: **Takeshi Kurita**
Institution: **Northwestern University at Chicago**
Grant No.: **5R01HD064402-04**

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 health care 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.

IC: National Institute on Drug Abuse
Title: Development of the Basal Telencephalic Limbic System
PI: Joshua G. Corbin
Institution: Children's Research Institute
Grant No.: 3R01DA020140-09S2

This renewal application is focused on the study of the development of the basolateral complex and medial nucleus of the amygdala. Collectively, these nuclei regulate major aspects of limbic system function. Our previous studies have identified distinct progenitor pools in the developing telencephalon that contribute to postnatal neuronal cell diversity in these amygdala subdivisions. Based on this work, in this project we will test two hypotheses. First, we will test the hypothesis that embryonic transcriptional factor expression diversity within amygdala progenitor pools underlies differential postnatal amygdala neuronal subtype fate and patterns of axonal connectivity. Second, we will test the hypothesis that key transcription factors that are expressed in these progenitor domains are required for the development and/or connectivity of postnatal amygdala neurons that are derived from these populations. Testing of these hypotheses will be accomplished using a combination of cutting-edge approaches including genetic fate mapping, electrophysiology, axonal tracing, and conditional loss of function.

IC: National Institute on Drug Abuse
Title: Human Methamphetamine Vaccine: Translational Avant-Garde Award
PI: Thomas Richard Kosten
Institution: Baylor College of Medicine
Grant No.: 3DP1DA033502-03S1

Four factors make this methamphetamine (MA) vaccine ready for clinical translation: (1) Our candidate vaccine has optimal adjuvant and antibody responses. 2. Our partnering Chinese manufacturer has Chinese FDA support for the vaccine IND and matching clinical study funds. (3) The PI has 15 years' experience developing medications in China and a successful cocaine vaccine. We can accelerate MA vaccine development well beyond the 15 years needed for cocaine in the USA, because the manufacturer has Chinese government financial and FDA support and commercial incentives from the lack of approved treatments for MA. Our R01-DA023898 has identified an optimal carrier protein—keyhole limpet hemocyanin (KLH), which is already approved for human use—and an approved Chinese squalene lipid adjuvant that is better than standard alum to optimize the anti-MA antibody response to vaccination. The optimal KLH-adjuvant vaccine combination will be determined within two years by correlating the quality and quantity of the induced antibodies with inhibition of MA locomotion and self-administration behavior in rats and primates. We then rapidly moved into cGMP synthesis, animal toxicology, CMC, IND filing, and phase 1 and 2a clinical trials in years four/five. (4) Concurrently with this Chinese human vaccine, we plan to renew R01-DA023898 to develop a similar lipid adjuvant vaccine in collaboration with the Sabin Vaccine Institute, which is moving to Baylor in July 2011 and has a squalene adjuvant (Easai, E6020) with FDA approval. These two linked programs will have major practical impacts on MA's profound morbidity in the USA and China through collaborative vaccine development between American and Chinese investigators and manufacturers to produce a first- and potentially a second-generation vaccine quickly into clinical development in the USA and Asia.

IC: National Institute of Dental and Craniofacial Research
Title: A Multi-Omic Analysis of the Vaginal Microbiome During Pregnancy
PI: Gregory Allen Buck
Institution: Virginia Commonwealth University
Grant No.: 1U54DE023786-01

In the U.S., the annual cost of health care for newborns with complications approaches $26 billion, and worldwide, preterm birth is the leading cause of morbidity and mortality among neonates. Despite improved survival rates, the past few decades have seen no significant decrease in preterm births. It is becoming more clear that the billions of bacteria that colonize the human body play important roles in the health of the individual. However, the role of the millions of bacteria and other microbes that colonize the human female urogenital tract in prenatal health and birth of a healthy baby remains obscure. Previous to the recent development of "omics" technologies (i.e., genomics, transcriptomics, proteomics, metabolomics, interactomics, etc.), it was not possible to study these microbial populations in any in depth or highly efficient way. Many of these organisms have never been characterized, and a fairly large fraction have not been successfully cultured. Herein, we propose to use these "omic" technologies to dissect the bacterial populations that inhabit and colonize the female urogenital tract of pregnant women to assess the role(s) of these organisms in maintenance of health or in the cause of disease in these women and their babies. An understanding of the roles these organisms play in the health of the female urogenital tract will lead to better, more efficient prenatal and postnatal care, likely leading to diminished levels of preterm birth and infant morbidity and mortality.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: A Transgenerational e-Intervention for Gestational Diabetics and Their Offspring
PI: Wanda K. Nicholson
Institution: University of North Carolina at Chapel Hill
Grant No.: 1R21DK095189-01A1

Gestational diabetes, defined as glucose intolerance that first occurs or is first identified in pregnancy, is part of a vicious cycle that contributes to the epidemic of diabetes and obesity across generations. In utero alterations to fetal metabolism due to prolonged glycemic exposure have life-long consequences for the newborn; namely an eightfold risk of diabetes, obesity, and the metabolic syndrome. The expectant mother with gestational diabetes is at greater risk for long-term obesity and overt diabetes. In our pilot study, "Weight Loss Interventions after Delivery" (aka First WinD), we tested a postpartum-specific intervention that included face-to-face individual and group sessions. The intervention was successful in achieving weight loss over the study period, but two important issues were raised: (1) attending in-person visits proved challenging for participants, due to the competing demands of parenting and work; and (2) participants verbalized missed opportunities during pregnancy and delivery to learn about the implications of GDM for their own health and the well-being of their infants. Building on our experiences with First WinD, our objective is to develop and pilot-test a novel, theory-driven, multimodal intervention called e-GDM. E-GDM will address the logistical issues associated with

in-person visits by incorporating an alternative delivery model, but it may also be an effective way of addressing knowledge gaps of mothers about the downstream consequences of GDM. We propose a transgenerational approach to breaking the cycle of diabetes and obesity in gestational diabetics and their offspring. We propose an intervention that starts during pregnancy and extends seamlessly through the first 6 postpartum months—a critical metabolic period for the mother-child dyad. Our specific aims are to: (1) with input from women with current or recent GDM, develop a theory-driven healthy lifestyle intervention, e-GDM, that is delivered via state-of-the-art computer technologies, coupled with periodic in-person group visits; (2) conduct a small pilot RCT of the intervention versus usual care on (a) measures of maternal and infant outcomes, and (b) process outcomes; and (3) conduct a preliminary assessment of intervention effects to calculate effect sizes to design a larger scale trial. Maternal outcomes are A1C, postpartum weight loss (6 weeks–6 months postpartum). Infant outcomes are birth weight and 6 weeks, and 6 months weight and length z-scores, and waist circumference. Process outcomes are adherence/participation with protocol, improved eating behaviors and physical activity, postpartum depression symptoms, self-efficacy, social support, acceptability, and costs. If effective, our intervention could significantly change how GDM is currently treated in clinical practice.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Action for Health in Diabetes Continuation (Look AHEAD)**
PI: **Rena R. Wing**
Institution: **Miriam Hospital**
Grant No.: **2U01DK056992-15**

The aging of the population and the epidemic of obesity have led to a rapid increase in the number of older, obese individuals with diabetes. Little is known about the long-term health effects of lifestyle intervention designed to lower weight and increase physical activity in this population. This application, which responds to RFA-DK-12-502, is submitted by one of the 16 clinical centers in the Action for Health in Diabetes (Look AHEAD) Consortium. All 16 clinical sites and the Coordinating Center have submitted parallel applications. This application proposes to continue the Look AHEAD clinical trial as an observational cohort study and to follow participants with new assessments of the health problems of greatest concern in older, obese individuals with type 2 diabetes. We will test whether random assignment to 9–11 years of intensive lifestyle intervention, compared to a control condition of diabetes support and education, results in improvements in (1) physical function, impairment, and disability; (2) cognitive function and impairment; (3) diabetes control and microvascular complications; (4) late life depression; and (5) fractures and cancers. Secondary aims are to examine whether subgroup differences observed during the trial (which raised concern about possible unfavorable effects of intensive lifestyle intervention in those with a prior history of cardiovascular disease) endure and whether the excellent weight losses achieved in the intensive lifestyle intervention arm are maintained despite the absence of continued intervention activities. The continuation will also support ongoing ancillary studies, maintain infrastructure for new ancillary studies, and sustain thorough analyses and publication of the data collected by Look AHEAD. We will continue to follow the Look AHEAD cohort (approximately 4,000 participants) across the 16 clinical sites. Participants entered the trial 9–10 years ago when they were obese or overweight and aged 45–76, and were randomly assigned with equal probability to either an intensive lifestyle intervention that has induced sustained weight loss and increased physical activity or

control condition (diabetes support and education). Both arms have had excellent retention. Interventions were discontinued in September 2012, but follow-up of the cohort continues. This application will fund one additional clinic visit and ongoing telephone-based outcome assessment. This application builds on the remarkable success of the Look AHEAD in inducing and sustaining weight loss and retaining participants. The planned continuation addresses important public health priorities for a rapidly growing and understudied segment of the U.S. population in a cost-effective manner, leveraging the extensive resources available from Look AHEAD.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Brain Imaging-Based Strategies for Treating UCPPS Pain**
PI: **Apkar Vania Apkarian**
Institution: **Northwestern University**
Grant No.: **1R01DK100924-01**

This is a one-year R01 application in response to RFA-DK-12-025, entitled Urologic Chronic Pelvic Pain Syndrome (UCPPS) Research (R01). There are no effective treatments for UCPPS. Recent preliminary results from the Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network indicate global and local brain anatomical and functional abnormalities in men with UCPPS. Thus, renormalization of the urological pain-related brain reorganization is a viable and objective target for treating UCPPS. Our recent human studies in other chronic pain conditions indicate that placebo alone may be an efficient treatment in some patients. Also, our animal studies show that D-cycloserine (DCS, targeting the frontal cortex) can reverse many of the signs of neuropathic pain in rodents. These results indicate that urological pain relief by placebo and by DCS are potential therapy options for UCPPS, each of which may be mediated through distinct brain circuitry. Here we test the efficacy of DCS and placebo, in comparison to each other and to no-treatment, in a double blind, three-armed, brain imaging-based randomized clinical trial in men with UCPPS. Brain anatomy and function are monitored repeatedly, and urological pain is measured with questionnaires and using a smart phone App (to collect pain ratings in the natural setting of everyday life, 3 times a day). Participants undergo a 2-week observation period, a 3-month treatment period, a 2-week washout period, and a final period wherein participants choose to continue on one of the two treatments for another month. The trial will permit us to address three specific aims: Aim 1: Evaluate differential efficacy for UCPPS urological pain relief between placebo and DCS. Aim 2: Evaluate differential brain functional biomarkers for treatment response and treatment propensity, for placebo and for DCS. Aim 3: Demonstrate that brain morphology renormalizes in treatment responders. Given the financial and time constraints of this RFA, the study is powered to be a proof of concept and to demonstrate the strength of the methodology in providing objective evidence for individualized treatment choices when evaluating novel therapies in UCPPS.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Cyclosporine in Interstitial Cystitis: Efficacy, Safety and Mechanism of Action
PI: Daniel Shoskes
Institution: Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Grant No.: 1R01DK100936-01

Interstitial cystitis (IC), also referred to as painful bladder syndrome (PBS), is a condition with significant impact on quality of life. Therapy with oral cyclosporine A (CyA) has shown some efficacy in this condition and is a fifth-line therapy in the Guidelines of the American Urological Association. However CyA is a toxic drug with known nephrotoxicity and potential for hypertension, infection, and neurotoxicity. While CyA is an immunosuppressive drug, it-s target of action, calcineurin, is also present in neural cells suggesting that the effect of CyA on the symptoms of IC may be neurally modulated as well. We propose a prospective open-label study of CyA in patients with IC with careful clinical monitoring of efficacy, features of disease (UPOINT phenotype) that leads to treatment success, monitoring of drug levels, detailed monitoring of renal function, monitoring of changes in nerve function, and measuring changes in inflammatory mediators in the blood and urine that indicate successful outcomes of cyclosporine treatment. Thirty adults with IC/PBS who have failed at least 2 other classes of medical therapy will be enrolled in an open-label, 3-month trial of oral CyA, starting at 3 mg/kg/day in 2 divided doses. Patients will be assessed pretreatment, at 3 months and 1–2 months after stopping. We will first examine the clinical efficacy and side effects of cyclosporine treatment in patients with IC/PBS refractory to first-line therapies. Patients will be assessed with C2 blood levels for dose adjustment. Renal function will be assessed with a nuclear GFRs. Patients will be clinically phenotyped with the validated UPOINT system and clinical outcomes correlated to the phenotype. We will then measure the effects of cyclosporine treatment on current perception and pain threshold using a Neurometer before, during, and after treatment. Hyperalgesia will be assessed for sensation perception and pain threshold at 3 frequencies that measure function of 3 nerve types (C, A-delta, A-beta fibers). We expect symptom improvement to correlate with reduction in hyperalgesia, especially in the C fibers. Finally, we will identify changes in inflammatory mediators in the blood and urine of IC/PBS patients that indicate successful outcomes of cyclosporine treatment. RNA and protein will be extracted from blood and urine samples before, during, and after therapy. Gene expression and protein signatures will be compared between patients' pretreatment and 15 normal controls to identify candidate biomarkers. ELISA will test protein levels of inflammatory mediators and proteins that have been shown to be increased in the urine of IC/PBS. These genes and proteins will be following, during, and after therapy, and changes correlated with degree of clinical improvement. We hope to show that CyA can be an effective therapy for recalcitrant IC/PBS, which can be safely administered with appropriate monitoring and identify which patients benefit most from treatment.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Diabetes Prevention Program Outcomes Study
PI: Marinella Temprosa
Institution: George Washington University
Grant No.: 5U01DK048489-20

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 multicenter, 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 short-term 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. This application is designed to support completing the second five-years of DPPOS, focusing on complications that require more time to develop.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Genetics and Genomics of Maternal Glycemia During Pregnancy
PI: William L. Lowe
Institution: Northwestern University
Grant No.: 1R01DK097534-01A1

The intrauterine milieu of the developing fetus, as determined largely by maternal metabolism, impacts not only outcome at birth but later outcomes as well. Offspring of mothers with preexisting or gestational diabetes mellitus (GDM) have an increased risk of metabolic disorders in childhood, including obesity, impaired glucose tolerance, and higher lipid levels. Maternal glucose levels less than those diagnostic of GDM may impose similar risks later in childhood and adulthood. Maternal metabolism is determined by both genetic and environmental factors. As a first step in defining factors that impact maternal metabolism, we used genome-wide mapping to identify genetic loci associated with measures of maternal metabolism in four different race groups (Northern European ancestry, Afro-Caribbean, Thai, and Mexican-American). This was done using DNA samples and phenotype data collected as part of the

Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study, an observational study which addressed the hypothesis that hyperglycemia in pregnancy less severe than overt diabetes is independently associated with increased risk of adverse maternal and neonatal outcomes. Meta-analysis across the four race groups identified seven loci, which demonstrated genome-wide significant (i.e., p-value $< 5 \times 10^{-8}$) association with maternal fasting or 2 hr. glucose levels or fasting C-peptide during an oral glucose tolerance test. Two of these loci have not previously been reported to be associated with metabolic traits in genome-wide association studies. We now propose to build upon these initial observations by addressing the hypothesis that common, low-frequency and rare genetic variants contribute to the defined associations and that the functional consequence of many of the causal variants will be altered gene expression. To address this hypothesis, we will perform the following specific aims. (1) To use targeted genomic capture and next-generation sequencing to identify additional common as well as low-frequency and rare variants within four of the associated loci. This will be done using DNA from Northern European ancestry, Thai, Mexican-American, and Afro-Caribbean HAPO mothers with values of fasting or 2 hr. glucose or fasting C-peptide in the lowest and highest deciles of values for the specific trait. (2) To prioritize variants for further characterization using a large and comprehensive suite of existing tools and publically available functional genomics datasets to infer potential function for each variant. (3) To use high-throughput approaches to define the functional impact of variants prioritized in Aim 2, with a focus on those predicted to affect gene expression. (4) To demonstrate that variants which have a functional impact are associated with the different metabolic traits by genotyping the identified SNPs in up to 12,000 additional HAPO mothers from the four race groups. Accomplishing these aims will provide fundamental new insight into genetic factors regulating maternal metabolism during pregnancy, which has important implications for fetal outcome and, more importantly, long-term health outcomes of both the mother and her offspring.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Role of TRPA1 & TRPV1 in Pain and Voiding Symptoms in a New Mouse CP/CPPS Model**
PI: **Charles J. Bieberich**
Institution: **University of Maryland, Baltimore County**
Grant No.: **1R01DK100908-01**

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) affects as many as 16% of men and has enormous quality of life and economic consequences. Currently, there is a dearth of treatment options to manage the pain and voiding symptoms that typically accompany this disease. The development of effective therapies can be greatly facilitated by the development and deployment of small animal models that recapitulate key pathological features of human CP/CPPS. We have recently developed a transgenic mouse CP/CPPS model based on inducible expression of the pro-inflammatory cytokine IL-1β in the prostate gland. These mice develop chronic prostatitis that can be regulated by administration of doxycycline in the drinking water, and show clear evidence of inflammatory pain and changes in micturition pattern. The overarching goal of the work proposed here is to dissect the molecular basis of the inflammatory pain and voiding symptoms to inform new therapeutic strategies to treat this disease. We propose to determine the roles played by two transient receptor potential channels (TRP), TRPA1 and TRPV1, in mediating physiological responses to prostatic inflammation. Both TRPA1 and TRPV1 are activated by agents produced in inflammatory environments and mediate

inflammatory symptoms in other tissues. We will approach this problem from a multidisciplinary perspective, bringing together the expertise of a mouse developmental geneticist who specializes in developing mouse models of prostate disease and a mouse sensory neurophysiologist who specializes in the function of TRP channels. The successful completion of the proposed work will determine whether TRPA1 and/or TRPV1 are viable therapeutic targets to treat human CP/CPPS symptoms, and will provide a new paradigm to dissect the role of any gene in the etiology or progression of this disease.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Serotonin in Stress-Induced Bladder Hypersensitivity**
PI: **Meredith T. Robbins**
Institution: **University of Alabama at Birmingham**
Grant No.: **1R01DK100904-01**

The present set of studies seeks to determine whether serotonergic systems exert differential effects on nociceptive processing in models of deep tissue hypersensitivity. A single Specific Aim is thus proposed: To characterize the effect of stress and a systemically administered SSRI and SNRI on both bladder and somatic sensory processing in female rats with and without pristane-induced arthritis. The initial experiments will expand upon preliminary studies and will assess the effect of systemic administration of an SSRI, paroxetine, and an SNRI, milnacipran, on stress-induced bladder hypersensitivity, measured by urinary bladder distension-evoked (UBD) visceromotor reflex responses (VMRs), following chronic exposure to a psychological stressor, water avoidance. Somatic nociception and locomotion will also be measured in these animals. A second set of experiments will examine whether exposure to chronic psychological stress alters mechanical paw withdrawal threshold and locomotion in rats with pristane-induced arthritis and will ascertain the effect of both reuptake inhibitors on stress-induced changes. Nociceptive responses to bladder distension will also be measured in these animals to determine whether comorbidity with a somatic disorder alters effects of serotonin reuptake in visceral systems. The proposed studies will not only provide insight into the role of stress as a potential exacerbator of multiple types of deep tissue pain but will also yield a better understanding of serotonergic systems related to pain modulation. By utilizing two separate animal models these studies will be some of the first to define the relationship between stress and symptom exacerbation in pains with both visceral and somatic origins. By using two different classes of drugs, these studies will give a clinically relevant comparison of currently available drug options.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **The role of DAMPS in painful bladder syndrome**
PI: **Fletcher A. White**
Institution: **Indiana University–Purdue University Indianapolis**
Grant No.: **1R01DK100905-01**

Bladder pain syndrome (BPS or interstitial cystitis, IC) patients typically exhibit marked tenderness of pelvic floor musculature, and treatments directed solely at those muscles often resulted in marked improvement of bladder symptoms. This debilitating syndrome of unknown etiology is often postulated, but not proven, to be associated with microbial infection. To better understand the mechanisms that contribute to BPS/IC, we will study an animal model in which

pelvic floor muscle injury alone (somatic injury) the degree to which damage-associated molecular patterns (DAMPs) signal through neuronal receptors that recognize pathogen-associated molecular patterns (PAMPs). A potential neurobiological mechanism for the behavioral changes observed with this injury model is the increased nociceptive signaling present in bladder-associated sensory ganglia. To this end, validation of our injury paradigm in the rodent as an experimental representation of BPS/IC provides us with a number of parameters with which to test potential mediators of somatic and visceral hypersensitivity. Furthermore, the outcomes of these proposed experiments may also provide potential therapeutic targets. Taken together, the use of a clinically-relevant animal model will provide us with the unique opportunity to improve PBS/IC diagnostic and treatment paradigms and increase the understanding of the mechanisms underlying the development and maintenance of chronic pelvic pain conditions in women.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Treatment of Bladder Pain by Novel Glycosaminoglycan Derivatives**
PI: **Siam Oottamasathien**
Institution: **University of Utah**
Grant No.: **1R01DK100868-01**

Interstitial cystitis (IC)/painful bladder syndrome (PBS) is a debilitating chronic urologic condition. Over 3 million women above the age of 18 in the U.S. suffer from unrelenting pelvic pain, significant urinary symptoms, recurring urinary infection, bladder fibrosis, and renal failure. In 2007, the cost and disease burden associated with IC/PBS was analyzed by the Urologic Diseases in America Project and found to exceed $750 million annually. We have developed a mouse model of inflammatory cystitis utilizing LL-37, a natural antimicrobial peptide produced in the genitourinary system. Our model recapitulates key aspects of IC/PBS including the induction of profound bladder inflammation, production of bladder-specific pain, urothelial cell injury, glycosaminoglycan (GAG) layer dysfunction, and accumulation of mast cells. To further establish the physiologic relevance of LL-37 induced cystitis, our group has shown that human urinary LL-37 levels were significantly elevated in pediatric spina bifida patients. In addition within our mouse model, we've demonstrated LL-37 could elicit profound dose dependent bladder inflammation involving the urothelium. Furthermore, the propagation of inflammation involves mast cells in a dose-dependent fashion. Mast cells have been well described to be a central cell type mediating pain in patients with IC/PBS. The exact role of mast cell mediated bladder pain in LL-37-induced cystitis remains unclear and will be further investigated in the proposed research. We hypothesize that LL-37-induced cystitis pain intimately involves mast cells. This hypothesis will be tested in Specific Aim 1, by elucidating mast cells as a key effector cell type utilizing our surrogate model. From a therapeutic standpoint, our group has developed novel patented compounds known as semisynthetic glycosaminoglycan ethers (SAGEs) that attenuate the inflammatory effects of LL-37 by direct immune modulation and interference with mast cell activation. Our preliminary data suggests treatment with SAGE compounds truncates both inflammation and pain observed in LL-37-induced cystitis. The exact mechanism behind how our SAGEs inhibit mast cell derived bladder pain remains unclear and will be further investigated in the proposed research. We hypothesize that mast cell mediated cystitis pain can be attenuated with SAGE compounds. This hypothesis will be tested in Specific Aim 2, by investigating SAGE attenuation of mast cell mediated bladder pain. This integrated proposal is innovative with high impact because it will further

define mast cell driven cystitis pain and provide detailed knowledge about the pain attenuation properties of our SAGE compounds. These data also provide significant opportunity with a high likelihood of success to further develop novel SAGE compounds as potential pharmaceutical interventions to attenuate not only inflammation associated with IC/PBS but inhibit mast cell mediated bladder pain.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Urinary Metabolites in IC PBS Diagnosis**
PI: **Jayoung Kim**
Institution: **Cedars-Sinai Medical Center**
Grant No.: **1R01DK100974-01**

The goal of this project is to identify and validate interstitial cystitis/painful bladder syndrome (IC/PBS)-associated urinary metabolites. IC/PBS is a debilitating condition that presents with a constellation of symptoms including bladder pain, urinary urgency, frequency, nocturia, and small voided volumes in the absence of other identifiable etiologies. The diagnosis of IC/PBS remains dependent on subjective parameters, leading to extreme difficulties in accurately phenotyping patients. Our central hypothesis is that IC/PBS-associated metabolites in the urine of IC/PBS patients can segregate patients from control subjects, and that their levels are correlated with clinical symptoms. This hypothesis is based on our proton nuclear magnetic resonance (NMR) spectroscopy findings identifying urine metabolites that appear to stratify IC/PBS patients from healthy controls. We propose to substantially build on these results and determine whether candidate urine metabolites are diagnostic indicators of IC/PBS. To test this hypothesis we will (Aim 1) identify IC/PBS-associated metabolites in urine using two independent platforms, proton NMR spectroscopy and quadrupole time-of-flight (Q-TOF) mass spectrometry. We will determine whether candidate metabolites segregate IC/PBS patients from control subjects and are associated with clinical severity, including chronic bladder pain. In order to achieve a deeper understanding of the underlying biological nature of this condition, we will identify pathologic networks associated with IC/PBS using integrative bioinformatics. We will also (Aim 2) create a Cedars-Sinai Medical Center IC/PBS urine biorepository and will conduct preliminary validation studies of IC/PBS metabolites. Our long-term goals include the identification of diagnostic urinary biomarkers that can serve as noninvasive and accurate means of diagnosing IC/PBS and stratifying these patients from patients with other bladder or pelvic floor conditions. We also seek in the long-term to validate molecular targets for therapeutic strategies. This study has a significant potential clinical impact because results may lead to clinical methods to increase diagnostic accuracy and an improved understanding of the molecular basis of IC/PBS and its relationship to urologic conditions with overlapping symptoms.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Validation in Transgenic Animal Models of Clinical Correlates of IC/PBS
PI: Yi Luo
Institution: University of Iowa
Grant No.: 1R01DK100891-01

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic inflammatory condition of the urinary bladder characterized by symptoms of chronic pelvic pain and urinary frequency and urgency in the absence of other identified etiologies for these symptoms. IC/PBS is a significant disease and can severely affect quality of life. Since the etiology of IC/PBS remains unknown, current treatments are largely empirical and vary in their efficacy. To improve patient care, novel therapies are greatly needed. A valid animal model is required for deciphering the mechanistic insights of the disease for therapeutic development. Based on accumulating evidence supporting a component of inflammation/autoimmunity in at least a subset of IC/PBS patients, we have developed transgenic cystitis models (URO-MCP-1 and URO-OVA) to facilitate the studies of the human disease. The URO-MCP-1 model secretes monocyte chemotactic protein-1 (MCP-1) by the urothelium and mimics the hypersensitive bladders of IC/PBS patients. By contrast, the URO-OVA model expresses a membrane form of the model antigen ovalbumin (OVA) as a self-antigen on the urothelium and mimics immune/autoimmune bladder inflammation in certain IC/PBS patients. The two models represent two distinct pathogenic pathways (LPS-induced vs. autoimmune-based cystitis); however, they appear to share a common central inflammatory response and replicate many clinical correlates seen in IC/PBS patients. Moreover, these models are responsive to immunomodulatory agents, offering unique potential for therapeutic development. The fundamental goal of this study is to validate the clinical relevance of the animal models for future clinical trials. The validation will be conducted in multiple aspects based on clinical findings in IC/PBS patients. These will include the hallmark symptoms of pelvic/bladder pain and urinary frequency and urgency, potential key biomarkers, and cortisol dysregulation (Aim 1). In addition, we will also develop mechanism-specific targeted therapy for bladder inflammation. Novel therapies consisting of both systemically and locally acting immunomodulatory agents (mNOX-E36 and RDP58) will be formulated for treating bladder inflammation in the animal models (Aim 2). It is our expectation that at the completion of this study, we will have validated the relevance of the animal models and developed novel pharmacological therapies for bladder inflammation in these models. A valid animal model is critical for better understanding of the mechanisms behind IC/PBS and for developing effective interventions for this refractory human disease.

IC: National Institute of Environmental Health Sciences
Title: Ex Vivo Female Reproductive Tract Integration in a 3D Microphysiologic System
PI: Teresa K. Woodruff
Institution: Northwestern University at Chicago
Grant No.: 5UH2ES022920-02

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 acts 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 individual 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.

IC: **National Institute of General Medical Sciences**
Title: **Pharmacogenetics of Phase II Drug Metabolizing Enzymes**
PI: **Richard M. Weinshilboum**
Institution: **Mayo Clinic, Rochester**
Grant No.: **5U19GM061388-14**

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 of the 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.

IC: **National Institute of Mental Health**
Title: **Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia**
PI: **Deanna L. Kelly**
Institution: **University of Maryland, Baltimore**
Grant No.: **5R01MH090071-03**

Risperidone is available generically and is 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 toward better tailoring and personalizing antipsychotic treatment, particularly for women who suffer from these problems.

IC: **National Institute of Mental Health**
Title: **Sex Differences in Acute Estradiol Regulation of the Synaptic Proteome**
PI: **Catherine S. Woolley**
Institution: **Northwestern University**
Grant No.: **1R21MH099572-01**

The long-term goal of this research is to identify molecular targets that could be used for new mental health therapeutics, particularly for affective disorders that differ between the sexes. We will approach this goal by identifying synaptic proteins that are acutely regulated by estradiol (E2) and/or agonists selective for the β form of the estrogen receptor (ER-β) in the hippocampus of adult male and female rats. The rationale for this approach is as follows: First, the hippocampus is a brain region implicated in affective behaviors, and E2 or ER-β agonists infused directly into the hippocampus acutely decrease anxiety-related behaviors in females but not in males. Second, there is strong evidence that E2 is produced locally as a neurosteroid in the hippocampus of both sexes, providing a physiological source of E2 that could acutely modulate affective behavior in vivo. Third, we have found that E2 and ER-β agonists have differential effects on synaptic transmission in the hippocampus of males and females with the same time course as their effects on anxiety-like behavior in females. These findings support the idea that sex differences in acute ER-β-dependent synaptic modulation in the hippocampus could contribute to sex differences in anxiety-like behaviors. An essential step in moving these behavioral and electrophysiological studies toward future, focused efforts to develop novel mental health therapeutics is to identify specific molecular mechanisms that act downstream of acute E2-ER-β signaling to modulate hippocampal synaptic physiology and behavior. Here, we propose to use two unbiased and complementary proteomics approaches to identify synaptic proteins that are acutely regulated by E2 and/or ER-β agonists in the hippocampus of male and female rats. In Aim 1, we will use two dimensional difference in gel electrophoresis followed by mass spectrometry to identify synaptic proteins that are differentially regulated by acute ER-β activation in the hippocampus of males vs. females. In Aim 2, we will use strong cation exchange chromatography and titanium dioxide enrichment of phosphopeptides, followed by mass spectrometry to identify synaptic proteins that are differentially phosphorylated by acute ER-β activation in the hippocampus of males vs. females. Upon completion of this project, we will have a broad and unbiased profile of synaptic proteins, the levels, and/or phosphorylation of which differ between males and females, and/or that are differentially regulated by acute ER-β activation in the hippocampus of males vs. females. Because we will use treatments and timing that are the same as in ongoing behavioral and electrophysiological studies, we will be able to relate specific molecular changes that we discover with proteomics to sex differences in regulation of anxiety-like behaviors and of synaptic function in the hippocampus. Discovery of sex-specific mechanisms of synaptic protein regulation in the hippocampus could identify biomarkers for susceptibility to affective disorders and ultimately lead to sex-specific treatments.

IC: National Institute of Mental Health
Title: Sex Differences in Stress-Induced Genome-Wide Transcriptional Profiles
PI: Scott J. Russo
Institution: Icahn School of Medicine at Mount Sinai
Grant No.: 1R21MH099562-01

Depression and anxiety disorders are large health burdens to our society with reported yearly prevalence rates of 9%–18% in the general population. Although women are twice as likely to suffer from depression or anxiety and exhibit more severe symptoms, the great majority of studies at the basic science level have used only male rodents to determine the underlying biological mechanisms. As a consequence, there is far less known about the mechanisms of depression in females. Here we use the chronic variable stress (CVS) paradigm, a model that induces robust depression- and anxiety-like behavior in mice. Our findings show that females are more sensitive to CVS than males on 5 established depression and anxiety behavioral and neurochemical domains. For example, females exhibit greater immobility on the forced swim test (FST), anhedonic responses on sucrose preference tests (SPT), decreased time grooming on the splash test, increased latency to feed on novelty suppressed feeding (NSF), and increased serum corticosterone levels. Although the direct mechanisms driving these sex differences are unclear, we used RNA sequencing and found that there are approximately 800 genes regulated by CVS in males and females, and less than 3% of them overlap. Interestingly, CVS regulates more genes in males than females, suggesting that the lack of behavioral response in males may not be a passive one. Rather, males may engage alternate transcriptional pathways providing a mechanism for acting coping. In this application, we will measure the detailed sex differences in stress-induced changes across the transcriptome using high-resolution, paired-end RNA sequencing and advanced bioinformatics analysis to identify splicing events, alternative promoter usage, and microRNA processing. All data sets will be further analyzed into functional biological clusters to determine sex differences in the major pathways regulated by stress. We believe that this work will provide an enormously important resource of information for future stress studies and initiate a program to test the functional relevance of these transcriptome differences. The latter will aide in the development of new personalized anti-anxiety and anti-depression therapeutic strategies.

IC: National Institute of Mental Health
Title: Specificity and Validity of Oxidative Stress Model of Chronic Fatigue Syndrome
PI: Dikoma C. Shungu
Institution: Weill Cornell Medical College of Cornell University
Grant No.: 1R01MH100005-01

Chronic fatigue syndrome (CFS) is a complex multi-system disorder, which is often misdiagnosed as a psychiatric illness. As a result, the diagnosis of CFS is highly controversial. Discovery of CFS-specific biomarkers that can differentiate the disorder from phenotypically similar psychiatric conditions, such as major depressive disorder (MDD), could thus have a profound impact, not only for how the disorder is generally perceived and managed, but also for the development of objective diagnostic tests, for identification of new therapeutic targets, as well as for advancing scientific understanding of CFS. Recently, using advanced magnetic

resonance neuroimaging techniques and a standardized battery of clinical assessments in 15 patients with CFS, in 15 patients with MDD, and in 13 healthy controls, the applicants discovered strong experimental evidence, including a mean deficit of 36% in the most abundant antioxidant in living tissue, glutathione (GSH), increased ventricular cerebrospinal fluid (CSF) lactate, and decreased regional cerebral blood flow (rCBF) compared to controls, which suggested increased oxidative stress as a pathophysiological model of CFS. However, while highly promising and intrinsically consistent, both the validity and the specificity of this oxidative stress hypothesis for CFS remain uncertain, as (a) the essential findings of the study have yet to be replicated, and (b) the same types of abnormalities were found in MDD compared to controls. On the other hand, with comparisons revealing trend-level differences between CFS and MDD, the investigators hypothesized that limited sample size, coupled with the inherent clinical heterogeneity of the two disorders, likely limited the power of their pilot study to detect potential differences between the two disorders. Therefore, to address this potential limitation and to attempt objective differentiation of CFS and MDD—a daunting and continuing challenge—the investigators propose: (1) to replicate in larger cohorts the results of their pilot neuroimaging study that suggested the oxidative stress hypothesis of CFS; (2) to extend the support and evidence base for the model through measurements of several established markers of oxidative stress in plasma, urine, and CSF samples from all the subjects; (3) to correlate the resulting objective outcome measures with clinical indices of overall health and functional disability in all subjects; and (4) to attempt to decrease the inherent clinical heterogeneity in both the CFS and MDD groups through stratification or subtyping techniques based on clinical variables that are unique to each disorder, and then to compare the outcome measures between the resulting subgroups. The expectation is that this approach would identify subgroups of CFS and MDD patients between which significant differences in outcome measures exist that can enable objective differentiation of the two disorders, thereby establishing the outcome measures as bona fide diseases biomarkers, and supporting oxidative stress as a valid and specific pathophysiological model for CFS.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Hispanic Stroke Prevention Intervention Research Program**
PI: **Ralph L. Sacco**
Institution: **University of Miami Miller School of Medicine**
Grant No.: **3U54NS081763-01S1**

Hispanics are the largest minority group and by 2050 will be constitute 30% of the U.S. population. Although Mexican Americans are the largest subgroup, Caribbean Hispanics are the second largest subgroup in the U.S. The aging and rapid growth of the Hispanic population will lead to increases in the impact of stroke. Innovative strategies are needed to reduce stroke risk and eliminate disparities among Hispanics. Our Hispanic Stroke Prevention Intervention Research Program is a collaborative application from the University of Miami and the University of Puerto Rico aimed at reducing stroke disparities in the Hispanic community. The central theme of our program is risk factor control among Hispanics at risk of stroke. In project I, we will assess in a randomized trial the effectiveness of an innovative secondary stroke prevention intervention program to improve the control of risk factors, using a health care delivery model that has been successful for chronic disease management in minority communities, integrates pharmacists in the enhancement of adherence, and uses state-of-the-art mobile information technology. In project II, we will systematically evaluate the determinants of blood pressure

variability and glucose control among high-risk Hispanic family members of stroke patients. We will assess novel psychosocial, sociocultural, healthcare system, and biological variables as part of a conceptual model that incorporates psychosocial adversities, reserve capacity, and cumulative vulnerabilities as determinants of 24-hour blood pressure variability. In project III, we will create the Florida Puerto Rico Stroke Registry by collating data from 140 hospitals that are currently collecting Get With the Guidelines-Stroke data to help identify stroke disparities by race, ethnicity, and region and educate stakeholders in approaches to improve stroke quality regarding stroke disparities. Our program includes three cores: administrative core, the research/education training core, and the data management and statistics core. Our multidisciplinary program unites investigators across two minority-serving institutions, addresses significant gaps in our knowledge of stroke risk in Hispanics, and will provide results that can have an immediate impact on future primary and secondary stroke prevention efforts.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Los Angeles Stroke Prevention/Intervention Research Program in Health Disparities**
PI: **Barbara G. Vickrey**
Institution: **University of California, Los Angeles**
Grant No.: **3U54NS081764-02S2**

The Los Angeles Stroke Prevention/Intervention Research Program in Health Disparities is a partnership of UCLA, four medical centers in the Los Angeles County safety net system, Healthy African American Families, and representatives from multiple community organizations serving low-income minority communities that span the Los Angeles basin. In this most diverse county in the US in race/ethnicity, we propose a multidisciplinary, highly collaborative Program to create and test sustainable interventions to reduce or eliminate racial and ethnic disparities in the occurrence of stroke, and to generate new knowledge about mechanisms for such disparities. Project I creates a strong community-based component with community health workers and mobile health technology to create a full-fledged Chronic Care Model intervention that will be tested relative to usual care in 500 patients with a recent stroke seen in the Los Angeles County safety net. A cost analysis and a formative evaluation will guide development of a financial sustainability plan. Project II will elucidate the role of novel biological and social risk factors for stroke risk and trends over time, in a national dataset. Project III builds on an existing close partnership with the City of Los Angeles Department of Aging to develop and test a culturally tailored behavioral stroke risk factor reduction/walking intervention—delivered by senior center staff—with 240 high-risk seniors from Korean, Chinese, African-American, and Hispanic racial/ethnic groups. Four cores include an Administrative Core A that supports all three projects; a Research Education and Training Core B that will recruit, retain, and develop stroke disparities-relevant curriculum for academic researchers, community research support personnel, and other community stake holders; a Biomarker Collection and Analysis Core C to support Projects I and III biomarker data collection, consulting for all three projects, and development of educational programming on biomarkers; and a Community Engagement, Outreach, and Dissemination Core D that supports and interacts with all three projects by promoting and sustaining community-academic partnerships through bidirectional knowledge sharing and by creating strategies for disseminating advances in knowledge about stroke prevention disparities research through outreach to affected communities locally and nationally.

Research Enhancement Awards Program

IC: National Cancer Institute
Title: Early Life Determinants of Accelerated Pubertal Development in Adolescent Girls
PI: Ai Kubo
Institution: Kaiser Foundation Research Institute
Grant No.: 1K07CA166143-01A1

Dr. Kubo's long-term career goal is to understand early-life determinants of cancer risk factors that relate to obesity and metabolic dysregulation, and to identify high-risk subpopulations that can benefit from early intervention strategies. Her primary research aim is to examine whether factors such as intrauterine exposure to maternal gestational diabetes (GDM), excessive gestational weight gain, obesity, and rapid infant weight gain increase the risk of accelerated pubertal onset in adolescent girls, an important breast and reproductive cancer risk factor. Her secondary aim is to explore the causes of the observed racial/ethnic differences in timing of puberty. No previous studies have examined these associations. These research goals will take advantage of electronic health data that are available in Kaiser Permanente Northern California (KPNC), a large integrated health plan that covers about 450,000 girls. Two specific approaches are proposed: (1) Linkage of mothers' and daughters' electronic health data in an ongoing prospective study of predictors of sexual maturation in adolescent girls (U01 ES/CA019435) (Study 1); and (2) Establishment of a new cohort of 20,000 multiethnic mother-daughter pairs using the electronic databases within KPNC (Study 2). Study 1 will utilize data from the CYGNET study (PI: Lawrence H. Kushi, ScD), which has been following 444 girls annually since 2005 with extensive information on pubertal development and anthropometric measures. The KPNC GDM and Pregnancy Glucose Tolerance Registry (Director: Assiamira Ferrara, MD, PhD) will be linked to the CYGNET data to accomplish study 1. In addition, the Registry will be used to establish a new cohort of mother-daughter pairs. This will allow Dr. Kubo to gain experience and skills in establishing and following a cohort based on KPNC electronic medical record data, and to explore racial/ethnic differences in pubertal onset. Electronic documentation of Tanner stage (an established five-stage classification scheme to assess pubertal development) from routine pediatric visits has recently been implemented at KPNC, and this availability on a large and diverse pediatric population makes this study unique and innovative. The candidate's research goals will be complemented with formal, mentored training through coursework and tailored tutorials in pediatric endocrinology, intergenerational transmission of metabolic dysregulation, advanced biostatistics, cancer prevention and health disparities, and responsible conduct of research. KPNC's Division of Research is an ideal environment for the proposed training because it provides unique and extensive electronic databases, access to data from a large, multiethnic membership, and internationally recognized multidisciplinary experts. The planned scientific training and mentorship will build on the candidate's previous training in nutrition and cancer epidemiology, and uniquely position her to attain her goals. The proposed studies will provide crucial skills in establishing a new cohort, providing a platform for Dr. Kubo to develop successful R01 research to further elucidate early life determinants of pubertal onset and other cancer risk factors.

IC: National Cancer Institute
Title: Genetics of Mammographic Density in Ashkenazi Jews
PI: Elad Ziv
Institution: University of California, San Francisco
Grant No.: 1R21CA179442-01

Mammographic density (MD) is a strong risk factor for breast cancer and is also a highly heritable trait with ~ 60%–70% of the variance due to genetic factors based on twin studies. MD is also higher in families with a strong history of breast cancer. Genome-wide association studies (GWAS), which focus on common genetic variants, have identified several single nucleotide polymorphisms (SNPs) associated with MD. However, these SNPs explain a very small fraction of the variance of MD, suggesting many other genes are involved. Linkage studies have identified some loci that may be associated with this trait, but no genes have been mapped yet by linkage analysis. Thus, the vast majority of the heritability of mammographic density remains unexplained and is likely due to rare variants. We have recently identified an association between higher mammographic density and Ashkenazi Jewish ancestry. Since Ashkenazi Jews are a founder population, genetic mapping in this population may have several advantages. In particular, Ashkenazi Jews share extensive chromosomal segments that are identical by descent (IBD) due to a small number of founders. We propose to leverage the IBD segments to help map loci for mammographic density. In particular, we plan to search for regions that are IBD among Ashkenazi Jewish women in the top quintile of age and body mass index (BMI)-adjusted mammographic density for shared IBD segments and compare these to Ashkenazi Jewish women in the lowest quintile of age and BMI-adjusted mammographic density. We will then select the top regions and sequence them in the high-density women and low-density comparison group to identify the genetic variants most likely to be associated with this trait.

IC: National Cancer Institute
Title: Role of Obesity and Breast Fat Tissue Inflammation in Breast Cancer Promotion
PI: Marta Torroella-Kouri
Institution: University of Miami Miller School of Medicine
Grant No.: 1R21CA176055-01

The purpose of the present application is to generate the initial data on the plausible role that local breast adipose tissue may have in breast cancer progression in conditions of obesity/overweight. To do this, we will use diet-induced obesity mouse models of breast cancer. This work is a natural complement and extension of our ongoing NIH-funded work. Most studies linking obesity and cancer have focused on the systemic effects of adiposity. Particularly in breast cancer, little attention has been paid to whether obesity also promotes this disease through its effect on local adipose tissue inflammation and innate immune signaling in the breast—where cancer occurs. We propose that in conditions of obesity/overweight the local adipose tissue in the breast becomes inflammatory and contributes to cancer development in great part by recruiting larger numbers of tumor-promoting inflammatory macrophages to the breast tumor microenvironment. We will use an innovative experimental design to examine our hypothesis in diet-induced obese mice. We will gauge breast adipose tissue's capacity to promote tumor development using two other well-known fat depots as reference: visceral and subcutaneous fat depots, which exhibit high and low degrees of inflammation, respectively. To do this, we will

analyze tumor progression, macrophage recruitment, and production of inflammatory molecules in tumors arising from tumor cells implanted on these fat locations. Finally, we will use a novel compound belonging to a new family of small molecules discovered by our team. These molecules—termed leukadherins—reduce inflammation via activation of Mac-1 integrin. We will use Leukadherin-1 (LA-1), the most potent of the leukadherins, in an in vivo setting to examine its impact on tumor progression and macrophage recruitment. For this, we will treat obese and lean tumor-bearing mice with increasing doses of this compound. Also, we will in vitro pretreat macrophages with different concentrations of LA-1 to determine whether this compound modulates macrophage's inflammatory signaling pathways and expression of inflammatory molecules. We envision that results from the present proposal will enable us to reveal the existence of a role for local breast adiposity and related molecules in obesity. Importantly, our work will also serve as means to assess the effect of these novel anti-inflammatory compounds in the control of breast cancer. A high-fat diet, overweight, and reduced physical activity are common lifestyle aspects among African American and Latina women that increase cancer risk—these minority women also exhibit more aggressive breast cancers with less favorable prognosis. The experiments proposed in this application address in an innovative fashion the nature and control of breast adipose tissue inflammation and its impact in breast cancer within obesity. There is an urgent need to build up studies to better understand the biology of cancers across ethnicities, and to develop tools that will more accurately predict their prognosis and design their customized treatment strategies.

IC: **National Institute on Aging**
Title: **Hot Flashes and Memory Dysfunction in the Perimenopause**
PI: **Miriam T. Weber**
Institution: **University of Rochester**
Grant No.: **1R03AG045612-01**

The overall aim of this investigation is to determine if vasomotor symptoms (VMS: hot flashes and night sweats) are a mechanism for memory changes in the transition from premenopause to perimenopause to postmenopause. The menopausal transition (MT) is associated with subtle declines in processing speed, motor function, verbal fluency, and verbal episodic memory1–4. Evidence suggests a direct influence of hormonal transitions on these sexually dimorphic cognitive domains, though the exact mechanism is not known. It has been proposed that vasomotor symptoms (VMS, hot flashes and night sweats), are associated with cognition during the MT, but prior studies have focused exclusively on subjectively reported, but not objectively measured, VMS. The current application builds on prior work from this laboratory demonstrating cognitive declines in the first year after the final menstrual period, and that objectively measured VMS are associated with verbal episodic memory in post-menopausal women. The specific aims are to examine the relationship between objectively measured hot flashes and cognitive function, both immediately and longitudinally across the MT, after accounting for objectively measured sleep. In this study, ambulatory monitoring of VMS and sleep will be incorporated into an ongoing, NIA-funded prospective study of cognitive changes during the MT to evaluate the immediate and cumulative effect of hot flashes on cognition. It is hypothesized that objective VMS will have a negative impact on verbal memory performance in perimenopause and that changes in hot flash frequency will predict changes in verbal memory performance over time. Findings from these studies will inform our understanding of memory dysfunction in the MT and

the potential of using VMS as a measure of risk for cognitive decline, which would highlight an important target for therapeutic intervention.

IC: National Institute on Alcohol Abuse and Alcoholism
Title: Neurobehavioral and Emotional Deficits in Male & Female Alcoholics
PI: Sara Jo Nixon
Institution: University of Florida
Grant No.: 1R01AA022456-01

As detailed in PA-11-047 (Women and sex/gender differences in drug and alcohol abuse/dependence), gender differences in the etiology, progression, and consequences of substance use disorders (SUDs) remain incompletely understood. The current proposal focuses on one important aspect of this gap: consequences. More specifically, it is directed to clarifying how men and women may differentially experience the neurobehavioral consequences of alcohol dependence. It is noteworthy that most research directed to neurobehavioral assessments has focused on traditionally defined neurocognitive/neuropsychological domains. Another compromised component of neurobehavior and a key aspect of successful adaptation, emotional processing, has been examined primarily in a separate literature. To better understand the breadth of neurobehavioral compromise, concurrently assessing neurocognitive and emotional performance in men and women is required. Furthermore, although studies of community samples typically reveal a female advantage on these tasks, gender differences among alcoholics are infrequently addressed. To enhance interpretation and direct future research, it is imperative that this work be conceptually driven. In response to these issues, we propose to assess cognitive and emotional functions in sufficient samples of male and female detoxified alcoholics (n = 100, 50 females) and community controls (n = 100, 50 females) to address both main and interaction effects. Guiding this work is a conceptual model, which directs testable hypotheses, thereby informing future research and providing clinically relevant information concerning the processes underlying alcohol-related neurobehavioral (i.e., cognitive and emotional) impairment.

IC: National Institute of Allergy and Infectious Diseases
Title: Epigenetic regulation of decidual inflammation
PI: Adrian Erlebacher
Institution: New York University School of Medicine
Grant No.: 1R01AI106745-01

The development of strategies to prevent preterm birth and other complications of human pregnancy has been greatly hindered by our current lack of understanding of underlying pathogenic mechanisms. In particular, little is known about the intrinsic inflammatory characteristics of the decidua, the specialized uterine stromal tissue that surrounds the fetus and placenta. This proposal is based upon recent work from my laboratory on the molecular pathways that control decidual inflammation and leukocyte trafficking in the pregnant mouse uterus. We have found that the differentiation of endometrial stromal cells (ESCs) into decidual stromal cells (DSCs) entails the epigenetic silencing of select inflammatory chemokine genes through their promoter accrual of the H3K27me3 repressive histone mark. This novel developmental program dramatically reduces the potential of the decidua to manifest an inflammatory response and accumulate activated T cells. In unpublished data, we have found

that DSC differentiation also entails the silencing of Cxcl12 encoding the multifunctional chemokine CXCL12, and Csf1 encoding the macrophage growth factor CSF-1. Together, these findings raise the question of whether an analogous "decidual gene silencing" program is active in human DSCs, and suggest that dysregulation of this program may underlie a variety of placental/decidual pathologies. The proposal is divided into three Specific Aims. Aim I seeks to gain greater insight into the breadth, molecular characteristics, and functional significance of decidual gene silencing, again using mice as a model organism. These experiments will establish a foundation for evaluating decidual gene silencing in human pregnancy and for considering its potential significance with regards to human pregnancy complications. Aim II, which constitutes the bulk of the proposal, employs fresh first-trimester decidual specimens and a number of biochemical techniques to determine whether decidual gene silencing is a feature of human pregnancy. Aim III develops a novel, histone mark immunostaining/DNA fluorescence in situ hybridization (DNA-FISH) protocol for detecting the decidual gene silencing program at the single cell level so that potential dysregulation of this program can ultimately be detected in archived placental/decidual pathological specimens.

IC: **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
Title: **A Drug Delivery Platform For Near-Term Treatment of Proteolytic Disease**
PI: **Jeffrey Michael Karp**
Institution: **Brigham and Women's Hospital**
Grant No.: **1R56AR063866-01A1**

Delivering drugs to patients in a safe, effective, and compliant manner is a major challenge for treatment of many types of disease. Effective oral dosing to achieve high concentrations of drugs within specific tissues while minimizing systemic toxicity remains a significant challenge. Additionally, conventional polymeric drug delivery systems such as implants, injectable microspheres, and patches are used by tens of millions of people annually, yet often produce suboptimal drug release profiles. We aim to develop an autonomous drug delivery system that titrates the amount of drug released in response to a biological stimulus, ensuring the drug is released only when needed at a therapeutically relevant concentration. In collaboration with Dr. Tony Aliprantis, a Rheumatologist at the Brigham and Women's Hospital, we aim to demonstrate an in vitro and in vivo proof of concept for this technology in models of inflammatory arthritis. In the U.S. alone, it is estimated that 2.5 million people suffer from rheumatoid arthritis with a monetary cost measured in the billions. This work will assess the hypothesis that drug-based hydrogels, containing enzyme labile linkers, that are tailored to disassemble in response to enzymes expressed during exacerbations from inflammatory arthritis can serve as an effective on-demand approach for local long-term drug delivery to treat inflammatory joint disease. These gels will be tested using a novel in vitro 3-dimensional synovial micromass organ culture method that faithfully replicates many aspects of the synovial lining physiology and architecture. The gels will also be tested in the rodent model of inflammatory arthritis. This application will focus on addressing the following aims. Aim 1: (a) Synthesize prodrug-based hydrogels that disassemble in response to MMPs those are upregulated within joints in IA, and (b) confirm capacity for IA synovial fluid to disassemble prodrug hydrogels in an MMP-specific manner. Aim 2: Confirm MMP selectivity and "on-demand" disassembly in synovial micromass organ culture. Aim 3: (a) Demonstrate on-demand

disassembly of MMP-specific prodrug hydrogels in vivo, and (b) Demonstrate capacity for prodrug-based hydrogels to ameliorate inflammatory arthritis in vivo.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Interferons and Cytotoxic Lymphocytes in Dermatomyositis and Cutaneous Lupus
PI: Livia A. Casciola-Rosen
Institution: Johns Hopkins University
Grant No.: 1R56AR062615-01A1

Interferons (IFNs) and cytotoxic lymphocyte (CTL)-induced death are major pathogenic factors underlying injury in cutaneous lupus (CLE) and dermatomyositis (DM), but the extent of, and manner in which these pathways interact remains unclear. This dual PI program will define pathogenic mechanisms in CLE and DM, with a view to improved precision in diagnosis, disease monitoring, and therapy. Numerous gaps exist in the diagnosis and management of these diseases, including incomplete understanding of the components participating in amplification of immune-mediated tissue damage, and lack of precise probes and biomarkers for diagnosis, subclassification, and prediction/monitoring response to therapy. The proposal is based on significant preliminary data, broad scientific and clinical expertise, and a well-established and growing resource of extensively defined clinical materials. Our recent studies have identified a distinct cutaneous phenotype (in seronegative DM patients) associated with autoantibodies to MDA5, an autoantigen regulated by type I IFNs and cleaved during lymphocyte-mediated cytotoxicity. Our preliminary studies show that there are novel type I and/or type II IFN-inducible autoantigens targeted in DM and SLE (such specificities are undetected in conventional antibody screens) and provide evidence for expression of type II-IFN-specific markers preferentially in a subset of CLE patients, suggesting that this pathway might be therapeutically tractable in some CLE patients. Additionally, we have recently defined novel keratinocyte-specific autoantigens recognized by antibodies from patients with DM/CLE, and have identified 1 to date: keratin-5, an immature type II keratin expressed in basal keratinocytes. Several IFN-induced and keratinocyte-specific autoantigens are modified during UVB- or CTL-induced cell death, placing these antigens at the hub of damage and repair pathways in interface dermatitis. The specific goals of this proposal are: (i) generate and validate innovative tools (novel autoantibodies recognizing IFN-induced or proliferative keratinocyte autoantigens, and markers of CTL- mediated cell death in the skin) to define and quantify pathogenic pathways active in DM and CLE; (ii) interrogate disease mechanisms in affected patient skin by defining the site(s) of novel autoantigen expression and define whether CTL activity is focused on these cells; and (iii) use novel precision markers of 3 distinct mechanistic pathways in DM/CLE to define which pathways change in response to new therapeutic intervention and are associated with the most striking clinical effects. The proposed studies will provide powerful new tools to precisely define the activity of pathogenic pathways in specific target tissues in individual patients in vivo, thereby facilitating diagnosis, prediction, and monitoring of clinical course in autoimmune skin diseases. The studies will address whether disease subsets defined using these markers respond differently to newly introduced therapy, providing proof of concept that specific pathway markers in target tissue can be used for patient classification and selection of therapy.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Pre-osteoclast Fusion
PI: Paul R. Odgren
Institution: University of Massachusetts Medical School
Grant No.: 1R01AR061504-01A1

Bone resorption by osteoclasts (OCs) exceeding formation by osteoblasts (OBs) is a biological problem with a central role in widespread and costly disorders, including osteoporosis, osteo- and rheumatoid arthritis, periodontal disease, and prosthesis/implant loosening. Delineation of mechanisms and regulation of the fusion of mononuclear precursors into multinucleated OCs is important since fusion is needed for normal bone resorption. In our studies of gene expression changes during OC differentiation, we discovered OC-STAMP (osteoclast-stimulatory transmembrane protein) and noted a series of striking similarities to a factor shown by others to be essential to fusion, called DC-STAMP. Similarities include (1) up-regulation of mRNA and protein upon stimulation of OC precursors by RANKL; (2) predicted topology of transmembrane (TM) helices; (3) presence of a DC-STAMP family consensus sequence in the C-terminal half of OC-STAMP; (4) suppression of formation of multinucleated osteoclasts in vivo and in vitro by either knockout, knockdown, or antibody; and (5) stimulation of fusion upon overexpression. Both proteins are highly conserved in terrestrial vertebrates. In a model of acute, induced OC differentiation in an osteopetrotic rat model, we present preliminary evidence that anti-OC-STAMP antibody suppresses osteoclastogenesis in vivo. (A recent report validated our hypothesis that OC-STAMP -/- mice would, like DC-STAMP -/- mice, have mononuclear OCs.) This proposal will investigate pre-OC fusion under 3 Specific Aims to clarify its role in OC cell biology and activity in vivo, as a potential therapeutic target to control bone loss, and in relation to DC-STAMP as a fusion factor. SA1 will establish the membrane topology of both OC- and DC-STAMP (DC-STAMP has been reported to be a 7-TM superfamily member, yet different algorithms predict different topologies). Information gained should facilitate next-generation antibodies and/or inhibitory peptides directed at proven extracellular loops of these fusigens and provide a basis for further hypotheses about activities and regulation. Under SA2, OC- and DC-STAMP knockout mice will be produced (requests for existing lines were refused). We will confirm the skeletal and OC phenotypes of both strains in our hands, and we will use cells derived from them to perform fusion experiments to determine interaction or interdependence of OC- and DC-STAMP for fusion. Studies will be done to identify potential ligands and regulatory factors for OC- and DC-STAMP. Under SA3, we will increase the size of our preliminary study of acute, in vivo OC inhibition in tl/tl rats with anti-C-STAMP antibody. We will also investigate the effects of anti-[fusigens] antibody inhibition in the proven, ovariectomized rat model of osteoporosis using athymic rats. Together, these studies should provide significant new information about the topology and cell biology of both OC-STAMP and DC-STAMP, about pre-OC fusion, about the phenotypic impact of loss of OC-STAMP on the skeleton, and whether in principle, inhibition of pre-OC fusion is a valid approach to stemming bone loss in vivo.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: The Blimp-1 SLE Risk Variant Regulates Inflammatory Function in Dendritic Cells
PI: Sun Jung Kim
Institution: Feinstein Institute for Medical Research
Grant No.: 1R56AR065209-01

Genome-wide association studies (GWAS) have identified many genetic loci, which are associated with SLE; however, we still need to understand the contribution of each to disease initiation or pathogenesis. Specifically, GWAS identified that B lymphocyte-induced maturation protein-1 (Blimp-1) has a susceptibility polymorphism for systemic lupus erythematosus (SLE) rs548234, but neither the significance of the polymorphism for Blimp-1 expression and function, nor its significance for SLE pathogenesis has been identified. We have generated a novel mouse model of SLE in which Blimp-1 is deleted in a dendritic cell (DC)-specific manner (DCBlimp-1ko mice). Compared to the other established models, DCBlimp-1ko mice show a more pronounced gender dependent disease development, similar to the human disease. Moreover, the lupus-like phenotype in DCBlimp-1ko mice depends on the presence of estrogen. Blimp-1 deficient DCs show an activated phenotype and increased expression of proinflammatory cytokines following toll-like receptor (TLR) stimulation. We determined that Blimp-1 directly regulates expression of microRNA Let-7c in DCs, thus Blimp-1 induction leads to an aberrant increase of Let-7c and a decrease in the Let-7c target molecule, suppressor of cytokine signaling-1 (SOCS-1). We investigated the function of DCs from healthy individuals with the SLE risk allele of Blimp-1. Our preliminary studies demonstrate that there is a decrease in the level of Blimp-1 and increase in Let-7c in DCs of risk allele carriers. The differential expression of Blimp-1 and Let-7c is DC specific since there is no significant difference in Blimp-1 expression between B cells of risk allele and non-risk allele carriers. DCs of risk allele carriers also secrete an increased level of IL-6 following TLR stimulation. Finally, these phenotypic and functional changes depend on gender, since male risk allele carriers exhibit a much milder phenotype. We hypothesize that Blimp-1 has a critical immune tolerogenic function in DCs. In this proposal, we will identify how the risk allele affects the expression of Blimp-1 in DCs. We will identify target molecules of Blimp-1, which regulate the proinflammatory phenotype in DCs. We will also investigate the role of estrogen in Blimp-1 expression or function. Finally, we will compare risk allele or non-risk allele SLE patients to determine whether a similar pattern of DC function occurs in all SLE patients. Where limitations to human studies are great, we will employ the DCBlimp-1ko mouse model. There are strong similarities between human Blimp-1 risk allele carriers and DCBlimp-1ko mice, and these similarities give us a unique opportunity to understand its contribution to human disease pathogenesis.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **A Systems Science Approach to Understanding Sexual Risk Behavior in Young Women**
PI: **Sara A. Vasilenko**
Institution: **Pennsylvania State University**
Grant No.: **1R03HD077011-01**

Young women are at disproportionate risk of STIs and their consequences, with the highest rates of chlamydia and gonorrhea, as well as outcomes such as pelvic inflammatory disease, infertility, and cervical cancer. This disease burden has a disparate effect on some groups of young women, such as racial/ethnic minorities and women of low socioeconomic status. To date, most research and prevention programs have focused on individual-level predictors of sexual risk behavior measured at a single time point (e.g., behavioral intentions, attitudes). However, individuals' intentions to engage in risky or protective behaviors may vary across contexts and over the course of relationships. By applying a cutting-edge analytic technique to richly detailed, intensive longitudinal data, we will extend research on sexual risk behavior to address the relationship dynamics that influence these behaviors. This project will make use of data collected weekly from nearly 1,000 young women over 2.5 years, including detailed information about their relationships, sexual behavior, contraceptive use, attitudes, and intentions. We will apply a novel analytic technique, the time-varying effect model, to understand women's sexual risk behavior over the course of the relationship with a sexual partner. This project has three specific aims. First, we will model patterns of young women's non-use of condoms over the course of sexual partnerships. Second, we will examine how women's intentions to use condoms differentially predict condom non-use over the course of sexual partnerships. Finally, we will delve into sources of disparities in sexual health outcomes by examining how these patterns of sexual risk behavior may differ by race/ethnicity, socioeconomic factors, and urbanicity. By modeling how sexual risk behavior evolves over the course of a relationship, the proposed project will inform the creation of more effective prevention programs that are targeted to high-risk populations and relationships contexts.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **The Evolutionary and Molecular Mechanisms Underlying Sperm Performance in an Emergency**
PI: **Heidi S. Fisher**
Institution: **Harvard University**
Grant No.: **1K99HD071972-01A1**

Genes contributing to reproductive success in laboratory mice have provided important insights into the molecular, developmental, and physiological processes underlying mammalian reproduction and have served as models for studies of human infertility. Traditional strains of laboratory mice, however, are limited in the degree of variation in reproductive traits compared to the extent of variation observed in nature. In contrast, a close relative to the laboratory mouse, deer mice in the genus Peromyscus, exhibit striking differences in reproductive anatomy, sperm production, morphology, and motility among species. This variation is due to the extreme

divergence in mating system within the genus. In species in which females mate multiple times over a breeding season, there is intense competition between ejaculates of different males for fertilization of her eggs. Accordingly, there is strong selective pressure on male reproductive traits that improve fertilization success in promiscuous species; in closely related monogamous species, however, selection is relaxed. Thus, the diversity of reproductive traits in Peromyscus makes them a valuable model for studies aimed at understanding the genetic basis of male fertility but, in addition, they also offer an entirely new perspective on gametic interactions. When sperm are released from these mice, they form cooperative units—multiple cells form groups within the female reproductive tract, which enable them to swim with greater motility compared to individual sperm. In at least one species, the species in which sperm competition is most intense, sperm are able to recognize the most related cells and selectively group with them; in fact, this form of cellular recognition is so refined that sperm from one male can even discriminate against sperm from a full sibling littermate. In contrast, sperm from a monogamous species group indiscriminately. The proposed study is designed to exploit the natural variation in male reproductive traits as well as the unique cellular recognition and aggregation behavior of Peromyscus sperm to reveal the genes that contribute to fertilization success. The primary goal in the mentored phase of this project is to identify genetic regions and ultimately genes influencing a morphological trait of sperm that is associated with motility and reproductive success using a genetic mapping approach combined with gene expression studies of the testicular tissue that represent different stages of spermatogenesis. During the independent phase of this project the focus will be on exploring sperm aggregation behavior to understand both how groups form using integrative electron microscopy and why they do—by asking what is the effect of cooperative sperm migration within the female reproductive tract and in complex environments? Finally, with an understanding of the physical mechanisms involved in sperm aggregation, this study will apply similar genetic and genomic techniques implemented in the mentored phase to reveal the genetic basis of sperm aggregate size and the molecular mechanisms involved in cellular recognition, discrimination, and adhesion in sperm. In total, this work will shed new light on the genetic basis of traits associated with male fertility and offer a unique perspective on gametic recognition and adhesion.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Vitamin D Supplementation in Older Adults with Urinary Incontinence**
PI: **Alayne Denise Markland**
Institution: **University of Alabama at Birmingham**
Grant No.: **1R21DK096201-01A1**

Urinary incontinence (UI) affects many older women and greatly reduces quality of life. In the U.S., the most common type of UI in older adults is urgency UI and mixed-type UI. The most common type of medication used for urgency and mixed UI is an antimuscarinic drug. However, most patients on UI medications do not become completely dry, and medications are often discontinued due to costs, negative side effects, or perceived inefficacy. Clearly, more efficacious treatments for UI are urgently needed. Evidence emerging from epidemiologic and clinical cohort studies indicates that lower vitamin D levels are associated with increased risk for UI, suggesting that vitamin D may have a role in maintaining continence in women. Because the potential benefits of vitamin D may extend to several organ systems, it is quite possible that vitamin D may maintain continence by supporting skeletal muscle strength and normal detrusor

activity. In the proposed study, we hypothesize that adequate vitamin D supplementation (raising serum levels to 30 ng/mL or above) will improve UI symptoms in older women with vitamin D deficiency (25(OH)D serum levels less than 20 ng/mL). The primary aim of the proposed double-blind, randomized, placebo-controlled pilot trial is to estimate the effect size of weekly vitamin D supplementation in older women with UI and vitamin D deficiency. The second aim is to evaluate if improving serum 25(OH)D levels affect other urinary and bowel symptoms. The third aim is to identify potential mechanisms that may contribute to improved UI symptoms in a subgroup of women, including increased pelvic floor skeletal muscle strength, decreased detrusor muscle over activity, improved mobility, and inflammatory urinary biomarkers. Post-menopausal women with vitamin D deficiency (n = 100) will be recruited and randomized to receive weekly oral placebo or 50,000 IU vitamin D3 (cholecalciferol) for 12 weeks. Our treatment regimen is intended to achieve serum 25(OH)D levels of 30 ng/mL or above. Changes in UI-episodes will be assessed by a 7-day bladder diary and other validated measures of urinary and bowel symptoms, administered at baseline and after 12 weeks of intervention. Serum calcium and 25(OH)D levels will be monitored at: baseline, 6-week visit, and the end of 12 weeks of the intervention. Urodynamic (done in 50% of the study group), an assessment of pelvic floor strength, urinary collection for further testing, and mobility will be performed at baseline and 12 weeks. The expected outcomes will provide new knowledge regarding the impact of vitamin D supplementation on UI symptom improvement and inform a larger, randomized controlled clinical trial involving vitamin D supplementation.

IC: **National Institute of General Medical Sciences**
Title: **Sexual Identity and Germ Cell Differentiation in the Drosophila Ovary**
PI: **Helen Karen Salz**
Institution: **Case Western Reserve University**
Grant No.: **1R01GM102141-01A1**

In adults, tissue maintenance and repair depends on a stable population of stem cells that can give rise to both self-renewing and differentiating daughter cells. An understanding of how this process is regulated is of fundamental importance because an excess of differentiation can lead to stem cell depletion and tissue senescence, while a failure to enter the differentiation pathway can lead to an accumulation of proliferating cells and tumor formation. A comparison of male and female germline stem cell (GSC) behavior in Drosophila ovaries and testis, two of the premier model systems for the study of stem cells in their natural environment, reveals sexually dimorphic adaptations of the regulatory mechanisms governing the self-renewal/differentiation decision. Little attention, however, has been paid to how these differences are achieved. Data emerging from the Salz lab supports a novel model in which the female-specific RNA binding protein Sex-lethal (Sxl) jointly controls sexual identity and the self-renewal/differentiation decision in the germline. GSCs without Sxl protein fail to successfully execute the self-renewal to differentiation cell fate switch. The failure to differentiate is accompanied by the inappropriate expression of a set of male specific markers, continued proliferation, and formation of a tumor. Sxl encodes a ubiquitously expressed female-specific RNA binding protein. In somatic cells, it globally regulates all aspects of female-specific development and behavior. Its mode of action in the germline, however, remains poorly understood. The studies in this new proposal address this issue using an integrated experimental approach that combines classical and molecular genetics with RNA/protein biochemistry. In Aim 1, we focus on how Sxl controls germ cell differentiation, beginning with our studies showing that Sxl prompts the exit from the stem cell

fate by repressing translation of the conserved stem cell factor nanos. In Aim 2, we focus on how Sxl maintains sexual identity, beginning with preliminary studies showing that Sxl acts through the Jak/Stat signaling pathway to repress male-specific germ cell behavior. The knowledge generated by the studies in this proposal will illuminate the intrinsic regulatory mechanisms that integrate sexual identity and the self-renewal/differentiation decision, and will provide information about why disruptions in this pathway lead to germ cell tumors. Information from model systems such as the Drosophila germline will provide key insights into how stem cells control the self-renewal/differentiation decision in other, less experimentally tractable systems. More generally, the information gained from our animal model studies will illuminate strategies used by RNA regulators to differentially regulate gene expression in time and space.

IC: **National Institute of Mental Health**
Title: **Sex Differences in Cognitive Response to a Hydrocortisone Challenge in HIV**
PI: **Leah Helane Rubin**
Institution: **University of Illinois at Chicago**
Grant No.: **1R21MH099978-01A1**

Cognitive deficits persist despite the availability of effective therapies for HIV. New data indicates that, in contrast to men, delayed memory impairments are a central feature of cognitive impairment in HIV+ women. Furthermore, stress interacts with HIV serostatus to negatively impact verbal memory in particular. This application proposes to investigate stress-associated increases in glucocorticoids (GCs) as a potential contributor to verbal memory deficits in HIV+ women. GCs are released after a stressor and are the key mediator of the relationship between stress and memory dysfunction in non-HIV-infected individuals. Correlational evidence suggests that healthy women are more vulnerable to the cognitive effects of GCs than healthy men. Here, we propose to extend this research to HIV and specifically examine the causal role of GCs response on cognitive function. Specifically, we propose to investigate sex differences in the impact of hydrocortisone on cognitive function in HIV in a double-blind, placebo-controlled, cross-over study in 82 HIV+ adults (41 men, 41 women). An innovative feature of this design builds on recent evidence that the effects of GCs on cognition depend on the timing of the cognitive assessment in relation to stress hormone exposure. Therefore, we propose to examine how GCs impact cognitive function both acutely (30 minutes post-intervention) and after a delay (240 minutes post-intervention). We hypothesize that the magnitude of acute and delayed impairments on verbal memory will be greater in HIV+ women compared to HIV+ men. To the best of our knowledge, this will be the first pharmacologic challenge study to elucidate the cognitive effects of GCs in HIV. Such a demonstration will provide critical insights into stress-related increases in GCs as a mechanism underlying the apparent greater deficit in verbal memory in HIV+ women compared to men. Identifying this mechanism is a critical first step in the design of clinical trials aimed at lowering stress and GCs in order to improve cognitive function, particularly in HIV+ women.

Specialized Centers of Research on Sex Differences

IC: National Institute on Aging
Title: Sex-Specific Risk for Vascular Dysfunction and Cognitive Decline
PI: Virginia M. Miller
Institution: Mayo Clinic, Rochester
Grant No.: 5P50AG044170-02

Cardiovascular disease and cognitive decline are two related conditions disproportionately affecting men and women across their lifespan. This interdisciplinary program will utilize innovative tools imaging and diagnostic techniques to understand how changes in blood supply to the brain affect cognition in 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.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Sex Differences in Musculoskeletal Conditions Across the Lifespan
PI: Nancy E. Lane
Institution: University of California, Davis
Grant No.: 5P50AR063043-02

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 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; an epidemiologic study on the relation of sex differences in bone shape to occurrence, severity, and prognosis of osteoarthritis; a 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 to 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. Public Health Reference: This translational SCOR grant, "Sex Differences in Musculoskeletal Diseases Across the Lifespan," focuses on four musculoskeletal diseases or syndromes that differ by sex and include peak bone mass (a laboratory-based project), carpal tunnel syndrome (epidemiologic and observational), osteoarthritis of the knee (observational), and kyphosis (exercise intervention). Each project will carefully determine the sex differences in relation to the musculoskeletal diseases and inform preventive and clinical practices.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function**
PI: **Wendy M. Kohrt**
Institution: **University of Colorado Denver**
Grant No.: **5P50HD073063-02**

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 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 I (clinical): Bioenergetic and Metabolic Consequences of the Loss of Ovarian Function in Women (PI: W. Kohrt); (2) Project II (preclinical): Effects of Pre-existing Obesity on Consequences of the Loss of Ovarian Function (PI: P. MacLean); and (3) Project III (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, 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Birth, Muscle Injury, and Pelvic Floor Dysfunction**
PI: **John O. L. DeLancey**
Institution: **University of Michigan**
Grant No.: **5P50HD044406-12**

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 4 schools and 2 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 I, "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 II, "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 III, "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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Genes, Androgens, and Intrauterine Environment in PCOS**
PI: **Andrea Dunaif**
Institution: **Northwestern University**
Grant No.: **5P50HD044405-12**

The NU SCOR explores the overarching hypothesis that genetic variation resulting in hyperandrogenemia produces the phenotypic features of the 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 I and II are clinical research projects, and Project III will utilize a novel non-human 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 I 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-β signaling, Wnt signaling, insulin signaling, gonadotropin action, and extracellular matrix, as well as rare variants in genes in novel pathways. Project II 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 III will develop a novel non-human 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.

IC: **National Institute on Drug Abuse**
Title: **SCOR on Sex and Gender Factors Affecting Women's Health**
PI: **Kathleen T. Brady**
Institution: **Medical University of South Carolina**
Grant No.: **5P50DA016511-12**

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 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. Close collaboration with the MUSC BIRCWH program, 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 using emerging technology in closely aligned clinical and basic science projects. The overarching goals of the 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.

IC: **National Institute on Drug Abuse**
Title: **Sex Differences and Progesterone Effects on Impulsivity, Smoking and Cocaine Abuse**
PI: **Marilyn E. Carroll**
Institution: **University of Minnesota**
Grant No.: **5P50DA033942-02**

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) To 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) To 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 no pregnant 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.

IC: National Institute on Drug Abuse
Title: Yale-SCOR on Gender-Sensitive Treatment for Tobacco Dependence
PI: Sherry Ann McKee
Institution: Yale University
Grant No.: 5P50DA033945-02

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 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 inter-related 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. Our specific aims and objectives of the Yale-SCOR are to: Aim 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. Aim 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. Aim 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.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Center for Neurovisceral Sciences and Women's Health
PI: Emeran A. Mayer
Institution: University of California, Los Angeles
Grant No.: 5P50DK064539-12

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 2 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 3 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 2 themes through 3 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 3 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 that can be identified by their responsiveness to a selective CRFIR antagonist.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Molecular and Epidemiologic Basis of UTI in Women**
PI: **Scott J. Hultgren**
Institution: **Washington University in St. Louis**
Grant No.: **5P50DK064540-12**

Antibiotic resistance is reaching a tipping point such that certain common infections with Enterococcus, MRSA, and E. coli are becoming untreatable. Developing anti-virulence drugs which target pathogenic nodes to disarm the pathogen so that innate defenses can eradicate it represents a hopeful strategy to develop new anti-infectives. In order to develop such preventive and therapeutic strategies, the molecular pathogenesis of sex-specific infectious disease processes must be better understood. Thus, it is critical to elucidate the molecular basis of host-pathogen interactions that result in persistence and/or the formation of reservoirs that seed recurrent infections and whether sex-specific differences alter the pathogenesis. Similarly, it is important to identify mechanisms by which a dysbiotic microbiota develop to predispose to an infection and the ramifications of sex differences on these processes and on host immune responses to invading pathogens and/or risk for downstream sequelae. Understanding the influence of hormones on host-pathogen interactions and differences in disease progression and therapeutic responses in females and males is also critical in order to gain a holistic molecular picture of pathogenesis. These factors are of particular interest in this SCOR as they relate to the urogenital tract, in which we have demonstrated host reservoirs and chronic persistent infections in female and male mouse models as well as modulatory effects of urogenital microflora on disease progression. In this proposal, we concentrate our efforts on the study of urinary tract

infections (UTI). UTI is a disease which: (i) primarily affects otherwise healthy females (50% of women will have a UTI); (ii) is associated with significant morbidity and economic impact, with over $2.5 billion spent annually on treatment; (iii) is becoming increasingly caused by antibiotic-resistant pathogens; (iv) is highly recurrent (25%–50% chance of second infection despite appropriate treatment for a first infection); (v) can become chronic (placebo studies show a 50% incidence of chronicity without antibiotic treatment); (vi) increases in frequency and potential for complications during specific stages of a woman's life, such as during pregnancy; (vii) can lead to complications, including sepsis and renal scarring in children, and is linked to preterm birth; (viii) affects males at the extremes of life (infants and elderly men); and (ix) represents a major complication in hospitalized patients. The objectives of our interdisciplinary team are to use an interwoven combination of clinical and basic research to better understand the epidemiology, pathophysiology and mechanisms involved in the initiation, progression, and outcome of UTIs. Project 1: We seek in this proposal to understand the complexity of host-pathogen interactions that determine the onset and progression of UTI. In Aim 1 we seek to elucidate bacterial mechanisms important in the formation of intracellular bacterial communities (IBCs) and the subsequent development of chronic cystitis. In Aim 2, we seek to analyze the correlation between IBC numbers during acute cystitis and propensity for chronic cystitis and to explore host epithelial mechanisms that are likely to restrict the development of IBCs. In Aim 3, we will utilize an innovative metabolomics approach to assess small molecules in urines collected from women with acute UTI who do and do not develop recurrence, and urines from pregnant women and male/female infants and animal studies. In Aim 4, in we will assess sex influences on UPEC pathogenesis, specifically the effects that co-inoculation of vaginal microflora with UPEC have on pathogenesis and disease outcome. Project 2: We will perform the first longitudinal study of its kind to investigate whether colonization by specific combinations of urogenital bacteria is associated with increased susceptibility of the pregnant host to acute or recurrent UTI or asymptomatic bacteriuria (ASB). Moreover, we will investigate whether these combined bacterial etiologies create a synergistic risk of preterm birth (PTB). In Aim 1, we will evaluate the effect of urogenital Group B Streptococcus (GBS) and bacterial vaginosis (BV) status on susceptibility to ASB and UTI in pregnancy. In Aim 2, we will interrogate the role of ASB recurrence in the persistent risk of PTB following acute bacteriuria, and in Aim 3, we will investigate polymicrobial synergy as a risk factor in bacteriuria-associated PTB. The completion of this study should inform new strategies to prevent urologic conditions and their complications in pregnancy. Project 3: We will investigate the hypothesis that sex- and age-specific differences in innate and adaptive responses to E. coli UTI exist and impact risk for recurrence. We will analyze serum and urine samples from male and female infants at the time of acute UTI and in convalescence, analyzing inflammatory cytokines, immune cell populations, sex hormones, novel biomarkers, and evidence of IBC formation compared to samples from control infants and from adult women (Aims 1 and 2). In Aim 3, we will use a surgical murine UTI model to corroborate host-response and other data obtained from our collected human samples in male and female mice, to test new hypotheses generated from work performed in Project I (e.g., bacterial and host mechanisms), and to study the effects of hormonal perturbation on the establishment of UTI, IBC formation and progression to chronic cystitis, and host immune responses. Admin Core: The objective of the Administrative Core is: (i) to oversee and coordinate interactions among the leaders and staff of the three proposed projects in order to achieve the overall SCOR program goals, (ii) to efficiently and professionally coordinate financial and scientific progress reporting to NIH, and (iii) to facilitate total program review and advice from our advisors.

IC: National Institute of Mental Health
Title: Prepubertal Stress, Windows of Risk, and Sex Bias for Affective Disturbance
PI: C. Neill Epperson
Institution: University of Pennsylvania
Grant No.: 5P50MH099910-02

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 (MOD) 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, MOD 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 premenstrum (premenstrual dysphoric disorder), the postpartum (onset/relapse bipolar disorder, MOD), 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 lifespan, including pregnancy (Projects I & III) and aging (Projects II & III). In addition, mechanistic epigenetic studies will examine sex differences in response to stress during this sensitive window of brain maturation (Project III). 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.

APPENDIX C

ORWH-Cofunded Research Summaries, FY 2014

Contents

Administrative Supplements Program

IC: **National Center for Complementary and Integrative Health**
Title: **Improving Treatment Adherence in HIV-Positive Youth Through Mindfulness Training**
PI: **Erica Maria Smit Sibinga**
Institution: **Johns Hopkins University**
Grant No.: **3R01AT007888-02S1**

Stress is an important factor in treatment compliance in adults with HIV, and sex/gender appears to contribute. This research project evaluates the effectiveness of mindfulness-based stress reduction on improving HIV medication adherence in HIV-infected urban youth. The supplement will expand efforts to assess sex/gender effects by enhancing measurement of emotion control and levels of the stress hormone cortisol.

IC: **National Cancer Institute**
Title: **Comparative Modeling of Lung Cancer Control Policies**
PI: **Chung Kong**
Institution: **Massachusetts General Hospital**
Grant No.: **3U01CA152956-05S1**

This research project uses modeling techniques to assess the impact of computed tomography (CT) screening on lung cancer incidence. Chest CT scans can be harmful to females who have a stronger susceptibility to the deleterious effects of ionizing radiation to the breast. The supplement will use the parent grant's lung cancer risk-prediction model to calculate gender differences in radiation risk.

IC: **National Cancer Institute**
Title: **Waterpipe Tobacco Smoking Among U.S. Adolescents and Young Adults**
PI: **Brian A. Primack**
Institution: **University of Pittsburgh**
Grant No.: **3R01CA140150-05S1**

Waterpipe tobacco smoking is on the rise in adolescents and young adults, and it exposes them to many of the same chemicals, as do cigarettes. Midway through the funding period, this research project discovered that young women may be particularly attracted to this activity. The supplement will take a second look at sex differences in observational data collected and will also conduct separate focus groups with women and men.

IC: **National Heart, Lung, and Blood Institute**
Title: **Molecular and Functional Mechanisms of Pediatric Heart Failure**
PI: **Brian L. Stauffer**
Institution: **University of Colorado Denver**
Grant No.: **3R01HL107715-03S1**

This research project aims to improve understanding about how a child's heart responds to heart failure, providing a basis for targeted medical treatment specific to children. To date, results suggest significant sex differences in pediatric heart failure. The supplement will add hearts to the heart-tissue bank funded by the parent application to enable further analyses of sex differences.

IC: **National Heart, Lung, and Blood Institute**
Title: **PET Imaging of Thrombus**
PI: **Peter D. Caravan**
Institution: **Massachusetts General Hospital**
Grant No.: **3R01HL109448-03S1**

Blood clots are central to several diseases such as stroke, heart attack, and pulmonary embolism. This research project has developed a noninvasive, direct imaging method to detect blood clots, as well as their disappearance after treatment with so-called clot-busting drugs. Because estrogen appears to prevent clots, this supplement will use monitor clots during stroke in male and female rats, as well as in female rats with their ovaries removed (with or without supplemental estrogen treatment).

IC: **National Heart, Lung, and Blood Institute**
Title: **Right Heart-Pulmonary Vascular Interactions in Bronchopulmonary Dysplasia**
PI: **Marlowe Eldridge**
Institution: **University of Wisconsin–Madison**
Grant No.: **3R01HL115061-03S1**

Premature birth frequently leads to a chronic lung disease known as bronchopulmonary dysplasia (BPD), which affects children throughout life. This research project is tracking the lung- and heart-health outcomes of very low-birth weight infants from the New Born Lung Project (with and without BPD), who are now young adults or school-aged children (two separate groups). Female rats with experimental BPD develop lung and heart problems later in life, and the supplement will compare male and female rats to characterize the effects of sex and sex hormones on these health outcomes.

IC: **National Heart, Lung, and Blood Institute**
Title: **Striatin, Aldosterone, and Hypertension**
PI: **Gordon H. Williams**
Institution: **Brigham and Women's Hospital**
Grant No.: **3R01HL114765-02S1**

Striatin is a protein that interacts with steroids in the body to help control the heart and blood vessels. New data from this research project indicates that striatin may work differently in female mice compared to male mice. The supplement will enable the addition of female mice to experiments to permit statistically stronger comparisons of males and females, toward a better understanding of sex differences in cardiovascular disease.

IC: **National Heart, Lung, and Blood Institute**
Title: **Sulfonylurea Receptor 1 (SUR1): A Novel Therapeutic Target in Ischemic Stroke**
PI: **J. Marc Simard**
Institution: **University of Maryland, Baltimore**
Grant No.: **3R01HL082517-09S2**

This research project aims to expand understanding of cell death after stroke-affected brain tissue is deprived of oxygen. Females are more vulnerable than males to a type of cell death called apoptosis that occurs after a stroke; a protective effect appears to arise from genes encoded on the Y chromosome in males. The supplement will add female rodents to allow sex-based comparisons.

IC: National Heart, Lung, and Blood Institute
Title: Using Networks To Assign Gene Function in Lung Disease
PI: John Quackenbush
Institution: Dana-Farber Cancer Institute
Grant No.: 3R01HL111759-02S1

For every cigarette smoked, women appear to develop more severe chronic obstructive pulmonary disease (COPD) at an earlier age than do men. This research project is using systems biology methods to find genetic variations associated with COPD and to identify how those variations relate to disease. The supplement will continue the effort, identifying and exploring sex-specific COPD signaling pathways.

IC: National Institute on Aging
Title: Alzheimer's Disease Neuroimaging Initiative
PI: Michael W. Weiner
Institution: Northern California Institute for Research and Education
Grant No.: 3U01AG024904-09S5

This research project is searching for relationships among the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics of Alzheimer's disease, from early disease to dementia. The supplement will study the influence of sex/gender on the development and progression of Alzheimer's disease, including the role of the ApoE-e4 genotype, a potent genetic risk factor for sporadic and late-onset familial Alzheimer's.

IC: National Institute on Aging
Title: Energetics Disparities and Lifespan: A Unified Hypothesis
PI: David B. Allison
Institution: University of Alabama at Birmingham
Grant No.: 3R01AG043972-03S2

This research project tests the hypothesis that animals (including humans) respond to perceived threats to their energetic security by switching life strategies to: (i) build and preserve energy stores to protect themselves against true food scarcity that may occur later, and (ii) extend lifespan to breed more slowly and/or in better times. The supplement will add female mice to ongoing studies on the role of hunger perception to assess changes in the rate of aging and longevity.

IC: National Institute on Aging
Title: Site-Directed Oxidative Modification of Muscle Protein Structural Dynamics
PI: David D. Thomas
Institution: University of Minnesota
Grant No.: 3R37AG026160-09S2

This research project aims to understand how muscle proteins become damaged by oxidation—the addition of oxygen atoms that occurs during both aging and degenerative disease. Particular focus is on two key muscle proteins: calmodulin and myosin. The supplement will use animal models of myosin function to study estrogen-mediated sex influences.

IC: National Institute on Aging
Title: The Effects of Aging on Experimental Models of Pain Inhibition and Facilitation
PI: Joseph L. Riley
Institution: University of Florida
Grant No.: 3R01AG039659-04S1

This research project employs cutting-edge pain-testing techniques to identify aging-related changes in older adults. The supplement will continue to investigate these changes, aiming in particular to identify sex differences in the age-related effects of estrogen and testosterone on molecular aspects of pain control.

IC: National Institute on Alcohol Abuse and Alcoholism
Title: Cherokee Nation Prevention Trial: Interactive Effects of Environment and Screening, Brief Intervention, and Referral to Treatment (SBIRT)
PI: Kelli Ann Komro
Institution: University of Florida
Grant No.: 3R01AA020695-04S1

This research project funds a community-based, randomized trial testing the effectiveness of two unique interventions in high-risk and underserved, rural, northeastern Oklahoma communities that are mostly Native American. The interventions include community environmental change and brief intervention and referral. The supplement will provide additional resources to further investigate disparate health outcomes among Native American young women.

IC: **National Institute on Alcohol Abuse and Alcoholism**
Title: **Facilitating Adolescent Self-Change for Alcohol Problems**
PI: **Sandra A. Brown**
Institution: **University of California, San Diego**
Grant No.: **3R01AA012171-13S2**

This research project is testing the effectiveness of a school-based brief intervention to stop hazardous drinking at six socioculturally and ethnically diverse schools. The supplement will determine how gender and ethnicity influence outcomes for adolescents participating in this alcohol prevention program.

IC: **National Institute on Alcohol Abuse and Alcoholism**
Title: **Multisite School-Based Evaluation of a Brief Screener for Underage Drinking**
PI: **Jonathan G. Tubman**
Institution: **American University**
Grant No.: **3R01AA021888-02S1**

This research project is validating the NIAAA/American Academy of Pediatrics two-item screener for underage alcohol use, toward identifying risk for subsequent development of alcohol-use problems and disorders. The supplement will expand the assessment to explore gender differences in aggression and bullying behavior and their effects on alcohol use during adolescence.

IC: **National Institute on Alcohol Abuse and Alcoholism**
Title: **The Role of Serotonin in Alcohol Withdrawal-Induced Anxiety**
PI: **Thomas L. Kash**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **3R01AA019454-05S1**

This research project is studying how alcohol exposure alters emotional behavior and brain function. The supplement will assess effects of long-term alcohol vapor exposure on anxiety and depression-like behavior in female mice, and it will also look at alcohol's effects on female brain circuitry.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Enhancing Neonatal Immunity to Streptococcus Pneumoniae**
PI: **Richard Malley**
Institution: **Children's Hospital Corporation**
Grant No.: **5R01AI100114-03**

This research project examines the neonatal immune response to an experimental vaccine against Streptococcus pneumonia, an important cause of childhood disease in the United States and throughout the world. Because pneumococcal infection rates differ between males and females,

as does the production of antibodies, the supplement will investigate whether immune responses differ between female and male mice.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Immune Responses of the Epithelium in Chronic Rhinosinusitis with Polyps**
PI: **Andrew P. Lane**
Institution: **Johns Hopkins University**
Grant No.: **5R01AI072502-07**

Using patient samples and experimental animals, this research project studies how cells lining the nose and sinuses affect immunity against inhaled microorganisms, sometimes leading to the painful condition sinusitis. The supplement will investigate sex differences in nasal and sinus-cell antimicrobial activity and immune effects.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Modeling Distinct Neonatal Purine Metabolism to Inform Vaccine Development**
PI: **Ofer Levy**
Institution: **Children's Hospital Corporation**
Grant No.: **5R01AI100135-03**

This research project measures components in blood samples to model immune responses to vaccines in human newborns and infants. The supplement will characterize sex-specific immune responses, which will require larger samples of blood cells to enable statistical power to compare human female- and male-infant responses.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Role of Rapid IFN-γ Secretion by CD8+ T cells in Clearance of Food Borne Listeria**
PI: **Sarah E. F. D'Orazio**
Institution: **University of Kentucky**
Grant No.: **5R01AI101373-03**

This research project is identifying molecular determinants (genes, proteins) that protect some people from the serious, sometimes deadly, consequences of infection with Listeria monocytogenes. This bacterium can contaminate "ready-to-eat" food products such as unpasteurized cheeses, deli meats, and produce. The supplement will add male mice to the experimental design of the parent grant, which focused on female animals only due to their heightened risk to Listeria effects.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Virologic Correlates of Heterosexual Transmission**
PI: **Eric Hunter**
Institution: **Emory University**
Grant No.: **5R37AI051231-13**

In the majority of cases of heterosexually transmitted HIV, infection occurs through a single genetic variant of the virus from the transmitting partner. This research project is investigating which biological properties of such HIV strains promote infection in a new host. The supplement will examine differences between male and female transmitting partners in early and later stages of infection.

IC: **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
Title: **Acute-to-Chronic Transition in Ergonomic Muscle Pain: Nociceptor Mechanisms**
PI: **Jon David Levine**
Institution: **University of California, San Francisco**
Grant No.: **3R01AR063312-02S1**

This research project studies molecular aspects of pain sensation during the transition from acute-to-chronic work-related musculoskeletal pain. The supplement will add female animals to study the effects of female sex hormones in two animal models of ergonomic muscle pain—one induced by eccentric exercise and the other by vibration.

IC: **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
Title: **Alternative NF-κB in Bone Microenvironment**
PI: **Deborah V. Novack**
Institution: **Washington University in St. Louis**
Grant No.: **3R01AR052705-08S1**

This research project is studying molecular aspects of osteoclasts, bone cells necessary for the maintenance of healthy bones but that are also present in bone tumors. The supplement will investigate molecular differences in osteoclast properties that affect male and female mice differently.

IC: **National Institute of Arthritis and Musculoskeletal and Skin Diseases**
Title: **Genetics of Cartilage Regeneration and Osteoarthritis**
PI: **Linda J. Sandell**
Institution: **Washington University in St. Louis**
Grant No.: **3R01AR063757-02S1**

This research project, using a mouse model, has identified several genes in males that support cartilage regeneration, and thus, prevention of osteoarthritis. The supplement will add female mice to look for differences in sex-based expression of those genes.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Innovative Efficacy Measures of Lupus Nephritis Therapies
PI: Hermine I. Brunner
Institution: Cincinnati Children's Hospital Medical Center
Grant No.: 3U01AR065098-02S1

Currently, diagnosis and monitoring of lupus nephritis, a serious complication of the disease lupus, is performed through a kidney biopsy—surgical removal of a sample of kidney tissue. Toward a noninvasive alternative, this research project is developing a method to detect lupus nephritis-associated proteins in a urine sample. The supplement will look at gender- and age-specific differences in the readout of the urine test that might affect its use in male and female children and adults.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: The Role of Cell Death in Lupus Nephritis
PI: Roberto Caricchio
Institution: Temple University
Grant No.: 3R01AR061569-03S1

This research project is testing the hypothesis that males and females with lupus acquire kidney damage through molecular pathways characterized by different types of cell death. The supplement will enable further study of sex influence by increasing the numbers of African-American and Hispanic male and female participants (their electronic medical records).

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Translating Molecular Signal Pathways to Orthopaedic Trauma Care
PI: Edward M. Schwarz
Institution: University of Rochester
Grant No.: 3P50AR054041-08S1

This research project investigates in both basic animal models and in human clinical studies the potential therapeutic role of parathyroid hormone in bone and joint trauma. The supplement will explore sex-based differences in bone regeneration and healing, especially in the function of female and male stem cells that surround bone, in response to treatment with parathyroid hormone after bone injury.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Cellular/Molecular Pathophysiology of Intellectual and Developmental Disabilities**
PI: **Stuart A. Lipton**
Institution: **Sanford-Burnham Medical Research Institute**
Grant No.: **3P01HD029587-19S1**

This research project aims to develop a new type of drug treatment, NitroMemantines, to prevent cognitive deficits in people with Down syndrome that are more common in males. Although the parent grant did not propose to study gender differences, the supplement will examine a range of characteristics in both male and female cells cultured from people with Down syndrome, or from mouse models, to look for sex differences.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Dynamic Stability in the ACL-Injured Knee**
PI: **Lynn Snyder-Mackler**
Institution: **University of Delaware**
Grant No.: **3R37HD037985-12S1**

This research project aims to determine the clinical features of recovery—such as the role and timing of rehabilitation—from anterior cruciate ligament (ACL) injury and reconstruction. The supplement will test the notion that ACL injury and reconstruction-related sex/gender differences can predict the extent of knee function and return to activity.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Role of miR-210 in Placental Mitochondrial Metabolism**
PI: **Leslie Myatt**
Institution: **University of Texas Health Science Center at San Antonio**
Grant No.: **3R01HD076259-02S1**

A pregnant woman's placenta can have a significant influence on the health of her developing fetus and even on the health of the child during his or her adulthood, a phenomenon known as fetal programming. This research project is studying molecular markers called micro-RNAs in pregnant women who are obese or who have severe pregnancy-related high blood pressure known as preeclampsia. The supplement will compare molecular characteristics of male and female placentas to identify sex differences in fetal programming.

IC: National Institute on Drug Abuse
Title: Genetic Influences on Inhibitory Control and Cocaine Sensitivity
PI: David Jentsch
Institution: University of California, Los Angeles
Grant No.: 3R01DA031852-03S1

This research project collects phenotypic (observable) data from a large panel of male-inbred mouse strains to identify genetic associations with the risk of intravenous cocaine self-administration. The supplement will perform the same studies but in adult female mice from 30 common, inbred mouse strains.

IC: National Institute on Drug Abuse
Title: International Collaborative of Prospective Studies of HIV and Hepatitis in IDU
PI: Kimberly Page
Institution: University of California, San Francisco
Grant No.: 3R01DA031056-04S1

This research project is a global collaboration that pools biological and behavioral data from nine prospective study groups of HIV and hepatitis C (HCV) in injection drug users conducted in four countries over 22 years. The supplement will follow up on the group's preliminary findings that female injection-drug users are significantly and independently more likely than male injection-drug users to spontaneously become HCV-free.

IC: National Institute on Drug Abuse
Title: Midbrain Neural Circuit Elements that Underlie Cue-Reward Associations
PI: Garret D. Stuber
Institution: University of North Carolina at Chapel Hill
Grant No.: 3R01DA032750-03S1

This research project aims to identify how nerve circuitry leads to the development and expression of psychiatric disease such as substance abuse disorders. The supplement will build on male-animal studies conducted within the parent grant by investigating nerve circuits that control reward in female rodents in response to infant-associated cues.

IC: **National Institute on Drug Abuse**
Title: **Neural Mechanisms of CBT in Cocaine Dependence (Gender Differences Supplement)**
PI: **Marc N. Potenza**
Institution: **Yale University**
Grant No.: **3R01DA035058-01A1S2**

This research project aims to identify neurobiological factors related to cognitive-behavioral therapy that affect cocaine dependence outcome and response, as well as to deepen understanding of how this treatment works and how long it remains effective. The supplement will employ functional MRI to identify sex-specific brain activation patterns linked to treatment outcomes in cocaine dependence.

IC: **National Institute on Drug Abuse**
Title: **Systems Genetic Analysis of Methamphetamines Motivational Effects in a Mouse AIL**
PI: **Abraham A. Palmer**
Institution: **University of Chicago**
Grant No.: **3R01DA021336-09S1**

Using behavioral models, molecular genetic techniques, and statistical methods, this research project is identifying genes in mice linked to preferences for the effects of certain drugs over the effects of others. The supplement will be used to increase the sample size of animals in the parent grant to follow up on data suggesting that females show greater sensitivity to various aspects of methamphetamine use and effects.

IC: **National Institute on Deafness and Other Communication Disorders**
Title: **Sex Differences in the Neurophysiology of the Olfactory System**
PI: **John P. McGann**
Institution: **Rutgers University**
Grant No.: **3R01DC013090-02S1**

This research project, which images brain activity in the olfactory (smell) system of living, transgenic mice, aims to identify the underlying biological factors behind why most women have a better sense of smell than men. Results from the parent grant show that female mice that tested without regard to estrous cycling produced different patterns of olfactory-related nerve input to the brain than did male mice. The supplement will assess whether circulating estrogen contributes to these differences by adding female mice to experiments.

IC: National Institute of Dental and Craniofacial Research
Title: Preventing Transition of Acute-to-Chronic Neuropathic Pain: Models, Mechanisms and Mediators
PI: Linda Watkins
Institution: University of Colorado Boulder
Grant No.: 3R01DE021966-03S1

This research project is investigating whether glial cells (non-nerve cells in the nervous system) affect the transition from acute to chronic pain as a result of a pronounced response to injury/inflammation. Results from this study indicate, counterintuitively, that male rats given the pain drug morphine at the time of an injury experienced pain. The supplement will assess whether the same is true in female rats.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Critical Translational Studies in Pediatric Nephrology
PI: Prasad Devarajan
Institution: Cincinnati Children's Hospital Medical Center
Grant No.: 3P50DK096418-02S2

This research project created a Pediatric Center of Excellence in Nephrology to support basic, translational, and clinical research on three pediatric kidney diseases that have major unmet needs: acute kidney injury, focal segmental glomerulosclerosis, and lupus nephritis. The supplement will look for sex differences in urine biomarkers for these conditions that were identified by the parent grant and may be useful in clinical trials and in managing patient illness.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Mechanism of Selenoprotein Synthesis
PI: Marla J. Berry
Institution: University of Hawai'i at Mānoa
Grant No.: 3R01DK047320-19S2

This research project studies how the chemical antioxidant selenium participates in metabolism in healthy and diseased cells. The project's preliminary results showed that male mice deficient in a selenium-linked protein were more prone to metabolic syndrome and learning problems. The supplement will study the potential protective effect of estrogen against these health issues in mice by studying a larger number of animals on specialized diets.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Metabolic Impact of Fructose Restriction in Obese Children
PI: Jean-Marc Schwarz
Institution: Touro University of California
Grant No.: 3R01DK089216-05S1

This research project is testing the effectiveness of dietary fructose restriction on diabetes and other consequences of obesity in Hispanic, white, and African American children. The supplement will evaluate potential liver-protective effects of estrogen and also identify sex-based differences in intestinal and liver metabolism.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Regulation of Sex Differences in Liver Metabolism
PI: David J. Waxman
Institution: Boston University
Grant No.: 3R01DK033765-31S1

This research project investigates how growth hormone controls liver function differently in males and females. The supplement will use molecular sequencing of mouse livers to identify all microRNAs (small RNA molecules that control gene and cell function), then search for sex differences in the association between certain microRNAs and growth hormone.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Role of Mesenteric Lymphatics and Dietary Endotoxin in Metabolic Syndrome
PI: Mariappan Muthuchamy
Institution: Texas A&M University Health Science Center
Grant No.: 3R01DK099221-02S1

People diagnosed with metabolic syndrome have three or more conditions that affect metabolism—central obesity, high blood sugar or fat, high blood pressure, and artery thickening—and this leads to increased risk of type 2 diabetes, fatty-liver disease, and cardiovascular diseases. This research project is studying how metabolic syndrome conditions affect the lymphatic system that manages fluid balance throughout the body, and whether those changes contribute to disease. The supplement will add experiments with sufficient numbers of animals to those studied in the parent grant to look for sex differences in factors that influence the flow of lymphatic fluid in the gut.

IC: National Institute of Environmental Health Sciences
Title: Children's Environmental Health and Disease Prevention Research Center at Dartmouth
PI: Margaret Rita Karagas
Institution: Dartmouth College
Grant No.: 3P01ES022832-02S1

This research project supports an ongoing study of pregnant women in New Hampshire who rely on well water in their homes to ascertain molecular changes and child health outcomes from placental exposure to arsenic that may contaminate wells. The supplement will analyze sex-specific differences in identified molecular markers of arsenic exposure.

IC: National Institute of Environmental Health Sciences
Title: CNS Glucocorticoid Epigenetic Changes of Pb Stress Effects
PI: Deborah A. Cory-Slechta
Institution: University of Rochester
Grant No.: 3R01ES021534-02S1

Environmental lead exposure and prenatal stress are co-occurring risk factors for impaired cognition in children, and they also increase risk for adulthood disease. This research project examines, in mice, chemical changes to DNA and proteins in the brain as a result of lead and stress exposure. The supplement will assess sex-specific effects within these molecular changes in the brain.

IC: National Institute of Environmental Health Sciences
Title: Developmental Programming of TCE-Induced Autoimmune Disease
PI: Kathleen M. Gilbert
Institution: Arkansas Children's Hospital Research Institute
Grant No.: 3R01ES021484-02S1

By awarding this supplement, male mice generated during the experiment process of developmental TCE exposure will also be utilized and evaluated for autoimmune outcomes. Results from this parent grant and supplement will provide important information on the mechanisms of TCE-induced autoimmunity.

IC: National Institute of Environmental Health Sciences
Title: Neurodevelopment and Improving Children's Health Following ETS Exposure (NICHES)
PI: Susan Kay Murphy
Institution: Duke University
Grant No.: 3P01ES022831-02S1

The experiments proposed will use a well-characterized rodent model to determine the functional importance of hippocampal and frontal cortical cholinergic systems in the differential impacts of prenatal nicotine and tobacco smoke extract in females and males.

IC: National Institute of General Medical Sciences
Title: An Intercross Between the Circadian and NF-κB Pathways
PI: Marina Antoch
Institution: Roswell Park Cancer Institute Corp
Grant No.: 5R01GM095874-04

This research explores how biological clocks and the immune system interact at the molecular level. The supplement will look for sex-specific differences in an organismal response (male or female mice) to acute stressors using a key immune regulatory system, the NF-κB signaling pathway.

IC: National Institute of General Medical Sciences
Title: PAAR: Pharmacogenomics of Anticancer Agents Research Group
PI: Mark J. Ratain
Institution: University of Chicago
Grant No.: 3U01GM061393-15S1

This research project is studying inherited variability in drug response to cancer therapies by describing drug actions and side effects that vary genetically. The supplement will characterize sex effects on these inherited drug-based effects.

IC: National Institute of General Medical Sciences
Title: Regulation of Kappa-Opioid Receptor-Mediated Signaling and Peripheral Analgesia
PI: William P. Clarke
Institution: University of Texas Health Science Center at San Antonio
Grant No.: 3R01GM106035-01A1S1

This research project aims to identify cellular mechanisms outside of the central nervous system (CNS) that use kappa-opioid receptors to control pain. The ultimate advantage of this approach is to develop treatments that do not produce CNS side effects such as addiction and its associated symptoms. The supplement will add experiments to the parent application to measure pain responsiveness in female rats.

IC: National Institute of General Medical Sciences
Title: The New Family of NEET Proteins: 2Fe-2S Protein Mediated Health and Disease
PI: Patricia A. Jennings
Institution: University of California, San Diego
Grant No.: 3R01GM101467-03S1

This research project is investigating the molecular properties of a newly identified type of protein (called NEET, and found in mitochondria) that is affected by thiazolidinedione-based diabetes medications and that may be useful for targeting breast cancer. The supplement will use both male and female breast cancer cell lines and both sexes of animal models to investigate sex-based characteristics of NEET proteins.

IC: National Institute of Mental Health
Title: Antipsychotic and Folate Pharmacogenetics—Gender Supplement
PI: Vicki L. Ellingrod
Institution: University of Michigan
Grant No.: 3R01MH082784-07S1

The parent research project is determining the effectiveness of folate supplements on metabolic syndrome in people with schizophrenia taking medications called atypical antipsychotics (AAP). The objective of this supplement is to measure gender-specific differences in global and gene methylation potentially related to AAP-associated metabolic syndrome in a well-characterized sample of age-, race-, and folate status–matched subjects. The central hypothesis is that lower methylation profiles, as well as gene-specific differences in methylation, are associated with AAP-related metabolic syndrome in schizophrenia and that female subjects exhibit a different epigenetic profile compared to males.

IC: National Institute of Mental Health
Title: Conte Center for Computational System Genomics of Neuropsychiatric Phenotypes
PI: Andrey Rzhetsky
Institution: University of Chicago
Grant No.: 3P50MH094267-04S1

This research project uses computational modeling to identify new ways to link genetic and environment factors with mental health conditions. The supplement will broaden modeling techniques to include those that assess sex differences in genetic risk for various neuropsychiatric conditions such as anxiety, schizophrenia, and depression.

IC: National Institute of Mental Health
Title: Iron and Mitochondrial Genomics in Neuro-inflammation and HAND: A CHARTER Study
PI: Todd M. Hulgan
Institution: Vanderbilt University
Grant No.: 3R01MH095621-04S1

This research project studies effects of HIV infection and treatment on the central nervous system (CNS), examining data and specimens from an ongoing genome-wide association study. The researchers are looking for genetic contributions to HIV effects—from DNA in the cell's nucleus (in chromosomes) and from DNA in mitochondria (another source of DNA in cells). The supplement will investigate sex differences in CNS effects by measuring mitochondrial DNA in spinal fluid and assessing its relationship to iron metabolism and inflammation.

IC: National Institute of Mental Health
Title: Neural Markers of Shared Gaze During Simulated Social Interactions in ASD
PI: James Charles McPartland
Institution: Yale University
Grant No.: 3R01MH100173-02S1

This research project uses high-speed eye tracking during face-to-face interactions to measure brain activity in adolescents with autism spectrum disorders. The supplement adds females with autism spectrum disorders, permitting determination of sex differences in visual attention and neural response to faces, eye contact, and facial affect.

IC: National Institute of Mental Health
Title: Psychiatric Outcomes of Children at High- and Low-Risk for Depression: Follow-up
PI: Maria Kovacs
Institution: University of Pittsburgh
Grant No.: 3R01MH085722-05S1

This research project is a follow-up study of children 9 to 21 years of age who are at high and low familial risk for depression. It uses both traditional neuropsychological tests and novel modifications of such tests that incorporate emotionally distracting features. The supplement will assess sex differences in depression during this high-risk developmental window for the diagnosis of depression and conduct/substance use-related disorders.

IC: National Institute of Mental Health
Title: Stress Exposure and Immune Outcomes in Children
PI: Thomas G. O'Connor
Institution: University of Rochester
Grant No.: 3R01MH097293-02S1

This research project leverages the NICHD-funded Family Life Project, which has followed approximately 1,200 at-risk children and families since birth to understand the role of stress on childhood immune health. The supplement will look for sex differences in the association between stress exposure and immune response by analyzing 880 blood samples for testosterone, estriol, 17-beta estradiol, and progesterone.

IC: National Institute of Mental Health
Title: The 5-HT Theory of Depression Tested in a Naturalistic Model of 5-HT Deficiency
PI: Marc G. Caron
Institution: Duke University
Grant No.: 3R01MH079201-08S1

This research project employs transgenic mice engineered to have lower than normal brain levels of serotonin, a neurotransmitter associated with mood. The goal of the project is to understand molecular and behavioral consequences of reduced serotonin, which is linked to depression in humans. The supplement will develop a new model to tests serotonin deficiency effects on social stressors since the current model is only applicable to male animals.

IC: National Institute on Minority Health and Health Disparities
Title: Research on Sex/Gender Differences
PI: Robert J. Freishtat
Institution: Children's Research Institute
Grant No.: 3R01MD007075-03S1

This research project studies males and females with asthma to determine whether vitamin D enhances the effectiveness of inhaled steroid treatment of asthma, especially in urban African American youth. To follow up on preliminary results, the supplement will accelerate enrollment of females to look for sex differences in vitamin D effects on inhaled steroid responsiveness.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Administrative Supplement for Sex Differences: Sensory Plasticity in Migraine**
PI: **Kevin Christopher Brennan**
Institution: **University of Utah**
Grant No.: **3R01NS085413-01S1**

This research project is using imaging and other tests to study migraines—in particular how this pain disorder may be related to brain activity that re-sculpts nerve connections and circuits. The supplement will add female mice to experiments to determine the effects of sex hormones on these changes.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Center for Stroke Disparities Solution**
PI: **Gbenga Godwin Ogedegbe**
Institution: **New York University School of Medicine**
Grant No.: **3U54NS081765-02S2**

This research project funds the Center for Stroke Disparities Solutions, which aims to reduce stroke disparities with a particular focus on preventing recurrent stroke. Key approaches include targeting community-based health care providers and patients with interventions and educational materials on the link between high blood pressure and stroke. The supplement will test the effectiveness of a culturally tailored stroke intervention on women of color.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Neonatal Stroke: The Role of Microglia**
PI: **Zinaida S. Vexler**
Institution: **University of California, San Francisco**
Grant No.: **3R01NS044025-11S1**

This research project is investigating how cells called microglia that affect immune surveillance in the brain affect the risk of stroke in newborns, which often causes substantial disability throughout life. The supplement will determine whether the sex of an infant affects his or her vulnerability to stroke and related cell and tissue injury.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Novel Factors for Unexplained Phenotypes of Subclinical Carotid Atherosclerosis**
PI: **Tatjana Rundek**
Institution: **University of Miami Miller School of Medicine**
Grant No.: **3R01NS065114-04S1**

This research project is identifying non-symptom related (subclinical) molecular markers that link atherosclerosis with stroke risk. The supplement will increase sample size by adding data

from related experimental results, such that sex-specific differences in stroke risk can be accurately determined.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **The Role of MeCP2 in Rett Syndrome**
PI: **Janine M. LaSalle**
Institution: **University of California, Davis**
Grant No.: **3R01NS081913-11S1**

Rett syndrome is a debilitating neurodevelopmental disorder caused by genetic mutation within the X-chromosome-linked gene MECP2, and it primarily affects females. This research project focuses mainly on male transgenic mice, and thus the supplement will study the characteristics and effects of this genetic mutation in female mice.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Value of Personalized Risk Information**
PI: **David M. Kent**
Institution: **Tufts Medical Center**
Grant No.: **3U01NS086294-01S1**

This research project explores the value of providing individualized risk analyses to clinicians and patients across a broad range of medical interventions. The supplement will estimate sex-related differences in common cardiovascular and cerebrovascular disease outcomes by analyzing data from computational models of risk prediction.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Vascular Injury and Recovery in Diabetic Ischemic Stroke**
PI: **Adviye Ergul**
Institution: **Georgia Regents University**
Grant No.: **3R01NS083559-01A1S1**

This research project is studying how bleeding into the brain affects brain recovery after stroke in people with diabetes. Preliminary findings in male rats show that diabetes may worsen stroke outcomes. The supplement will conduct experiments in female rats to assess whether sex affects such outcomes.

IC: **Office of the Director**
Title: **The Genetic and Neuroanatomical Origin of Social Behavior**
PI: **Rodney C. Samaco**
Institution: **Baylor College of Medicine**
Grant No.: **3DP5OD009134-04S1**

This research project aims to understand fundamental neuronal and molecular changes related to abnormal social behavior in two mouse models of autism that have mutations in single genes. The supplement will assess sex differences by comparing findings in female mice with those obtained with male mice.

Advancing Novel Science in Women's Health Research

IC: National Cancer Institute
Title: Effects of Continuous Versus Cyclic Oral Contraceptives on Mammary Tumor Growth
PI: Patricia Ann Masso-Welch
Institution: State University of New York at Buffalo
Grant No.: 5R21CA170056-02

There is no question that breast cancer susceptibility is strongly correlated with lifelong exposure to estrogen and progesterone (E+P). Extension of E+P exposure using a widely employed hormone replacement therapy (HRT) increased breast cancer risk in postmenopausal women. Oral contraceptive (OC) use, in a manner similar to HRT, is an example of a widely used hormonal regimen with the potential to impact breast cancer chemoprevention in a huge population. Unlike HRT, OC are used over a large expanse of a lifetime, sometimes initiated as early as puberty, to control fertility and menstrual side effects. With the recent advent of the continuous dosing regimen, in which the hormone withdrawal period is eliminated, women have the option to undergo months or years of continuous hormonal exposure with no remodeling of the breast or uterus that normally accompanies cyclic dosing regimens. Based on the ability of OC to eliminate menstruation and accompanying side effects, it is not surprising that many of the ~ 21% of adult women in the US who are current users of OC have begun to shift to a continuous regimen. It is critical, therefore, to determine whether continuous exposure to OC carries a significant risk to increase breast cancer. Although we might predict an increased risk (based on the risks from HRT), cycling women experience two types of tissue responses that do not occur in menopausal women: (i) cycles of epithelial and stromal vascular (angiogenic) proliferation in response to hormones, and (ii) cycles of apoptosis and glandular and stromal vascular regression. These two observations suggest two alternate potential outcomes of continuous OC dosing: (i) If hormone-dependent epithelial and angiogenic proliferation is critical to breast cancer risk, we predict that continuos OC use will increase breast cancer risk; (ii) Alternately, if the glandular and stromal vascular regression and remodeling in response to hormone withdrawal contribute to breast cancer risk (as has been proposed for hormone withdrawal during post-lactational involution), then continuous dosing may decrease breast cancer risk. This proposal is designed to test these two alternate hypotheses. Aim 1 will compare the ability of cyclic (3 days on, 1 day off) versus continuous dosing +/- OC to alter spontaneous tumor development, progression, and metastases in the FVB-MMTV-Her-2/Neu model of spontaneous mammary tumorigenesis. Aim 2 will compare the ability of cyclic versus continuous dosing +/- OC to alter the mammary tumor growth using the TM2H transplantable mouse mammary tumor cell line. Mammary tumors from different treatment groups will be compared for alterations in expression of ER, PR, and Her2/Neu, vascularity and proliferative and apoptotic indices. The primary outcome of these studies is to define the effects of continuous dosing of OC on primary and metastatic mammary tumor growth in two distinct mouse mammary tumor models, relative to no OC or cyclic dosing of OC.

IC: National Cancer Institute
Title: Validation of a Risk Assessment Decision Rule for Epithelial Ovarian Cancer
PI: Nicole Denise Urban
Institution: Fred Hutchinson Cancer Research Center
Grant No.: 5R21CA179443-02

Our goal is to develop a risk-classification tool to identify post-menopausal women who are at high or elevated risk for epithelial ovarian cancer (EOC). We will develop and validate a risk-assessment decision rule based on serum markers CA125 and HE4, as well as epidemiologic risk factors, using a split-sample design and data from the Women's Health Initiative (WHI) Observational Study (OS), the WHI Clinical Trial (CT), and the Prostate, Lung, Colon and Ovary (PLCO) trial. A decision rule developed as preliminary work identified 10%–13% of all post-menopausal women as elevated risk and predicted 26%–58% of cases. Surgical prevention consisting of prophylactic removal of fallopian tubes (FTs) and ovaries is recognized as the best approach to prevent epithelial ovarian cancer (EOC) and especially high-grade serous cancer (HGSC) in high-risk women. We will develop a tool to categorize women into risk classifications that have clear clinical implications including recommendations for surgical prevention, imaging, surveillance, and routine care. In the first 2 aims, we will focus on development of the epidemiologic portion of the model because the serum marker portion of the decision rule has already been developed based on extensive published work. In Aim 3, we will validate the final decision rule that combines epidemiologic risk factors with serum markers. We operationally define high risk as relative risk (RR) of at least 6, and elevated risk as RR of at least 2. Aim 1: Using a randomly selected fraction of women participating in the WHI OS, WHI CT, and the PLCO trial, develop decision rules to identify women at elevated risk for EOC and HGSC using epidemiologic variables alone. Using the remaining women from each study, validate each decision rule within each population. Decision rules developed in this aim will be specific to each study population in order to take advantage of all of the epidemiologic data collected by each study. Aim 2: Cross-validate the decision rules developed in Aim 1 to identify the rule that best identifies women at elevated risk for EOC and HGSC across the 3 different populations. This will require refinement of the decision rules to accommodate differences in data collection across the cohorts. The study fraction used for development will be used to identify the best common rule, and cross-validation will employ the remaining validation fraction of women participating in the WHI OS, WHI CT, and the PLCO trial. This aim will identify the best epidemiologic decision rule for use in the overall decision rule to be validated in Aim 3. Aim 3: Using nested case-control study serum marker data as well as epidemiologic data from each study, validate the best decision rule from Aim 2 in combination with the serum marker component of the rule to identify women at elevated- and high-risk for EOC and HGSC in each of those populations. In this aim, we will validate the final decision rule that incorporates both epidemiologic risk factors and serum markers.

IC: National Heart, Lung, and Blood Institute
Title: Pregnancy Complications, Future Cardiovascular Disease Risk Factors, and Cardiovascular Disease Risk Prediction in Women
PI: Nisha Indravadan Parikh
Institution: University of California, San Francisco
Grant No.: 7R21HL115398-02

Currently available cardiovascular disease (CVD) risk scores in women usually include risk factors, which are gender-neutral and often lead to an underestimate of CVD risk. There are factors in the life course of women that are unique and gender-specific, which relate to long-term CVD risk. Pregnancy is considered a "cardiometabolic stress test" such that adverse pregnancy factors/outcomes in a woman predict future CVD risk factors and incident CVD. The American Heart Association's and American College of Cardiology's Effectiveness-Based Guidelines for CVD Prevention in Women recommend taking a pregnancy history for CVD risk stratification; however, it is unclear which pregnancy factors are independently related to CVD when taken together. Specific pregnancy factors that have been demonstrated to predict CVD risk factors and CVD include pregnancy-induced hypertension or pre-eclampsia, gestational diabetes, having a small for gestational age infant, a low or very high number of pregnancies, pre-term delivery, stillbirth, and a history of subfertility. We believe that a pregnancy risk score derived from these candidate pregnancy factors will help medical caregivers determine which specific factors in a woman's pregnancy history are most important as far as predicting future CVD risk factors and future CVD. A pregnancy risk score may help providers with personalized, earlier referral for upstream risk factor modification and may also allow a woman to assess her own CVD risk. In this proposal, we have the following three research goals: (1) To determine which subset of pregnancy-related factors is related to blood pressure, oral glucose tolerance test, and lipid profile, in the Västerbotten Intervention Programme (VIP) when linked to the Swedish population registers (estimated n = 16,041); (2) Utilize a multiple-marker approach to develop and validate a pregnancy factor risk index in the Swedish population registers (estimated n = 800,000); and (3) To determine whether the pregnancy factor risk score (developed in specific Aim 2) improves CVD risk stratification (discrimination, calibration, and net reclassification) above and beyond established CVD risk factors among women using the VIP dataset linked to Swedish population register.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Magnetic Resonance Imaging of Bound and Free Water in Cortical Bone
PI: Jiang Du
Institution: University of California, San Diego
Grant No.: 5R21AR063894-02

Routine clinical evaluation of osteoporosis (OP) has been limited to the assessment of bone mineral density (BMD) using dual energy x-ray absorptiometry (DEXA) and/or CT. The majority of bone, the organic matrix, and water, which together represent ~ 57% of bone by volume, are not accessible with these techniques. BMD alone predicts fractures with only a 30%–50% success rate. The missing factor may be the contribution of bone organic matrix and water. Bone water occurs at various locations and in different states. It is bound to the organic matrix or in "free" form in the Haversian and the lacunar-canalicular systems. The bound water

content reflects organic matrix density. The free water content can potentially provide a surrogate measure of bone porosity. However, neither DEXA nor CT can detect either bound or free water in cortical bone. We have developed ultrashort time-to-echo (UTE) magnetic resonance imaging (MRI) sequences with minimum TEs of 8 μs, and this makes it possible to detect water signal from bone. Total bone water can be quantified by comparing UTE signal from bone and a water phantom. Bound water can be selectively imaged with SIR-UTE sequences, which use a single adiabatic inversion pulse to invert and null the free water magnetization. Free water can be selectively imaged with DIR-UTE sequences, which saturate bound water while leaving free water magnetization unaffected. Bound water has ~ 10 times shorter T2* than free water. The two components may be separated with bi-component fitting. Free water has a short T2* but long T2, and may be imaged with FSE sequences. The UTE approach may detect the effect of Gadolinium chelates within cortical bone and study its perfusion at high resolution. This provides a new way to characterize cortical bone. In this proposal we hypothesize that bone water content and bone perfusion can be non-invasively assessed by novel MRI techniques and can serve as sensitive biomarkers of bone quality. We aim to develop novel UTE, SIR-UTE, DIR-UTE, and FSE techniques to measure total, bound and free water in cortical bone (Aim 1); to evaluate the accuracy of MR measures of two groups of women cadaveric human tibia specimens—the younger group (< 60 years old) and the older group (> 80 years old)—and correlate the results with cortical porosity determined by mCT and organic matrix content determined by ashing, as well as elastic properties (modulus, yield stress and strain) and failure properties (ultimate stress, failure strain and energy) determined by 4-point bending test (Aim 2); and to develop translational MR techniques to quantify total, bound, and free water as well as bone perfusion in two groups of postmenopausal women: i.e., below 60 without OP and above 80 with OP (Aim 3). The intention is to develop and validate these techniques in tissue studies and a small number of patients to provide preliminary data for an RO1 grant application on the use of MR in diffuse bone disease including OP, renal osteodystrophy, Paget's disease, and osteomalacia. The comprehensive characterization of bone in these conditions could have a profound impact in their diagnosis and treatment.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Role of MicroRNA-29 in Uterine Leiomyoma Pathogenesis**
PI: **Erica E. Marsh**
Institution: **Northwestern University at Chicago**
Grant No.: **5R21HD077479-02**

Leiomyomas are highly pervasive benign tumors of the uterus that have an overall prevalence of 70% in women by the age of 50. They are the leading cause of hysterectomy in the United States, accounting for almost 50% of the 600,000 hysterectomies performed annually and $34 billion in annual health care costs. Despite their prevalence and public health impact, the cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Phenotypically, these tumors are distinct from the adjacent normal tissue largely due to the overproduction of extracellular matrix component, especially the major fibrillar collagens (I, II, and III). We, and others, have demonstrated that in addition to differentially expressed genes between LEIO and MYO, there is differential expression of microRNAs, suggesting that they play a role in gene regulation of these tumors. MicroRNAs are a class of small non-coding RNAs that negatively regulate gene expression. While several studies have documented

hormonal and growth factor regulation of miRNAs in leiomyomata, none have demonstrated a functional role for them in terms of their main distinguishing pathological finding: excessive collagen deposition. Our lab has found that all of the members of the miR-29 family (29a, 29b, 29c) are down regulated in leiomyoma versus normal myometrial tissue. Based on recent studies in other fibrotic diseases and preliminary data included in this application, we hypothesize that this dysregulation of the miRNA-29 family plays a functional role in the aberrant extracellular matrix components found in leiomyomata. To address this hypothesis, we propose the following two specific aims: In Specific Aim 1, we seek to determine the mechanism by which TGF-β regulates miR-29 levels in uterine leiomyomas. TGF-β is known to be present in higher concentrations in leiomyoma versus adjacent normal myometrial tissue. To determine its role in the regulation of miRNA-29, we will perform SMAD2/3 knockdown and chromatin immunoprecipitation studies. In Specific Aim 2, we will determine the contribution of the miR-29 family (a/b/c) to the excess major fibrillar collagen production in uterine leiomyoma. The role of miRNA-29 will be assessed using knockdown and overexpression studies. The results from these studies will not only provide mechanistic information on the excess extracellular matrix seen in leiomyomas but will also lay the foundation for future preclinical studies as our understanding of both miRNAs in human disease and oligonucleotide based therapeutics continues to expand.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **STI Risk Among Adolescent Females: Activity Spaces and Spatial Mobility**
PI: **Anita Raj**
Institution: **University of California, San Diego**
Grant No.: **5R21HD073610-02**

The goal of this study is to determine the role of social spaces (locations where social interactions occur) and spatial mobility on risk for chlamydia and gonorrhea among adolescent girls living near the US–Mexico border. Adolescent girls have the highest burden of chlamydia (CT) and gonorrhea (GC) compared to any other age-sex group in the United States. Several studies have begun to examine how neighborhood or community-level structural factors may influence health risks, including sexual risk and sexual violence; however, these studies don't account for mobility of individuals across arbitrary neighborhood boundaries. The exposures and experiences that occur in adolescents' different social spaces shape their own behaviors, including those that put them at higher risk for STI and sexual violence. Mobility may impact not only exposure to different community-level structural factors, but also the number and type of social spaces frequented. Additionally, the rapid increase in the number and type of accessible technologies for communication has greatly impacted the manner in which socialization occurs. Understanding how adolescents incorporate this technology into identification of social spaces and attendance of social activities may help identify novel targets for sexual health interventions. In this study, we aim to (1) develop categories and measures to describe the types and characteristics of adolescents social spaces, including locations where adolescents may be exposed to sexual violence, and adolescents' patterns of mobility; (2) compare types of social spaces, including the geographic location of these spaces, and patterns of mobility between adolescents testing positive for CT and/or GC and those testing negative; and (3) to use qualitative methods to provide a deeper understanding of the role of communication technology

in adolescents' identification of activity spaces and engagement in social activities and related sexual and substance use risk behaviors. To meet these aims, we will conduct a case-control study among adolescent girls (age 15–19 years) in collaboration with a youth center and clinic in a culturally diverse neighborhood with a high proportion of ethnic minorities. Fifty cases (positive test for CT and/or GC) will be referred from the clinic, and 150 controls will be recruited from those seeking family planning/reproductive health services from the youth center. Participants will be asked to complete an interviewer-administered survey including questions about demographics, sexual/reproductive health, sexual and substance use behavior, and exposure to sexual violence, as well as a mapping component to identify social spaces using Google Earth. A sample of cases will be asked to participate in a second, in-depth interview about the use of technology in social activity decision-making. This study is consistent with the goals of the NIH ANSWHR PAS (PAS-10-226), offering an interdisciplinary study combining concepts of spatial mobility with a gendered perspective on STI risk among sexually active adolescent girls and will provide a framework to explore innovative structural-level interventions to reduce STI risk among this population.

IC: **National Institute of Environmental Health Sciences**
Title: **Arsenic Repression of GADD153 and Breast Cancer**
PI: **Keshav K. Singh**
Institution: **University of Alabama at Birmingham**
Grant No.: **5R21ES023091-02**

Arsenic is a well-known human carcinogen. Previous studies including human population studies provide an extensive and important link between the arsenic exposure and development of breast cancer. These studies suggest that arsenic accumulates in breast tissues and acts as an endocrine disruptor to promote development of breast cancer. Arsenic is one of the few human carcinogens that do not induce tumors in laboratory animals. Therefore, development of models for arsenic-induced breast cancer is critical for understanding the mechanism(s) underlying the tumorigenic process. We have developed a mammary epithelial cell model for arsenic-induced cancer. To replicate normal field exposure conditions, we exposed mammary epithelial cells to a low dose of arsenic for several months. We discovered that a five-month continuous exposure of mammary epithelial cells results in increased cell proliferation, increased wound healing, increased anchorage independent growth, as well as increased matrigel invasion. These studies suggest a tumorigenic transformation of mammary epithelial cells by exposure to arsenic. Mitochondria control cell growth and cell death. Mitochondria also perform other cellular functions including ATP production via mitochondrial oxidative phosphorylation (mtOXPHOS). Consistent with this finding arsenic-transformed cells show (1) altered mtOXPHOS Complex I and IV activities, (2) an altered expression of subunit NDUFB8 comprising mtOXPHOS Complex I, and (3) altered expression of COXII subunit comprising mtOXPHOS complex IV. Interestingly, our study suggests that arsenic-treatment did not induce changes in mtOXPHOS Complex II and III activities. These preliminary studies revealed that arsenic targets mitochondria and induces mitochondrial stress. Recent studies suggest that human cells contain mitochondria specific stress response pathway in which transcription factor GADD153 (also known as CHOP or DDIT3) plays a key role. We measured the expression of GADD153 and found that arsenic represses GADD153 expression. GADD153 is described to play a critical role in cell death, and suppression of GADD153 expression is known to protect cells from cell death. However, GADD153's role in arsenic induced carcinogenesis is unknown. We hypothesize that

arsenic represses expression of GADD153/CHOP/DDIT3 to protect cells from arsenic induced cell death, which contributes to tumorigenic transformation of mammary epithelial cells induced by arsenic. To address this hypothesis, we will: Aim 1: Determine a role for GADD153 in protection against cell death and mitochondrial stress induced by arsenic. Aim 2: Determine whether arsenic repression of GADD153 expression contributes to tumorigenic transformation of breast epithelial cells in vitro and in vivo in mouse xenograft model. The proposed studies should provide insight into the mechanism involved in arsenic induced breast tumorigenesis.

IC: **National Institute of General Medical Sciences**
Title: **Macrophage Phenotype as a Determinant of Outcome in Pelvic Organ Prolapse Repair**
PI: **Bryan Nicklaus Brown**
Institution: **University of Pittsburgh**
Grant No.: **5R21GM107882-02**

Pelvic organ prolapse (POP) results in 225,000–300,000 surgical procedures per annum and with costs exceeding $1 billion in the United States. Native tissue repair of POP is associated with high recurrence rates. Therefore, synthetic mesh, originally intended for abdominal wall hernias, has been increasingly used in repair of pelvic organ prolapse to improve anatomic success. However, surgeries which include mesh, such as the "gold standard" abdominal sacrocolpopexy and the newer vaginal mesh procedures, are associated with high rates of patient morbidity including higher rates of fistula formation, erosion, infection, and pain. The rates of these complications are significant enough to warrant FDA warnings in 2008 and 2011. Many of these complications have been directly attributed to the immune response of the host to the synthetic mesh. There is a lack of rigorous scientific studies characterizing the effects of this host response in the vagina and the design of mesh materials largely relies on data generated in abdominal hernia repair. As a result, clinicians may select products based upon the recommendations of a vendor or institution, leading to the use of mesh in women on a trial and error basis. Macrophages have recently been classified as having diverse and plastic phenotypes between M1 (classically activated; pro-inflammatory) and M2 (alternatively activated; regulatory, homeostatic) extremes. Increasingly, macrophage polarization and plasticity are being shown to play important, and determinant, roles in disease pathogenesis and tissue remodeling. The timely modulation of macrophage phenotype appears to be a crucial event in the tissue remodeling process. An increasing number of studies in the field of biomaterials have begun to apply these paradigms and concepts, and have shown that macrophage phenotype is a predictor of integration following placement. Briefly, the early macrophage response following implantation of biomaterials is a necessary and essential component of a beneficial response and that strategies which incorporate and modulate the host macrophage response rather than seek to avoid it result in improved tissue incorporation and long-term functional outcomes as a result. We, therefore, propose to investigate the role of macrophage polarization following placement of synthetic mesh in an in vivo transvaginal model to further elucidate how both individual mesh characteristics and modulation of macrophage phenotype in the immediate postoperative period can determine long-term incorporation or complications related to synthetic mesh placement. Completion of these studies on the evaluation and modulation of the host tissue response to synthetic mesh used in pelvic organ prolapse has the potential to inform the selection of mesh materials and to significantly affect the design of next generation mesh materials leading to improved patient outcomes.

Building Interdisciplinary Research Careers in Women's Health

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Careers in Women's Health**
PI: **Clay F. Semenkovich**
Institution: **Washington University in St. Louis**
Grant No.: **5K12HD001459-15**

Gender has complex and poorly understood effects on health throughout the different phases of life. The mechanisms underlying the unique course of several diseases affecting women remain unclear in part because of longstanding impediments to research efforts involving different disciplines. The long-term objective of this application, supporting the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program at Washington University, is to produce independent investigators conducting interdisciplinary research in women's health. The application 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. During the past 10 years, the Washington University BIRCWH Program has successfully achieved this aim through a combination of a mentored research experience (utilizing outstanding mentors representing a broad research base encompassing most of the diseases that differentially affect women), didactic training, interaction with scientists from other disciplines pursuing problems in women's health, establishing a visiting scientist program, and formalizing interdisciplinary research links with a substantial number of clinical programs in women's health. The Program now proposes to extend this 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 Infectious Disease Research (CWIDR) 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Careers in Women's Health at UC Davis**
PI: **Ellen B. Gold**
Institution: **University of California, Davis**
Grant No.: **5K12HD051958-10**

Over the past 4 years, the 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 crosscutting 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. The guiding values of our BIRCWH program include collaboration and celebration of diversity, traditions at UC Davis reflecting the demographics of our community. A formal evaluation program will drive continuous improvement to ensure that we nimbly respond to new research directions and techniques and the needs of our scholars and the women we serve.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Career in Women's Health (BIRCWH) Scholars**
PI: **Elizabeth S. Burnside**
Institution: **University of Wisconsin–Madison**
Grant No.: **5K12HD055894-08**

The goals of the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholars Program at the University of Wisconsin (UW) are (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 (WH). 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. We believe that integrating biomedical sciences, public health sciences, and sociocultural and behavioral sciences is a prerequisite to addressing the linkages of macro-societal issues with pathogenesis of disease, so important in addressing health disparities. Thus, the UW BIRCWH provides interdisciplinary and 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. To address not only the broad array of research areas outlined above but also the interdisciplinary nature of the possible candidates, the faculty is interdisciplinary and consists of physician scientists, perinatal researchers, sociologists, nurse scientists, nutritional scientists, epidemiologists, and economists. The outstanding research mentors selected for the BIRCWH

are enthusiastic about the opportunity to mentor more advanced Scholars through the BIRCWH. A major strength of the UW proposal is the integration of the BIRCWH Scholars into a thriving interdisciplinary WH and health equity and health disparities research network. 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. These future leaders in academic medicine will play a major role in improving the health and health care of all women, pushing forward the frontiers of WH research, bringing new knowledge to beneficial application, and framing the WH research agenda of the future.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Careers in Women's Health**
PI: **Katherine E. Hartmann**
Institution: **Vanderbilt University**
Grant No.: **5K12HD043483-13**

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. Scholars are selected by competitive review of applications from among early career faculty. Training is tailored to the individual investigator, in the context of structured interdisciplinary mentorship, and is overseen by the PI, Program Director and Assistant Program Director (each a former BIRCWH Scholar). BIRCWH program resources are further enhanced by myriad institutional resources that ensure our researchers thrive. Scholars form a mentoring panel, participate in regular BIRCWH work-in-progress presentations and seminars, receive formal evaluation each year, attend twice-monthly career development seminar series with other K-awardees, and are regularly exposed to case

studies on responsible conduct of research. They have access to: (1) an array of core labs and resources; (2) biostatistics consultations; (3) manuscript preparation work groups; (4) technical editing of completed products; (5) studios with experts to vet scientific ideas, research designs, and aims; (6) robust intramural pilot and feasibility funding; and (7) grant writing support including grant workshops, a funded grant library, and mock study sections. Tools are in place to evaluate both mentees and mentors and to continuously enhance our program. Further oversight is provided by an Advisory Committee and biennial external reviews. Combined, these efforts assure we carefully foster excellence in the next generation of women's health researchers.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Careers in Women's Health**
PI: **Nancy Catherine Andrews**
Institution: **Duke University**
Grant No.: **5K12HD043446-13**

Duke University, a research-intensive institution, and North Carolina Central University, 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 independent women's health researcher careers. 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 (1) Develop highly skilled, innovative junior researchers investigating women's health and sex/gender elements of health and disease across a woman's lifespan through the use of interdisciplinary approaches; (2) Foster 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. This application describes the major contributions of our Scholars to women's health research and the impact on our institutional environment related to women's health research. Scientific areas studied include pregnancy-related conditions that affect the mother, fetus, and neonate, as well as obesity, cardiovascular disease, and breast and gynecological cancers. The under-researched and poorly understood gynecological diseases of uterine fibroids, urogynecological conditions including pelvic floor prolapse, and diseases in elderly women such as depression are also addressed. We plan to support four junior faculty members (at least one individual from NCCU) at any one time. Scholars choose a primary mentor from a core group of nationally known senior investigators from both Duke and NCCU. A second mentor is chosen from among the entire senior faculty to maximize interdisciplinary collaborations. The career development program is individualized and spans two to five years depending on the research area and the Scholar's educational needs. The program consists of an intense hands-on research project supervised by mentors, a seminar series, training in responsible conduct of research, and didactic course work. An annual BIRCWH Symposium presents the work of BIRCWH Scholars to the wider research communities at Duke and NCCU. At the completion of the program, the Scholars are expected to have published their results in peer-reviewed journals and obtained funding as a Principal Investigator. The Scholars' progress is monitored by the Leadership Team and the Internal Advisory Board (IAB). This IAB and an

External Advisory Board evaluate the program and advise the Leadership Team. Thus, 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Careers in Women's Health at Michigan State**
PI: **Claudia B. Holzman**
Institution: **Michigan State University**
Grant No.: **5K12HD065879-05**

The ultimate goal of the Building Interdisciplinary Research in Women's Health (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. The Advisory Committee includes distinguished researchers and leaders, including the leaders of two NSF-funded initiatives to enhance faculty development at MSU. The proposed program will sponsor approximately eight BIRCWH scholars over the life of the grant. Each scholar will each receive two to four years of support, with a fifth year available with the recommendation of the Advisory Committee. Scholars will have at least 75% protected time (50% for surgeons). The MSU BIRCWH program includes a core curriculum and a curriculum tailored to the stage of development of the scholar and emphasizing responsible conduct in research. 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. The University and the participating Centers, colleges, and programs are fully committed to the success of the BIRCWH program. The program will help ensure that promising junior researchers have the protected time, mentorship, and training to become successful women's health researchers.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Research Careers in Women's Health in Pittsburgh**
PI: **Yoel Sadovsky**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **5K12HD043441-13**

The goal of this competitive renewal of our career development program, entitled Building Interdisciplinary Research Careers in Women's Health in Pittsburgh (BIRCWH@Pitt), is to build on our past programmatic success to train, nurture, and support talented University of Pittsburgh faculty scholars in interdisciplinary research across a woman's lifespan. Our objectives build on our unparalleled strength in reproductive sciences and women's health research, emanating from Magee-Womens Research Institute (MWRI) at the geographical center of the main campus of the University of Pittsburgh. MWRI is also adjacent to Magee-Womens 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, 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 in 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, attraction of new trainees through intellectual stimulation, motivation of new collaborative synergies, and implementation of sustainable women's health research. Cognizant of the fact that our scholars enter our program with diverse academic backgrounds and investigative skills, we have crafted individually tailored career development plans of 2–4 years, depending on each scholar's training and expertise. 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. We plan to train seven scholars with diverse research interests, each guided by an interdisciplinary group of three mentors, and overseen by an Advisory Committee comprised of researchers with heterogeneous scientific backgrounds. Resources garnered through our program are shared with other reproductive sciences trainees in the Department of OB/GYN, MWRI, and elsewhere in the University. Together, BIRCWH@Pitt emphasizes imaginative thinking, cross-fertilization and collaboration that bridges basic sciences and clinical medicine, and serves to propel our scholars to successful careers in women's health.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Building Interdisciplinary Women's Health at MUSC**
PI: **Kathleen T. Brady**
Institution: **Medical University of South Carolina**
Grant No.: **5K12HD055885-08**

This application from the Medical University of South Carolina (MUSC) requests support for renewal of the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program initially funded in 2007. 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 U.S. Since its inception, the MUSC BIRCWH has supported 9 Scholars, including 4 PhDs, 4 MDs, and 1 MD/PhD. 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 two and maximum of four years, depending on their level of training and experience at entry. We plan to have 5 Scholars in the program at any point in time, 4 supported by the BIRWCH program and 1 under-represented minority Scholar supported by an institutional commitment from the Dean of the College of Medicine. While each Scholar will have an individual career development plan, all will participate in core components, such as a seminar series focused on sex and gender issues in neuroscience research, MUSC's Sex and Gender Studies Research Day, and training in responsible conduct of research, providing ample opportunity for interaction and the development of interdisciplinary collaborations. 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 four 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. Their research interests are congruent with the special emphasis areas of prevention and treatment, and biological and behavioral basis of sex and gender differences, identified as high-priority areas in the new BIRCWH RFA-OD-11-002.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Career Development in Women's Health (CDWH)**
PI: **Andrea Dunaif**
Institution: **Northwestern University**
Grant No.: **5K12HD055884-08**

The Northwestern University (NU) Building Interdisciplinary Careers in Women's Health (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 the Feinberg School of Medicine (Medicine, Neurology, Obstetrics & Gynecology, Preventive Medicine, and Psychiatry & Behavioral Sciences) and the 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. It should be noted that many of the NU BIRCWH CDWH Mentors have longstanding programs that are interdisciplinary in nature, which means that they could fit well within more than one of our research categories. NU BIRCWH CDWH Scholars will be assigned Mentors from at least two different disciplines and training backgrounds for interdisciplinary research and career development. Each Scholar's Mentors will interact closely with the Scholar and provide guidance to develop a tailored career development plan as part of an interdisciplinary mentoring team. The Mentors are all committed to continuing their involvement throughout the award period. The Program will continue to be monitored by the External Advisory Committee whose members are all BIRCWH PIs at other institutions as well as by the Oversight Committee. Formal program evaluation has already been implemented by the NU Searle Center for Advancing Learning & Teaching.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Career Development Program in Women's Health Research at Penn State**
PI: **Carol S. Weisman**
Institution: **Pennsylvania State University Hershey Medical Center**
Grant No.: **5K12HD055882-08**

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 8 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 BIRCWH Program is overseen by an Advisory Committee including 11 senior administrators and faculty members from the three participating colleges. The 8 BIRCWH Scholars funded during the Program's first 5 years represented the fields of general internal medicine, endocrinology, infectious disease, kinesiology, physiology, psychology, and sociology/demography, and were recruited from a large, diverse applicant pool. 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Cincinnati Interdisciplinary Women's Health Research Career Training Grant**
PI: **Joel Tsevat**
Institution: **University of Cincinnati**
Grant No.: **5K12HD051953-10**

The overall objective of this competitive renewal application is to sustain an effective Interdisciplinary Research Careers in Women's Health Research (BIRCWH) Scholars Program, whose mission is to identify and train junior faculty members within the University of Cincinnati (UC) College of Medicine (COM) and the Cincinnati Children's Hospital Medical Center (CCHMC). The 2 institutions are located across the street from each other and share faculty, with all CCHMC faculty having appointments at UC. The 2 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. Our BIRCWH program has established a track record of developing junior faculty in the area of women's health. The first 3 Scholars who graduated were recruited to full-

time faculty positions—1 at University of Texas Southwestern, 1 at UCLA, and 1 at UC's Department of Environmental Health; all 3 are independently funded. The BIRCWH renewal application focuses in 6 main areas: cancer, developmental biology, pharmacology/pharmacogenetics, reproductive health, adolescent gynecology, and behavioral medicine. As with the first BIRCWH, we plan to train 4 scholars at a time: 2 MDs and 2 PhDs. Scholars will have 3 years of protected time for mentored research and career development. We have assembled a cadre of mentors who have at least $250,000 of funding, 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Hormones & Genes in Women's Health: Bench to Bedside**
PI: **Jill M. Goldstein**
Institution: **Brigham and Women's Hospital**
Grant No.: **5K12HD051959-10**

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 our Harvard 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 competing renewal application seeks to continue to support an integrated interdisciplinary training program that is based on a translational approach to understanding differential 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 Brigham & Women's Hospital (BWH) is and will continue to be the home site for this endeavor, in the broader context of a Harvard-wide training program. The program capitalizes on the long tradition of interdisciplinary research in women's health with Mentors who already collaborate across institutions at BWH, Massachusetts General Hospital, Beth Israel Deaconess Medical Center, Dana-Farber Cancer Institute, McLean Hospital, Harvard School of Public Health, Harvard Medical School, and the Eli & Edythe Broad Institute. Each of four Scholars is assigned a team of Mentors in order to operationalize the concept of training Scholars to think in a translational manner. Primary Mentors are in clinical or basic research and provide the site at which the Scholar works. Secondary Mentors are in basic or clinical research (as a counterpart to the Primary) and help to guide thinking, suggest coursework, and readings, depending on the Scholar's interest. Career Mentors advise Scholars in the relevant departmental and academic structures for career advancement. Mentors in health disparities expose Scholars to thinking about how the roles of hormones and genes in predicting morbidity are influenced by socioenvironmental factors. The Harvard BIRCWH program focuses on the following disorders, given either the known higher incidence in women than 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, uterine). By capitalizing on the vast resources and faculty at Harvard, we would argue that Harvard is an ideal site for continuing to offer an integrated, interdisciplinary, and truly translational program that is training the next generation of leaders in women's health.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Kansas BIRCWH Career Development Program in Women's Health**
PI: **Patricia A. Thomas**
Institution: **University of Kansas Medical Center**
Grant No.: **5K12HD052027-10**

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 a successful application for a 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 12 and 31 in the nation for NIH funding, respectively. Mentors are in five thematic areas related to women's health: (i) women's reproductive health; (ii) maternal health; (iii) pathogenesis of diseases prevalent in women; (iv) drug design, drug delivery, and pharmacogenomics; and (v) prevention, intervention, and health disparities. After the grant was funded, the KUMC BIRCWH K12 program provided advanced training and career guidance for 10 junior faculty members pursuing interdisciplinary research in women's health. Four years into the funded project, 7 IWHR Scholars have received extramural funding and at least 11 junior level (assistant professor) faculty members have been hired in tenure-track positions pursuing women's health research at the University of Kansas. 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. Successful renewal of the KUMC BIRCWH K12 Program will continue to positively impact the pursuit of women's health research in Kansas.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Maryland's Organized Research Effort in Women's Health**
PI: **Patricia Langenberg**
Institution: **University of Maryland, Baltimore**
Grant No.: **5K12HD043489-13**

The primary goal of the University of Maryland's proposed 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 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. The objectives of the program are (1) to continue to identify and recruit outstanding new investigators who are either already on the faculty of one of the professional schools at UMB or who would be excellent external candidates for faculty positions (special attention will be given to the recruitment and training of underrepresented minorities, those with disabilities, and women); (2) to continue to provide mentored interdisciplinary training in women's health research by developing individualized teams of mentors for each Scholar, taking advantage of the strong existing basic science, genomic and genetic, translational, clinical, behavioral, epidemiological, and health services research based at UMB, the institutional research infrastructure, and formal didactic training opportunities in design and conduct of research; (3) to provide junior investigators with training in the academic and professional skills needed to become successful independent scientific investigators; and (4) to continue to evaluate the MORE-WH program by tracking the career progress of its Scholars, by responding to the advice and critiques of our Internal and External Advisory Committees, and by continuing to employ feedback mechanisms for program modification.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Mayo Clinic Interdisciplinary Women's Health Research Program**
PI: **Walter A. Rocca**
Institution: **Mayo Clinic, Rochester**
Grant No.: **5K12HD065987-05**

The Mayo Clinic Interdisciplinary Women's Health Research (IWHR) Program is designed to be highly responsive to the "Building Interdisciplinary Careers in Women's Health" RFA-OD-09-006. Embedded in the design of our program are each of the overarching themes of the RFA, 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 Mayo Clinic is the collaborative and interdisciplinary nature of our clinical, educational, and research activities, which 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 cross 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 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. IWHR scholars will benefit from a structured, mentored research training experience including a didactic program appropriate to their background and career goals. The broad scope and interdisciplinary nature of our IWHR program reflects the intra- and interdisciplinary opportunities at Mayo and extends research in women's health beyond that which is currently represented at the other funded BIRCWH programs. Thus, the Mayo Clinic IWHR Program will help to sustain diversity and depth in women's health research for the Nation.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Michigan BIRCWH Career Development Program**
PI: **Timothy R. Johnson**
Institution: **University of Michigan**
Grant No.: **5K12HD001438-15**

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 4 scholars with a minimum of two clinician scientists and one or two nonclinical postdoctoral scientists per year for a minimum of two 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. The scholars will have 75 percent protected time for research and research career development. 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. Each plan will include an intensive supervised research experience, instruction, and assistance in grant writing/submission, experience in scientific writing, ongoing mentor feedback, formal annual evaluation, and instruction in the responsible conduct of research. 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. A senior Advisory Committee will oversee the program with emphasis on recruitment, selection,

assessment of progress, and post-completion tracking of scholars. Support provided by the grant will help assure continued success in our efforts to promote the transition of women's health researchers to scientific independence. Of the 17 scholars trained by the Michigan BIRCWH since 2000, 5 are currently associate professors in schools of medicine, public health, and literature and science; 11 are assistant professors in schools of medicine, nursing, social work, and literature and science; and one is a research investigator in social research, each conducting interdisciplinary research in Women's Health.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan**
PI: **Jeanne-Marie Guise**
Institution: **Oregon Health & Science University**
Grant No.: **5K12HD043488-13**

This competing renewal application seeks to continue and enhance the OHSU BIRCWH program entitled "Oregon BIRCWH: Scholars in Women's Health Research Across the Lifespan." Our 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/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 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. The institution is deeply committed to the BIRCWH, providing each scholar up to 50 hours of statistical support, tuition-free education through the Human Investigations Program, and direct financial contributions to support their research. We will continue the existing best practices that have made our program highly successful. In this renewal, we expand the centers, institutes, and mentors affiliated with the BIRCWH to address all 6 high-priority NIH ORWH research goals and propose the following innovative expansions to: (I) 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) disseminating best practices (lessons and tools) for mentoring nationally; and (II) 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. The Oregon BIRCWH is dedicated to training the next generation of leaders in women's health research

whose discoveries improve the health of girls, women, and populations. We are pleased with our program's and scholars' successes and are excited about the opportunities in this renewal to increasingly contribute at a national and programmatic level.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **The Colorado Building Interdisciplinary Research Careers in Women's Health Program**
PI: **Judith G. Regensteiner**
Institution: **University of Colorado Denver**
Grant No.: **5K12HD057022-08**

University of Colorado Anschutz Medical Campus (UCAMC) "Building Interdisciplinary Research Careers in Women's Health" (Colorado 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 the BIRCWH, exemplified by strong financial support from the Dean of the School of Medicine for the BIRCWH. The Leadership Team for the Colorado BIRCWH will be headed by Judith Regensteiner, Ph.D., who will continue as Principal Investigator/Program Director (PI/PD) with Nanette Santoro as co-PI/PD. Both have extensive mentoring and research experience. 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 3 interdisciplinary and interrelated focus areas across the lifespan in which UCAMC has great strength including (1) pregnancy: placentation, lactation, fetal/neonatal programming, (2) immunology/rheumatology/inflammation, and (3) adult health: obesity, menopause, aging, diabetes, and cardiovascular disease. Scholars will also have access to UCAMC's rich base of institutional research resources, including interdisciplinary programs and coursework, as well as substantial core facilities. Because of the complexity of most current research, interdisciplinary research teams are the wave of the future, and our BIRCWH Scholars should become extraordinarily well positioned to be the next generation of leaders in biomedical science. Given the success of our BIRCWH Scholars in the current program, we are eager to continue developing and improving our program through this renewal.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Tulane Building Interdisciplinary Research Careers in Women's Health (BIRCWH)**
PI: **Marie A. Krousel-Wood**
Institution: **Tulane University of Louisiana**
Grant No.: **5K12HD043451-13**

This is a competing renewal application for the Tulane BIRCWH Program, which has successfully trained a racially/ethnically and professionally diverse group of interdisciplinary researchers in women's health and increased awareness of women's health research at Tulane over the last 4 years. We propose now 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 2 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 address the most recent ORWH priorities. Scholar's 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). We propose to train 8 faculty Scholars for a minimum of 2–3 years (3 years minimum for physician-scientists). Ongoing and comprehensive evaluation will guide improvements to the program's demonstrated effectiveness in bridging research training and research independence for junior investigators focused on sex differences and CVD.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UCSF/Kaiser Permanente DOR Program for Developing Independent Women's Health Researchers**
PI: **Bernard J. Guglielmo**
Institution: **University of California, San Francisco**
Grant No.: **5K12HD052163-15**

This competing renewal application proposes continuation of the UCSF–Kaiser Department of Research (DOR) Bridging Interdisciplinary Research Careers in Women's Health (BIRCWH) K-12 Program. The program's aims are to: (1) recruit a superb and diverse group of early career women's health researchers; (2) provide them fiscal and individually tailored training and mentoring; (3) build upon our existing program by broadening it to specifically target important women's health topics that are understudied; (4) strengthen and integrate models of multidisciplinary research and develop researchers who foster linkages across disciplines and institutions; and (5) promote the prominence of and resources allocated to women's health research by mentoring BIRCWH Scholars and alumni in academic process and leadership. The 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 Advisor 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 in UCSF CTSI career development and training programs. The career development path for each scholar is tailored to the specific types of experience and mentoring that will most effectively support her or his transition to an independent clinical scientist. 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 program overall will continue to be a unique resource for the continuation and expansion of women's health science in the San Francisco Bay area.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UIC Program for Interdisciplinary Careers in Women's Health Research**
PI: **Stacie E. Geller**
Institution: **University of Illinois at Chicago**
Grant No.: **5K12HD055892-08**

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 four 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 PI or Co-I, published over 70 peer-reviewed manuscripts, and given more than 70 oral and poster presentations at national or international scientific conferences. We build on the strengths of our current program, particularly the integration of the BIRCWH with UIC's institutional and programmatic excellence in women's health research, UIC's proven institutional dedication to and success in mentoring new investigators, especially women, and our focus on and alignment with ORWH's 2020 Strategic Plan. 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); (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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UNC BIRCWH Career Development Program**
PI: **Eugene P. Orringer**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **5K12HD001441-15**

This application represents the competitive renewal of UNC's BIRCWH Award. 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 BIRWCH Program are to: (1) facilitate the mentored career development of junior investigators pursuing 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. In our application, we have focused on 8 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 UNC. In addition, each has theme has numerous, nationally recognized mentors who are willing and available to work with our BIRCWH Scholars. During our first 2 cycles of funding, the UNC BIRCWH Program has proven to be remarkably successful. Thus far, we have chosen and supported a total of 27 junior faculty members who exhibit broad diversity in terms of discipline, academic home, gender, ethnicity, and type of research. Finally, it is of note that each of the 20 graduates of our BIRCWH Program is the Principal Investigator on at least one NIH grant, grants that alone total over $33 million. Thus, the UNC BIRCWH Program has added a great deal to the UNC women's health research community, and we are convinced that it will continue to do so for many years to come. Relevance: 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **University of Minnesota Building Interdisciplinary Research Careers in Women's Health**
PI: **Nancy Cox Raymond**
Institution: **University of Minnesota**
Grant No.: **5K12HD055887-08**

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. To accomplish this goal, we will offer a program that ensures our UMN BIRCWH Scholars become premier interdisciplinary scientists. 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 address 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. Our career development program is organized around broad themes and includes increasing knowledge regarding: (1) research knowledge and skill development; (2) women's health and sex/gender difference research issues, methodologies, and emerging topics; (3) scientific dissemination; (4) interdisciplinary leadership development; (5) advocacy (e.g., translating research into policy); and (6) academic career development. The career development program will consist of required and individualized components, which will be delivered through didactic and experiential training methods designed to achieve the program goals. Scholar research projects that will be funded reflect (but will 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 including sex-specific basic mechanisms and disease presentation. Rationale and design of the program: We will make progress toward 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. Planned duration and projected number of scholars: The UMN BIRCWH program will fund four women's health researchers who are assistant professors in year one through four of their tenure track or clinical track appointment for up to three years. As Scholars complete the program, additional Scholars will be added.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **UTMB Women's Health Research Scholars Program**
PI: **Abbey B. Berenson**
Institution: **University of Texas Medical Branch at Galveston**
Grant No.: **5K12HD052023-10**

In response to RFA-OD-09-006, The University of Texas Medical Branch (UTMB) proposes a renewal of our successful BIRCWH Program to develop independent researchers in women's health. The Program includes 17 experienced senior investigators as Mentors from 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. The Candidate Pool is fed by a multilevel pipeline, including local departments, centers, and T32 programs, followed by applicants from UT System campuses designated as Hispanic-serving institutions. Additional efforts to obtain diverse applicants extend to the national level through advertisements and solicitations made with leading historically black colleges and universities. During the first cycle of funding, we trained 10 Scholars who received 12 awards from private and federal sponsors, including NIH. For our second cycle of funding, our Program will continue to use the mentored research experience as the core of Scholars' tailored career development plans. Multiple formal and informal venues provide ample opportunities for developing skills and collaborative interdisciplinary networks. Scholars may also obtain a M.S. or Ph.D. in clinical science. In addition, we will add a Resource Laboratory for individual assistance with methods development and statistical guidance. Our proposed renewal is supported by a significant institutional commitment assured by the Executive Vice President & Provost. A renewal will further

strengthen women's health research at UTMB and will ensure that more of our Scholars become independently supported investigators in the many areas of health that affect women over the lifespan.

IC: **National Institute on Drug Abuse**
Title: **Kentucky BIRCWH Program: Training the Next Generation of Women's Health Scholars**
PI: **Thomas E. Curry**
Institution: **University of Kentucky**
Grant No.: **5K12DA035150-03**

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. This approach will continue to provide our BIRCWH scholars with state-of-the-art multidisciplinary training, leading to their development as faculty with independent NIH funding. The focused areas targeted toward 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 positioned 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. Key aspects of training will include: (a) pairing the BIRCWH scholar with senior level scientists and former BIRCWH scholars, forming a research team and thus modeling interdisciplinary collaboration; (b) providing these teams with access to cutting-edge technologies; and (c) providing scholars with training in concepts relevant to women's health. A strength of our BIRCWH program is its multidisciplinary, cross-departmental, and interactive nature positioned in an area with unique health needs. As evident by the success of our former BIRCWH scholars, we are well positioned to continue the tradition of excellence in mentoring our scholars to become independent researchers in women's health.

IC: National Institute on Drug Abuse
Title: Yale BIRCWH Scholar Program on Women's Health and Addictive Behaviors
PI: Carolyn M. Mazure
Institution: Yale University
Grant No.: 5K12DA031050-05

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 U.S. 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. Yale's interdisciplinary research program on women's health, in collaboration with our internationally renowned research program on addictions, requests funding through the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Scholar Program (RFA-OD-09-006) for four BIRCWH Scholar positions. We have assembled an outstanding team of 25 experienced, productive, and dedicated Mentors 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, 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. Ultimately, the purpose of our program is to ensure the development of scientists who make enduring contributions to the prevention and treatment of addictive behaviors, which result in direct practical benefit for women and their families.

IC: National Institute of Environmental Health Sciences
Title: Women's Health and the Environment over the Entire Lifespan (WHEEL)
PI: Deborah A. Cory-Slechta
Institution: University of Rochester
Grant No.: 5K12ES019852-05

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 (IWHR) 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.

Conference

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Health and Wellness in Turner Syndrome in the 21st Century**
PI: **Gary Michael Silberbach**
Institution: **Oregon Health & Science University**
Grant No.: **1R13HD079209-01**

The meeting: "Turner syndrome health and wellness in the 21st Century: The crossroads of health care research and health care delivery" will be held on July 13th and 14th, 2014, in Jacksonville, Florida, in conjunction with the 27th annual meeting of the Turner Syndrome Society of the United States (TSSUS). TS health care delivery systems around the country are fragmented and lack resources. At the same time, there are vital yet unaddressed TS-related research questions that have the potential to shed light on a variety of disorders facing all Americans. Importantly, there has been no concerted effort by the health research community to articulate the important issues involved. As the initial step toward establishing a federally mandated comprehensive TS health care program, we will bring together a group of scientists, clinicians, and individuals with TS and their families in order to develop a strategic plan for the development of the Turner Resource Network (the TRN). This proposal is the product of a fruitful collaboration between the TSSUS, a grass roots organization that includes more than 3,000 girls and women with TS throughout the USA and a group of TS researchers/clinicians that form the TSSUS professional advisory board. We hope that our conference will serve to energize the stakeholders in both the scientific and health care delivery communities and will also kick start a national effort to improve the health and well-being of those living with TS. The major aims of this conference are to (1) Identify and discuss the major health care problems and unmet medical needs of the TS community, (2) Identify and discuss major research questions facing those with TS and how they might best be studied, (3) Discuss how a partnership between the NIH and the fledgling TS regional resource centers around the USA could work to accomplish research goals and to simultaneously deliver state-of-the-art health care to girls and women with TS, and (4) Establish a road-map going forward to establish the TRN within the next 4 years.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Organization for the Study of Sex Differences Annual Meeting**
PI: **Robert L. Meisel**
Institution: **University of Minnesota**
Grant No.: **1R13HD080243-01**

This proposal requests partial support for the Eighth to Tenth Annual Meetings of the Organization for the Study of Sex Differences (OSSD) to be held in 2014–2016. The 2014 Meeting will be held on the Twin Cities campus of the University of Minnesota, with the 2015 meeting held in San Francisco and the 2016 meeting in Philadelphia. The mission of the OSSD is to enhance knowledge of the biological basis of sex/gender differences in health and disease by facilitating interdisciplinary communication and collaboration among scientists and clinicians

from diverse scientific and professional backgrounds. The primary goal of the OSSD annual meeting is to provide a forum for scientists to explore aspects of sex differences research at the genetic, molecular, cellular, organ, and systems levels in humans and model systems. The annual meeting consists of three independent symposia (one focused on New Investigators), ten parallel session symposia, and two poster sessions (highlighting the work of new investigators and trainees). Preliminary symposium topics for the 2014 meeting include: treatment of disorders of sexual development and gender dysphoria; sex differences in epigenetic mechanisms; sex differences in addiction; sex differences in response to neonatal hypoxic insult; report from the NIH SCOR programs; sex differences in drug and device development; sex, hypertension, and the immune system; sex differences in the research pipeline; sex-specific risk for cardiovascular disease; and sex and gender differences in eating disorders. The OSSD Program Committee selects symposia topics from among proposals submitted by the membership. Proposals were selected on the basis of scientific merit, relevance to the goals of the OSSD, a balance of basic and clinical speakers, and rotation of topics of interest across annual meetings. The size and format of this meeting (150–200 participants) provides an excellent opportunity for networking opportunities and interactive discussions. Funds are requested to support registration fees for invited speakers (established, junior, and trainee), travel expenses for junior investigators and trainees, and expenses related to the OSSD Annual Meeting Program Book, and necessary audiovisual equipment rentals and associated technical support. The annual meeting program, including speaker and poster abstracts will be freely available on the OSSD website. We will partner with the University of Minnesota and the Mayo Clinic in Rochester, MN, to organize this event and will request support from the pharmaceutical and biotechnology industries, local businesses, and private donors and foundations to help cover non-NIH costs.

IC: **National Institute of Dental and Craniofacial Research**
Title: **Genetics and Epigenetics: Temporomandibular Disorders and Related Overlapping Conditions**
PI: **Allen W. Cowley**
Institution: **The TMJ Association**
Grant No.: **1U13DE024691-01**

The Seventh Scientific Meeting of The TMJ Association, "Genetic and Epigenetic Basis of Temporomandibular Disorders and Related Chronic Overlapping Conditions," is scheduled to be held on September 7–9, 2014, at the Federation of American Societies for Experimental Biology Conference Center in Bethesda, Maryland. The need for this meeting is driven by two critical issues. First, there are an estimated 36 million people affected by temporomandibular disorders (TMJD) in the U.S., the majority being women in their childbearing years with consequential physical, psychological, and financial burdens. Second, there continues to be a dearth of scientific understanding of the etiology and pathophysiology of these conditions, their comorbidities, and treatment. To stimulate research in this field, The TMJ Association has organized six scientific meetings beginning in the year 2000, which have convened interdisciplinary groups of scientists to characterize and address the complex symptoms and frequently found comorbid conditions in TMJD patients. The theme of the currently proposed meeting is built upon important new data from the OPPERA consortium and other studies, which have now demonstrated that TMJD are a complex family of conditions influenced by genes, sex, environmental, and behavioral triggers. These studies have provided a solid basis of understanding of the transcriptome and have identified polymorphisms associated with the

vulnerability of patients to TMJD. Given recent technological advances in genomic sequencing, it is now possible to undertake studies to explain how environmental factors and stressors affect the epigenome and the regulation of these genes. The proposed meeting will bring together experts to discuss and inform how the epigenome may expand our understanding of TMJD and the complex pathways that link the various associated comorbid conditions such as chronic pain. The meeting will engage key scientific leaders, NIH representatives, and patient advocacy representatives who will develop recommendations to advance research in this field. The specific aims are to determine: (1) What is currently known about the underlying mechanisms of chronic generalized persistent pain? (2) What are meaningful research strategies that could help decipher the rules by which gene networks are regulated and help understand how such regulation affects cellular function leading to the overlapping chronic conditions associated with TMJD and persistent pain? (3) How can studies of the epigenome expand our understanding of TMJD and chronic persistent pain? (4) What computational methods and gene regulatory models will be required to advance these studies? (5) How to probe cellular pathways to determine the effects of epigenetic modulation using novel computational tools? (6) How can these novel approaches be used to identify targets and develop new treatment modalities for TMJD and comorbid chronic pain conditions?

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Young Investigator Travel Support for 2014 APS Annual Scientific Meeting**
PI: **Charles E. Argoff**
Institution: **American Pain Society**
Grant No.: **1R13NS087941-01**

Support is requested for travel stipends to encourage the participation of young investigators at the annual meeting of the American Pain Society (APS). These young investigators are beginning their careers in basic and clinical research in pain. The APS is a multidisciplinary community that brings together a diverse group of scientists, clinicians, and other professionals to increase knowledge about pain and to transform public policy and clinical practice in order to reduce pain-related suffering. The annual APS meeting provides a unique forum for disseminating cutting-edge advances in evidence-based pain research and treatment in a setting that optimizes the interactions between scientists and clinicians. The annual meeting integrates basic, experimental, and clinical pain research, and encourages cross-fertilization among the participants. This bidirectional translational interchange between clinicians who diagnose and manage clinical pain and preclinical scientists who are elucidating pain mechanisms is the cornerstone of improved pain therapy and advances in pain management. We seek funds solely for the purpose of providing travel awards for young investigators who have submitted an abstract which has been accepted by our peer review process and therefore are engaged in research. These young investigators may be from any research training background (basic or clinical science, psychology, medicine, or biostatistics) and may be at any level in training, including students, residents, pre-doctoral trainees, postdoctoral fellows, or those who have completed their postdoctoral training within the last 3 years. All applicants must be APS members. Collectively, the APS Young Investigator Travel Awards program is designed to facilitate the mentoring and nurturing of the next generation of pain researchers.

Other Cofunding

IC: **Fogarty International Center**
Title: **Fogarty Global Health Fellows Coordinating Center**
PI: **Benjamin H. Chi**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **5R25TW009340-03**

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, and multilayered mentoring. Each primary training site has a lengthy history of NIH and U.S. government research funding, training of U.S. 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 as 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 U.S. 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 longstanding 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.

IC: Fogarty International Center
Title: Global Health Fellows and Scholars Research Training
PI: Lee W. Riley
Institution: University of California, Berkeley
Grant No.: 5R25TW009338-03

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, Ph.D. 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, non-communicable, 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 U.S. 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 underrepresented 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.

IC: Fogarty International Center
Title: Northern/Pacific Universities Global Health Research Training Consortium
PI: Joseph Raymond Zunt
Institution: University of Washington
Grant No.: 5R25TW009345-03

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; and bimonthly Internet-based research-in-progress sessions involving all Global Health Research 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 co-mentors from the academic programs that house the T32 grants from which Global Health Research Fellows are recruited; and (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 and a potential second year of fellowship funding for the most promising trainees; to assistance in 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 Research 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.

IC: **Fogarty International Center**
Title: **Tobacco Control Network Among Women in Parana, Brazil - II**
PI: **Isabel C. Scarinci**
Institution: **University of Alabama at Birmingham**
Grant No.: **5R01TW009272-03**

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 fewer 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 threefold: (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.

IC: **Fogarty International Center**
Title: **University of California Global Health Institute Program for Fellows and Scholars**
PI: **Craig R. Cohen**
Institution: **University of California, San Francisco**
Grant No.: **5R25TW009343-03**

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 all 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 online 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.

IC: **Fogarty International Center**
Title: **Vanderbilt-Emory-Cornell-Duke Consortium for Global Health Fellows (VECDor)**
PI: **Sten H. Vermund**
Institution: **Vanderbilt University**
Grant No.: **5R25TW009337-03**

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 U.S. 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 U.S. 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.

IC: **National Center for Advancing Translational Sciences**
Title: **Ex Vivo Female Reproductive Tract Integration in a 3D Microphysiologic System**
PI: **Teresa K. Woodruff**
Institution: **Northwestern University**
Grant No.: **4UH3TR001207-03**

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 acts 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 individual 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.

IC: **National Cancer Institute**
Title: **The National Person-Centered Assessment Resource (PCAR)**
PI: **David Cella**
Institution: **Northwestern University**
Grant No.: **1U2CCA186878-01**

Northwestern University (NU) proposes to refine and sustain a Research Resource infrastructure that will educate and enable researchers and other interested health professionals on the use and interpretation of person-centered health outcomes. Person-centered health outcomes are those that are reported or performed by an individual research participant or patient, and that have importance to the quality of life of that participant. We refer to this resource as The National Person-Centered Assessment Resource, or PCAR. Specifically, PCAR will support the use and enhancement of four measurement information systems, currently funded as separate NIH programs: The Patient Reported Outcomes Measurement Information System® (PROMIS®); The NIH Toolbox for Assessment of Neurological and Behavioral Function (NIH Toolbox); The Neurology Quality of Life Measurement System (Neuro-QoL); and The Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me). Across our six performance sites (Northwestern University, University of California at Los Angeles, University of California at San Diego; University of North Carolina, University of Pittsburgh, and American Institutes of Research), we possess all of the necessary capabilities to perform the tasks designated in RFA CA-13-008. These capabilities include psychometrics, survey research, biostatistics, population statistics, software design and maintenance, electronic data capture and secure storage, technical support, health information technology integration, educational methods, website design, dissemination and implementation methods, marketing and communication, and business development. PCAR will provide an integrated platform for automated use of these four measurement information systems. The PCAR platform is already compatible with various modes of information collection (including web/mobile-based entry, non-digital paper source data, and others). During the funded period, we will move to sustain this platform and the educational and statistical services around them, under a fee-for-service model that will support free and open distribution of static, downloadable measures as well as administration, scoring, and interpretation tools. PCAR will also be designed to allow resource users (i.e., external researchers and clinicians unaffiliated with the resource) to access and use any of the four systems together or in isolation and tailor use to meet the specific study needs, while capturing and transmitting participant data securely. This expansive national PCAR vision will be realized by surrounding a sustainable Research Resource, located at NU and already operational (with annual ex-NIH PCAR revenues approaching $1,000,000), with core supporting expertise in statistics, outreach, and administration, including project management and business development.

IC: National Eye Institute
Title: Broad Spectrum Molecular Therapy for Blinding Retina Disorders
PI: Jean Bennett
Institution: University of Pennsylvania
Grant No.: 5DP1EY023177-04

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; and (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. Successful application of optogenetic therapy will expand the number of disease targets that are potentially treatable by gene therapy dramatically. It will change the number of retinal gene therapy targets from the realm of isolated orphan diseases to conditions that are epidemic in nature. In addition, the reagents, strategies, and technical advances developed in this project will be useful for many other ocular and extra-ocular applications. Finally, not only could the results from this project lead to a significant improvement in the quality of life for millions of individuals, but they could also pave the way for development of novel gene therapy approaches for the treatment of other devastating sensorineural diseases.

IC: National Human Genome Research Institute
Title: African Collaborative Center for Microbiome and Genomics Research (ACCME)
PI: Clement Adebayo Adebamowo
Institution: Institute of Human Virology
Grant No.: 5U54HG006947-02

The African Collaborative Center for Microbiome and Genomics Research (ACCME) is a multi-country, multi-institutional collaborative research initiative involving the Institutes of Human Virology and Genome Sciences at the University of Maryland; the Department of Epidemiology and Public Health at the School of Medicine University of Maryland, Baltimore; University of

Abuja Teaching Hospital, Abuja, Nigeria and the Centre National d'Appui à la lutte contre la Maladie (CNAM) Mali. The objectives of the Center are to collaborate and implement high-impact research programs characterizing the human microbiome and its role in health and disease. Specifically, ACCME links and leverages existing funded research and program activities at the collaborating institutions to study the interaction between vaginal microbiome, host genetic factors, and molecular variants of human papilloma virus (HPV) to determine correlates of viral persistence in the causal pathway of cervical cancer, a major cause of preventable mortality on the African continent. Recent studies by the investigative team, employing bacterial culture-independent, "clone and sequence approach" employing 16S ribosomal RNA (rRNA) gene technologies have documented the complexity of vaginal microbiome and classified consistent microbial groupings termed "community state types" that open a new window to understanding the role that the vaginal microbiome plays in cervical cancer pathogenesis. In addition to contributing to knowledge about vaginal microbiome, HPV persistence, and cervical carcinogenesis, ACCME also develops capacity by training postdoctoral students to become the new generation of African scientific leaders while empowering hundreds of African scientists to conduct research in microbiome and genomics.

IC: **National Institute on Aging**
Title: **Health and Well-Being Effects on Later-Life Divorce and Subsequent Re-Partnering**
PI: **Susan L. Brown**
Institution: **Bowling Green State University**
Grant No.: **1R15AG047588-01**

The gray divorce rate has doubled in the past two decades, rising from 5 to 10 divorces per 1,000 married population, ages 50 and older. More than 1 in 4 people who divorced in 2010 were ages 50+ compared with less than 1 in 10 in 1990. The recent rise in gray divorce coupled with the aging of the population foregrounds the urgency of investigating the life course factors associated with divorce during older adulthood and the ramifications for individual well-being. It also raises new questions about what happens after a gray divorce: how common is re-partnering, whether through cohabitation or remarriage, and to what extent does re-partnering ameliorate any negative effects of divorce on individual well-being? Although gray divorce is accelerating, social scientists lack a basic understanding of divorce and re-partnering that occur during later life. We use prospective, longitudinal data from the 1992–2010 Health and Retirement Study to begin to fill this critical gap. We estimate discrete time event history models to assess the life course factors (e.g., empty nest, retirement, and poor health) that are associated with gray divorce and subsequent re-partnering. And, we use latent growth models to investigate how gray divorce is linked to trajectories in health and economic well-being, as well as the extent to which re-partnering offers appreciable gains in well-being. Throughout the project, we assess variation by gender, marriage order, and cohort. The implications of gray divorce are substantial, shaping not only the couple but also the well-being of family members, such as children and grandchildren, and the demands placed on broader institutional support systems designed for older adults and their families. Society at large will need to respond to the shifting (and potentially diminishing) family resources and supports that are available to older adults. As such, this project aligns with the research priorities of the NIA described in its strategic plan for research on aging in the 21st century. This project fully incorporates two undergraduate and one

graduate research assistant to expose students to all stages of the research process and enhance the BGSU research environment.

IC: **National Institute on Alcohol Abuse and Alcoholism**
Title: **Alcohol and Breast Cancer**
PI: **Jia Luo**
Institution: **University of Kentucky**
Grant No.: **2R01AA017226-07**

Alcohol consumption promotes the development of human cancers, and environmental factors play an important role in the etiology. Epidemiological studies indicate that alcohol consumption not only increases breast cancer risk, but also enhances the progression and the aggressiveness of existing breast tumors. Nonetheless, the mechanism by which alcohol contributes to breast tumor initiation or progression has yet to be established. ErbB2 is a member of epidermal growth factor receptor family. Amplification of ErbB2 is found in 20%–30% of breast cancer patients and is associated with poor prognosis. We have previously demonstrated that over-expression of ErbB2 sensitized breast cancer cells to alcohol-induced tumor promotion. Recently, we identified a novel component in ErbB2 signaling pathways that may regulate cancer cell aggressiveness, the p38γ. We hypothesized that alcohol enhances NOX-dependent production of ROS, which activates ErbB2 or MKK6. The activation of ErbB2 and MKK6 causes selective phosphorylation of p38γ, which recruits SAP97/DLG. The activated SAP97/DLG promotes epithelial to mesenchymal transition (EMT) and increases cancer stem cells (CSC) population and invasiveness of breast cancer cells. This leads to an enhanced aggressiveness. There will be three specific aims. Specific Aim 1 will determine the role of p38γ in alcohol-induced aggressiveness in vitro. Specific Aim 2 will investigate the mechanisms underlying alcohol-induced p38γ activation as well as the mechanisms of how p38γmediates aggressiveness of breast cancer cells. Specific Aim 3 will investigate the role of p38γ in alcohol-induced tumor aggressiveness in animal models. The study will not only explore the basic cell biology of breast cancer aggressiveness, but also elucidate the mechanisms of alcohol's tumor promotion action. The outcomes will help developing new therapeutic strategy for breast cancer treatment and alcohol-mediated tumor promotion.

IC: **National Institute on Alcohol Abuse and Alcoholism**
Title: **Function of Runx2 in Alcohol-Associated Breast Cancer**
PI: **Shuping Zhong**
Institution: **University of Southern California**
Grant No.: **1R21AA023247-01**

Alcohol consumption in women has been associated with an increased risk of breast cancer (~ 10%–50%/1–3 drinks a day), particularly in estrogen receptor positive (ER+) disease; however, its mechanisms remain to be elucidated. To date, there have been no reports on the role of MSK1 (mitogen-stress activated protein kinase), Runx2 (Runt-related gene 2), H3ph (histone H3 phosphorylation), and Brf1 (TFIIIB-related factor 1) in alcohol-associated mammary tumor formation. Our overall objective is to explore the molecular mechanism of alcohol-associated breast cancer by determining the role of alcohol-induced deregulation of Pol III genes (RNA polymerase III-dependent genes) in ER+ breast cancer. Deregulation of Pol III genes would

serve to enhance the protein synthetic capacity of cells, which is required to promote cellular growth, proliferation, transformation, and tumor development. Brf1 is a subunit of TFIIIB complex and specifically regulates Pol III gene transcription. Brf1 and products of Pol III genes, such as 5S rRNAs and tRNAs, are elevated in both transformed and tumor cells suggesting that they play a crucial role in tumorigenesis. Our studies indicate that enhancement of Brf1 and Pol III gene expression is correlated with tumor formation in alcohol-fed mice. We established that ethanol dramatically induces Pol III gene transcription in ER+ breast carcinoma cells. Alcohol increases ERα expression to enhance Brf1 and Pol III gene expression, where this process is mediated by alcohol-activated JNK1. Alcohol increases c-Jun expression and induces H3ph. Runx2 is regulated by ERα and JNK1 and is associated with mammary gland development and ER+ breast cancer. Importantly, our preliminary results indicate that alcohol activates MSK1, and that alcohol increases the activity of Runx2-dependent reporter and enhances expression of Runx2. Based on these studies, we propose a groundbreaking hypothesis that ethanol activates JNK1 and MSK1 to mediate H3ph. H3ph increases ERα expression, which modulates Runx2 activity. In turn, Runx2 upregulates Brf1 expression and Pol III gene transcription, thereby contributing to cell transformation and mammary tumor development. This application is a logical extension of our work to better define the role of MSK1, H3ph, Runx2, and Brf1 in alcohol-promoted mammary tumor development. To test this hypothesis, we will characterize alcohol-induced signaling events of deregulation of Brf1 and Pol III gene by inhibiting JNK1, MSK1, and Aurora B pathway. We will identify the epigenetic regulation of Brf1 by modified histone H3 and determine alcohol-induced H3 modifications, such as H3ph, H3ac (histone H3 acetylation), and H3me (histone H3 methylation). We will determine whether Runx2 modulates Brf1 expression and Pol III gene transcription by increasing and decreasing Runx2 expression and will identify whether MSK1 and H3ph mediate Runx2 expression. We will evaluate the role of Brf1 and MSK1 in alcohol-promoted mammary tumor formation by using Brf1 conditional KO mice and MSK KO mice. These studies using cell culture and animal models will characterize the roles of JNK1, MSK1, Aurora B, and H3ph as important signaling molecules to modulate Brf1 expression and Pol III gene transcription in alcohol-associated mammary tumor development. The results from this project will provide a potential treatment for patients with breast cancer.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Airway Inflammation and Airway Remodeling**
PI: **David H. Broide**
Institution: **University of California, San Diego**
Grant No.: **5U19AI070535-09**

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 noninvasive 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 IOFM Core is also proposed as requested by the RFA.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Airway Inflammation and HLA-G in Asthma**
PI: **Steven R. White**
Institution: **University of Chicago**
Grant No.: **5U19AI095230-04**

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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Epithelial Barrier Programs in Asthma and Allergic Disease**
PI: **Michael J. Holtzman**
Institution: **Washington University**
Grant No.: **5U19AI070489-09**

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.

IC: National Institute of Allergy and Infectious Diseases
Title: Epithelial Genes in Allergic Inflammation
PI: Gurjit K. Khurana Hershey
Institution: Cincinnati Children's Hospital Medical Center
Grant No.: 5U19AI070235-09

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.

IC: National Institute of Allergy and Infectious Diseases
Title: Host and Viral Determinants of Infant and Childhood Allergy and Asthma
PI: Ray Stokes Peebles
Institution: Vanderbilt University
Grant No.: 5U19AI095227-04

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 2,000 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Pathophysiologic and Therapeutic Mechanisms of Aspirin-Exacerbated Respiratory Disease**
PI: **Joshua A. Boyce**
Institution: **Brigham and Women's Hospital**
Grant No.: **5U19AI095219-04**

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 hyper-responsiveness 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.

IC: **National Institute of Allergy and Infectious Diseases**
Title: **Role of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin in Asthma**
PI: **Joel Barry Baseman**
Institution: **University of Texas Health Science Center at San Antonio**
Grant No.: **5U19AI070412-09**

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 histopathological 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.

IC: National Institute of Allergy and Infectious Diseases
Title: T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy
PI: Andrew D. Luster
Institution: Massachusetts General Hospital
Grant No.: 5U19AI095261-04

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.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Influence of PTSD Symptoms on Chronic Pain Development After Sexual Assault
PI: Samuel A. McLean
Institution: University of North Carolina at Chapel Hill
Grant No.: 1R01AR064700-01A1

Each year, more than 100,000 U.S. women seek emergency medical care after sexual assault (SA). Most women do not return for/receive further care related to SA after initial emergency evaluation. Thus, the emergency care visit represents a unique opportunity to identify SA survivors for preventive interventions to improve recovery. Cross-sectional studies indicate that chronic musculoskeletal pain (MSP) is reported by many SA survivors and is associated with

substantial suffering and poor health outcomes. However, no prospective studies evaluating chronic MSP outcomes after SA have been performed, and therefore a firm etiologic link between SA and chronic MSP has not been established. In a recent prospective pilot study (n = 83), the investigators found that 41% of women SA survivors enrolled developed chronic moderate or severe MSP. Initial pain scores collected from all women approached for pilot study participation showed that more than half of those at high risk of chronic MSP consented and enrolled in the pilot study. In addition, data collected indicate that women SA survivors who participated in the pilot study are the same group of SA survivors who would be willing to participate in preventive intervention trials. However, currently no information exists regarding key factors that influence the transition from acute to chronic post-SA MSP to inform the design of such trials. Available evidence suggests that posttraumatic stress disorder (PTSD) symptoms may be key factors mediating the transition from acute to chronic post-SA MSP. PTSD symptom clusters have been found to mediate the transition from acute to chronic MSP in other trauma populations, and the investigator's pilot data support these relationships in the study population. Importantly, despite evidence that PTSD symptoms are key factors mediating chronic post-SA MSP development, available data also indicate that not all individuals with acute MSP develop PTSD symptoms, and not all individuals with PTSD symptoms develop chronic MSP. This suggests that important individual differences moderate these relationships. Available evidence and the investigator's pilot data suggest that genetic variants affecting the function of hypothalamic-pituitary-adrenal (HPA) and catecholaminergic systems constitute such important individual differences. The investigators propose a prospective cohort study of women SA survivors (n = 900) evaluated 1 week, 6 weeks, 6 months, and 12 months after SA. A methodological approach including confirmatory factor analyses and structural equation modeling will be used to test the hypotheses that chronic MSP is common in the study population, that PTSD symptom clusters mediate the relationship between acute and chronic MSP after SA, and that the proposed genetic factors moderate these relationships. Results of this groundbreaking study will generalize to a large population of women SA survivors who experience a high burden of chronic post-SA MSP, and will inform the development of preventive interventions for this understudied population.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response**
PI: **Candace S. Brown**
Institution: **University of Tennessee Health Science Center**
Grant No.: **5R01HD065740-04**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **A Multi-omic Analysis of the Vaginal Microbiome During Pregnancy**
PI: **Gregory Allen Buck**
Institution: **Virginia Commonwealth University**
Grant No.: **3U54HD080784-02S1**

In the U.S., the annual cost of health care for newborns with complications approaches $26 billion, and worldwide, preterm birth is the leading cause of morbidity and mortality among neonates. Despite improved survival rates, the past few decades have seen no significant decrease in preterm births. It is becoming more clear that the billions of bacteria that colonize the human body play important roles in the health of the individual. However, the role of the millions of bacteria and other microbes that colonize the human female urogenital tract in prenatal health and birth of a healthy baby remains obscure. Previous to the recent development of "omics" technologies (i.e., genomics, transcriptomics, proteomics, metabolomics, interactomics, etc.), it was not possible to study these microbial populations in any in depth or highly efficient way. Many of these organisms have never been characterized, and a fairly large fraction have not been successfully cultured. Herein, we propose to use these "omic" technologies to dissect the bacterial populations that inhabit and colonize the female urogenital tract of pregnant women to assess the role(s) of these organisms in maintenance of health or in the cause of disease in these women and their babies. An understanding of the roles these

organisms play in the health of the female urogenital tract will lead to better, more efficient prenatal and postnatal care, likely leading to diminished levels of preterm birth and infant morbidity and mortality.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Brown/WIH Pelvic Floor Disorders Network (PFDN) Site**
PI: **Vivian W. Sung**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **5U10HD069013-04**

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 and expertise of our multidisciplinary 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 nonsurgical 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 longstanding, formal relationship with multidisciplinary 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 1,211 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 nonsurgical 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 longstanding 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Brown/WIH Women's Reproductive Health Research (WRHR) Career Development Program**
PI: **Maureen G. Phipps**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **5K12HD050108-10**

The purpose of the Brown/Women & Infants Hospital WRHR Program is to train a new cadre of women's health translational researchers with expertise and research skills to develop innovative research in women's reproductive health from basic science to clinical applications relevant to public health. Scholars for the Brown/WIH WRHR Program will be recruited from local and national fellowship programs and junior faculty positions. The overarching goal for the program is to provide a supportive and stimulating research environment that enables well-qualified, junior faculty physician-scientists to develop into leaders in women's reproductive health research with expertise in clinical translational research. Translational research areas include: fetal development, reproductive toxicology, perinatal genetics, pregnancy epidemiology and outcomes, gestational diabetes, postpartum depression, women's cancer epidemiology, environmental health, biomarkers and treatment development, ovarian preservation, HIV, infectious diseases, incontinence, adolescent decision-making, substance abuse, nutrition, obesity, cardiovascular disease, and aging. The training program involves a tailored research and career development plan that works by incorporating intensive multidisciplinary mentoring, didactic seminars, and practical hands-on research investigation. The immediate objective for the Program is to identify and train scholars who have the potential to develop as independent women's reproductive health investigators. The objective will be pursued by identifying promising scholars, training them in multidisciplinary translational research methods to pursue women's reproductive health research investigations, and mentoring scholars to become independent researchers. The long-term objective of the Program is to have an established, robust model training program for talented junior women's reproductive health researchers to develop into academic leaders who are capable of assuring what is discovered at the basic science bench is translated into outcomes that improve women's health. The long-term career objective for each scholar includes establishing an independent research career that involves training the next generation of women's reproductive health scholars.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Cleveland Clinic Clinical Site**
PI: **Matthew Barber**
Institution: **Cleveland Clinic Lerner College of Medicine of Case Western Reserve University**
Grant No.: **5U10HD054215-09**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Colorado WRHR Career Development Center**
PI: **Nanette F. Santoro**
Institution: **University of Colorado Denver**
Grant No.: **5K12HD001271-15**

The CU Denver Women's Reproductive Health Research (WRHR) Career Development Center provides a rich environment for the development of creative programs of research related to women's reproductive health while enhancing the pool of highly qualified obstetricians and gynecologists who pursue independent research careers. In this application, we request funds to support three scholars who will be faculty members of Obstetrics and Gynecology and who will utilize 75% of their time to train in a mentored position that will foster their development as independent clinician-scientists. Scholars will be recruited from a national pool of candidates who have completed a residency in obstetrics and gynecology, as well as a subspecialty fellowship, and show evidence of an intense desire to pursue the career of a clinician-scientist. The candidate may select any area of science relevant to obstetrics and gynecology, from a pool of outstanding mentors in obstetrics and gynecology, endocrinology, immunology, epidemiology, pediatrics, and psychiatry who are willing to supervise scholars. For example, specific training programs can be designed in a basic science such as immunology or molecular endocrinology, in translational science such as oncology or the endocrinology of diabetes, or in clinical science including outcomes research. Suitable mentors will be senior scientists with a track record of funding and training scholars. The scholar's progress will be tracked by an advisory committee of senior scientists and clinicians with interests similar to those of the scholar. The environment in the Department of Obstetrics and Gynecology includes a strong

Basic Reproductive Science research program, an interdisciplinary graduate program in Reproductive Science, an excellent program of seminar and journal clubs, and a clinical faculty with strong research interests who collaborate with members of other departments in the school.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **KUMC Women's Reproductive Health Research Career Development Program (K12)**
PI: **Carl P. Weiner**
Institution: **University of Kansas Medical Center**
Grant No.: **5K12HD065260-05**

Described herein is a training program in Women's Reproductive Health Research (WRHR) designed to develop 3 physician-scientists in the Department of Obstetrics and Gynecology at the Kansas University Medical Center (KUMC) over the next 5 years. We will take full advantage of the scientific wealth and infrastructure of the entire University of Kansas system. Among its faculty are more than 30 extramurally funded scientists pursuing basic and translational research in women's reproductive health, and it is these scientists that form the pool of potential mentors for the KU WRHR Scholars. Indeed, reproductive biology is among the top 3 institutional research missions at KUMC, and the Chair of Obstetrics and Gynecology has superb University support for Scholar development. The proposed program will add junior faculty with state-of-the-art research training in women's reproductive health to the region's main academic health center, stimulate women's reproductive health research in a collaborative fashion among disciplines, and secure an outstanding research experience for the Scholar leading to a successful, independent research career. The training and mentoring program encourages both basic and clinical science careers and is divided into two flexible but defined phases. In Phase I (years 1–2), basic science Scholars who have not done graduate level work will complete the core doctoral curriculum of the KU Interdisciplinary Graduate Program in the Biomedical Sciences. Clinical science Scholars will complete the KU Clinical Research Program designed to increase the number of funded clinical scholars committed to patient-oriented research. Phase I completion brings Phase II, where the Scholar spends 3 years conducting research and writing grants/manuscripts. Throughout, they are mentored by a primary mentor selected at program application and a mentoring team that includes a member of the Internal Advisory Committee. Program success is defined by progression of Scholars through academic ranks, the achievement of independently funded research and program feedback after graduation. We will be successful if our Scholars are published, funded, promoted, tenured, establish an independent research program, and make significant contributions to women's health research.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **OB/GYN Faculty Research Career Development Program**
PI: **William Walton Andrews**
Institution: **University of Alabama at Birmingham**
Grant No.: **5K12HD001258-15**

We propose to renew the UAB Women's Reproductive Health Research (WRHR) Career Development Program, which has been dedicated to providing junior OB/GYN faculty with the research skills that can be applied to the study of important reproductive health problems in women. The primary objectives of the Program will be: (1) To recruit junior faculty (scholars) to the UAB Department of OB/GYN who are motivated to develop an independent research career; (2) To promote the career development of these scholars by providing degree oriented (master of science in public health in clinical and translational science) or other advanced training in the principles and techniques of biomedical research; and (3) To integrate the career development of these scholars within research projects in scientific areas of emphasis with important relevance to women's reproductive health. We anticipate attracting trainees of diverse backgrounds involved in basic biomedical, translational, and clinical research, covering the disciplines of gynecologic oncology, urogynecology, reproductive endocrinology and infertility, genetics, and maternal-fetal medicine. The Program will utilize specifically selected NIH-funded senior UAB Program mentors, the resources of the UAB Center for Women's Reproductive Health (CWRH), the newly established UAB Center for Clinical and Translational Science (CCTS), and other UAB campus resources to guide the research career development of these scholars. The Principal Investigator and the Program Director, with the assistance of an Advisory Committee and Minority Recruitment consultants, will be responsible for managing all aspects of the Program and for formally tracking the performance of the Program and scholars. The UAB Department of OB/GYN and the Program have a broad range of funded research interests in which the scholars could be mentored. This Program model was successfully implemented during the past decade and has a proven track record of developing OB/GYN physician-scientists.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pediatric CFS in a Community-Based Sample**
PI: **Leonard A. Jason**
Institution: **De Paul University**
Grant No.: **5R01HD072208-02**

Existing published pediatric epidemiologic CFS studies are similar to the first generation of adult CFS prevalence studies in that they have had either poor sampling plans (e.g., recruitment at medical centers; Nijhof et al., 2011), or systematic biases that excluded certain people such as youth of lower socioeconomic status and those of color who were less likely to have access to health care (Dobbins et al., 1997), or failed to include a medical examination (Jones et al., 2004). We will determine the prevalence of pediatric CFS in a demographically diverse sample of participants unbiased by illness, help-seeking behaviors, or differential access to the health care system. In addition, we will assess orthostatic intolerance (OI) symptoms in a community-based sample of children with pediatric CFS, who are unbiased by help-seeking behaviors or differential access to the health care system. In the proposed study, the quantifiable response to a

mental task undertaken during orthostatic stress (a) will operationally define central fatigue and neurocognitive impairment, and (b) will be applied as a biomarker for community-based CFS when compared to a community-based control group. We believe that cognitive fatigue, cognitive loss, and dizziness are a function of abnormalities in cerebral blood flow as it relates to total cardiac output, total blood volume, regional blood flow, and blood volume distribution during the orthostatic stressor. In addition, we will be able to resolve discrepant findings regarding cerebral blood flow, which, we believe, are due to the differing ways of measuring the response of cerebral blood flow velocity to arterial pressure. In summary, this proposed study will determine the prevalence of pediatric CFS in a community-based sample, as well as the relative frequency of CFS among various groups (e.g., different age groups, genders). This study will also identify the prevalence of orthostatic abnormalities among youth with CFS and controls and will examine its relationship with neurocognitive functioning.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pelvic Floor Disorders Network**
PI: **Charles William Nager**
Institution: **University of California, San Diego**
Grant No.: **5U10HD054214-09**

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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pelvic Floor Disorders Network: Duke University Clinical Site**
PI: **Anthony G. Visco**
Institution: **Duke University**
Grant No.: **5U10HD041267-15**

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 nonsurgical management of urinary incontinence (Ul), pelvic organ prolapse (POP), fecal incontinence, and defecatory dysfunction. Last year, our Division cared for more than 1,550 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: multichannel 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), (2) InterStim vs. Botox RCT (ROSETTA, Dr. Amundsen, full protocol), and (3) 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 nonsurgical 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pelvic Floor Disorders Network Clinical Sites (U10)**
PI: **Lily A. Arya**
Institution: **University of Pennsylvania**
Grant No.: **5U10HD069010-04**

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 M.D., M.S. (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 multicenter 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 nonsurgical 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Perioperative Pelvic Floor Rehab: A Randomized Trial**
PI: **Holly E. Richter**
Institution: **University of Alabama at Birmingham**
Grant No.: **5U10HD041261-14**

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 (FI) 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 FI, 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 FI (although it is not yet FDA approved for this indication). We propose a randomized trial to credibly characterize the effect of SNM on FI 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Pittsburgh Pelvic Floor Research Program**
PI: **Halina M. Zyczynski**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **5U10HD069006-04**

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 and compare clinical outcomes of meshes whilst providing specimens for translational studies.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **RCT of Hypnotherapy vs. Tpolterodine for OAB: Voiding and Brain Activation Changes**
PI: **Rebecca Glenn Rogers**
Institution: **University of New Mexico Health Sciences Center**
Grant No.: **5U10HD069025-04**

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, multicenter 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 multicenter randomized trials and proven leadership and productivity. The UNM PFDN site brings to the Network a busy clinical service with large numbers of underrepresented 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Reproductive Sciences Research Career Development Center**
PI: **Thomas Richard Moore**
Institution: **University of California, San Diego**
Grant No.: **5K12HD001259-15**

The goal of this application is to build upon and enhance the outstanding academic training currently provided in the UCSD Women's Reproductive Health Research Career Development Center. WRHR Scholars are selected through nationwide searches by an Advisory Committee, comprised of internationally recognized researchers, that identifies high-performing OB/GYN physicians who aspire to scientific excellence in women's health and are committed to academic careers as physician-scientists. Scholars are matched with an established senior-scientist Mentor from a broad range of women's health interest areas including epidemiology, perinatal physiology and genetics, obesity and metabolism, urogynecology, reproductive endocrinology, and cancer. The program is flexibly organized into two phases: in the first 1 to 2 years, the Scholar works toward research competency; in the final 3 to 4 years, efforts are directed to achieving research independence and academic expertise. During Phase 1, didactic and practical

instruction supplements intensive laboratory work, and clinical work is minimized. First phase Scholars participate in the two-year CREST program in epidemiology, biostatistics, data management, and informatics. During a third optional year, an M.P.H. degree can be achieved. In Phase 2, Scholars join the UCSD NCLAM Leadership Program, which teaches academic development, leadership, and organizational effectiveness and prepares the Scholar to function as an accomplished Associate Professor. Individualized instruction in grant writing, ethics, and medical enterprise is conducted regularly. Throughout, the Center's Mentoring Committee closely monitors Scholars' progress in monthly meetings and an Individual Mentoring Committee (similar to a Ph.D. thesis committee), appointed specifically for each Scholar, meets twice yearly, ensuring that both the research environment and clinical demands are optimized and balanced. The Advisory Committee reviews Mentoring Committee reports annually and assesses each Scholar's advancement and reappointment to the program yearly. The well-established success of the Center over the last ten years will be enhanced and extended as a new a cadre of outstanding Scholars is recruited, trained, and transitioned into mature clinician-scientists.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Research Career Development in Obstetrics and Gynecology**
PI: **Serdar E. Bulun**
Institution: **Northwestern University**
Grant No.: **5K12HD050121-10**

The long-term goal of the WRHRCDC at Northwestern University is to continue to foster and develop an outstanding mentored, research training program for obstetrician-gynecologists, and to prepare our WRHR trainees (Scholars) to become independent investigators in women's health research. Since it has been first funded in 2005, our WRHRCDC has made major progress in reaching this goal. We have successfully trained 4 Scholars, who published 27 papers and received 18 grant awards including 6 from NIH, and have met all our WRHRCDC benchmarks. The Department of Ob/Gyn will continue to coordinate and administer the WRHRCDC Program and make full use of the scientific wealth and reproductive research infrastructure at Northwestern in its entirety. The key leadership at Northwestern made strong institutional commitments to the WRHRCDC Program. Sherman Elias, M.D., Chair of Ob/Gyn, and Serdar Bulun, M.D., the Division Director of Reproductive Biology Research, will continue to serve as the PI and WRHR Research Director, respectively. The Department of Ob/Gyn at Northwestern has traditionally recruited high-quality residents, subspecialty fellows and junior faculty; currently 16% of this group are underrepresented minorities (URM). One of our current WRHR Scholars is an URM. Thus, we have a large and active pool of candidates for WRHR Scholar selection. These Scholars will have an opportunity to choose between highly competitive clinical research teams or laboratories conducting research in the areas of reproductive endocrinology and infertility, maternal-fetal medicine, gynecologic oncology, and reproductive genetics, and covering the reproductive portion of hypothalamic-pituitary axis, ovary, uterus, placenta, and the fetus. The WRHR Scholars will interact with existing two P01, two U54, and one SCOR Center grants and one T32 training grant specifically in the area of obstetrics and gynecology. As the Northwestern WRHRCDC Program, we are fully equipped to continue to recruit top-quality obstetrician-gynecologists and train them to conduct research and compete for federal grants and

retain them as they become independent investigators. Our excellent track record during the past funding period strongly supports our application.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **University of Michigan WRHR Career Development Program**
PI: **Timothy R. Johnson**
Institution: **University of Michigan**
Grant No.: **5K12HD065257-05**

The goal of the University of Michigan WRHR Program is to increase the number and effectiveness of obstetrician/gynecologist scientists through a departmental-based, multidisciplinary, junior faculty development program. We propose to recruit physician faculty to develop their women's reproductive health research careers for a minimum of two and up to five years. Recruitment of scholars with outstanding potential will be primarily from obstetric/gynecology fellowship programs. During the past ten years, we have developed a track record of training a number of outstanding obstetrician/gynecologists in our department for careers in academic medicine. It is our goal to select the most promising candidates for appointment from three-year ABOG-approved subspecialty fellowships as well as minimally invasive surgery, family planning, genetics, breast and women's health fellowships, AGOS fellows, and Robert Wood Johnson Clinical Scholar programs to participate in the WRHR. Special medical school-wide programs are in place to recruit and support underrepresented minority scholars. From among the potential mentors in the department's Reproductive Sciences Program and related Initiative for Women's Health Researchers, we have chosen those with proven records of accomplishment in fostering research career development. The research programs of these mentors span cutting-edge cellular and molecular aspects of reproductive biology to translational and clinical research. We aim to target programmatic content in specific areas of pelvic floor and urogynecology research, reproductive science biology, and reproductive and perinatal genetics, where institutional strengths support development of junior faculty. A Career Development Program and Center Advisory Committee will assure that the scholars have the best possible environment for success. The program will be measured by the success of WRHR scholars achieving research independence and in receiving extramural funding. The University of Michigan has a current BIRCWH program. We request support for a WRHR program to focus specifically on developing careers of multidisciplinary trained obstetrician/gynecologists. The WRHR program will complement the BIRCWH program since only obstetrician/gynecologists will be candidates for the WRHR program and it will offer a distinct opportunity for these scholars to develop their research programs in areas of specialty-focused relevance and interest with excellent mentors, while at the same time providing an opportunity to interact with a different cadre of women's health scholars with many opportunities for cross-training and peer-support.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Xenograft Study on Growth-Control of Human Uterine Leiomyomata**
PI: **Takeshi Kurita**
Institution: **Northwestern University**
Grant No.: **5R01HD064402-05**

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 health care 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.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Action for Health in Diabetes Continuation (Look AHEAD)**
PI: **Rena R. Wing**
Institution: **Miriam Hospital**
Grant No.: **5U01DK056992-16**

The aging of the population and the epidemic of obesity have led to a rapid increase in the number of older, obese individuals with diabetes. Little is known about the long-term health effects of lifestyle intervention designed to lower weight and increase physical activity in this population. This application, which responds to RFA-DK-12-502, is submitted by one of the 16 clinical centers in the Action for Health in Diabetes (Look AHEAD) Consortium. All 16 clinical

sites and the Coordinating Center have submitted parallel applications. This application proposes to continue the Look AHEAD clinical trial as an observational cohort study and to follow participants with new assessments of the health problems of greatest concern in older, obese individuals with type 2 diabetes. We will test whether random assignment to 9–11 years of intensive lifestyle intervention, compared to a control condition of diabetes support and education, results in improvements in (1) physical function, impairment and disability; (2) cognitive function and impairment; (3) diabetes control and microvascular complications; (4) late life depression; and (5) fractures and cancers. Secondary aims are to examine whether subgroup differences observed during the trial (which raised concern about possible unfavorable effects of intensive lifestyle intervention in those with a prior history of cardiovascular disease) endure and whether the excellent weight losses achieved in the intensive lifestyle intervention arm are maintained despite the absence of continued intervention activities. The continuation will also support ongoing ancillary studies, maintain infrastructure for new ancillary studies, and sustain thorough analyses and publication of the data collected by Look AHEAD. We will continue to follow the Look AHEAD cohort (approximately 4,000 participants) across the 16 clinical sites. Participants entered the trial 9–10 years ago when they were obese or overweight and aged 45–76, and were randomly assigned with equal probability to either an intensive lifestyle intervention that has induced sustained weight loss and increased physical activity or control condition (diabetes support and education). Both arms have had excellent retention. Interventions were discontinued in September 2012, but follow-up of the cohort continues. This application will fund one additional clinic visit and ongoing telephone-based outcome assessment. This application builds on the remarkable success of the Look AHEAD in inducing and sustaining weight loss and retaining participants. The planned continuation addresses important public health priorities for a rapidly growing and understudied segment of the U.S. population in a cost-effective manner, leveraging the extensive resources available from Look AHEAD.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **MAPP Research Network, Second Phase**
PI: **Emeran A. Mayer**
Institution: **University of California, Los Angeles**
Grant No.: **2U01DK082370-06**

The goal of the MAPP Research Network is to provide new insights into underlying etiology, natural history, and risk factors of UCPPS in order to provide a translational foundation to facilitate future clinical intervention efforts and improve clinical management of the syndromes. The UCLA MAPP-II proposal builds on the significant insights gained from MAPP-I studies into symptom patterns, UCPPS subtypes, and various biomarkers, including brain signatures. In addition to be continued analysis of datasets generated in MAPP-I, it aims to identify factors associated with and predictive of symptom change, in both UCPPS subjects and in a rodent model. The UCLA proposal addresses these goals in four specific aims, all of which, if funded, are expected to be addressed collaboratively in transMAPP studies: Aim 1. To conduct a symptom pattern study across the MAPP Research Network, which will form the backbone for Aims 2 and 3. Aim 2. To determine functional and structural brain correlates of patient subgroups, symptom fluctuations, and natural history. Aim 3. To develop and apply enhanced functional assessments for UCPPS, including assessment of endogenous pain modulation systems. Aim 4. To evaluate central mechanisms underlying symptom fluctuations, including

stress mechanisms and related molecular brain changes in a rodent model of UCPPS. It is expected that the proposed studies will provide an unprecedented wealth of data, which will facilitate major breakthroughs in our understanding of UCPPS pathophysiology and identification of novel treatment approaches.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **PREPARE: A Randomized Trial of a Pre-pregnancy Weight Loss Intervention**
PI: **Victor J. Stevens**
Institution: **Kaiser Foundation Research Institute**
Grant No.: **1R01DK099882-01A1**

Almost half of pregnant women in the US begin their pregnancies obese or overweight, and more than half experience excessive gestational weight gain. These women are at increased risk for complications such as gestational diabetes, gestational hypertension, and pre-eclampsia. Obese women require more operative interventions at delivery and suffer more postpartum infections. Growing evidence suggests that a mother's weight at pregnancy onset, and excessive weight during pregnancy, are associated with an increased risk that her child will become obese and face obesity-related health issues. We have successfully helped women avoid excessive weight gain during pregnancy with a program started in the first trimester. However, organogenesis and metabolic programming begin early in the first trimester, well before the first prenatal visit. Therefore, waiting to address mothers' weight, physical activity, and diet is not optimal. We propose to conduct a randomized clinical trial to evaluate a comprehensive pre-conception program to help obese and overweight women improve diet and physical activity habits and lose weight prior to becoming pregnant, and to not gain excessive weight during pregnancy. Because women considering pregnancy have many demands on their time, we modeled our intervention after successful remote, yet frequent contact interventions. We will use face-to-face counseling with a personal health coach, followed by 24 months of frequent phone counseling with the same coach and access to a supportive website. The study will be conducted in an integrated health plan, Kaiser Permanente Northwest (KPNW). A random sample of women in KPNW have expressed high interest in a preconception lifestyle program. We will use KPNW's extensive electronic medical records to identify women with a high likelihood of pregnancy, and invite them to participate. We will implement a randomized clinical trial to test a personalized weight management intervention in comparison to usual care control for women with a BMI of 28 who are planning a pregnancy in the next two years. We believe that by improving mothers' weights, diet quality, and activity levels, the intervention will lead to offspring with lower birth weight (closer to national norms) compared to birth weights above norms in offspring of control mothers. We believe the intervention, delivered via telephone and website, will be highly acceptable to reproductive aged women. If we demonstrate that helping women start pregnancy at a healthier weight improves their own health and that of their children, this program could be quickly implemented in a variety of settings, and could have enormous potential to reduce obesity and improve public health for generations to come.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: University of Michigan MAPP Research Network Discovery Site
PI: Daniel J. Clauw
Institution: University of Michigan
Grant No.: 2U01DK082345-06

The University of Michigan MAPP Discovery Site has provided significant leadership to the first phase of the Multidisciplinary Approach to Chronic Pelvic Pain (MAPP) effort to study urinary chronic pelvic pain syndromes (UCPPS). We provided the initial (Clauw) and current (Clemens) network chairs, and leadership in phenotyping (Williams), quantitative sensory testing (Harte), and neuroimaging (Harris). In addition, we were an excellent recruitment site for the MAPP, with total numbers of participants enrolled (186) and retention of participants (92%) amongst the highest of any site. We propose to similarly provide organizational and scientific leadership in phase II of the MAPP. In addition to the performance of the UCPPS Symptom Pattern Study, we propose three additional aims we believe will bring innovative research methods and expertise to the broader trans-MAPP efforts. These aims are: (1) To continue our effective participation in trans-MAPP studies, including the UCPPS Symptom Patterns Study. (2) To perform an interventional phenotyping study that can either be immediately adopted trans-MAPP or serve as a pilot for a broader trans-MAPP effort in Phase II. This will be the first study ever to hypothesize that symptom profiles, quantitative sensory testing, and functional neuroimaging can be used to identify subsets of UCPPS patients (endo-phenotypes) that have differing underlying mechanisms and thus will respond to different treatments. In particular, we hypothesize that we can predict differential responsiveness to a UCPPS treatment thought to work primarily via central mechanisms (a tricyclic compound) vs. one that is primarily thought to work via more peripheral mechanisms (a NSAID). (3) To provide guidance and expertise for trans-MAPP genetic efforts. We propose to bring several colleagues with internationally recognized expertise in genetics into the MAPP to help inform and guide our trans-MAPP efforts, including the best strategies to use to analyze both Phase I and Phase II samples. We hypothesize that genetic variations will facilitate the identification of endo-phenotypes as well as the longitudinal course of UCPPS. (4) To provide a broader and more comprehensive set of quantitative sensory testing (QST) measures into the Phase II MAPP studies. Our group led the QST efforts in MAPP I, and for MAPP II have partnered with the UCLA site to implement an expanded QST testing protocol, including conditioned pain modulation (CPM), and assessment of thresholds for other sensory experiences (visual, auditory). We hypothesize that QST will allow us to better separate endo-phenotypes (especially by identifying UCPPS participants with pan-sensory hyper-responsiveness that is clearly CNS in origin) as well as predict a longitudinal course.

IC: National Institute of General Medical Sciences
Title: Pharmacogenetics of Phase II Drug Metabolizing Enzymes
PI: Richard M. Weinshilboum
Institution: Mayo Clinic, Rochester
Grant No.: 5U19GM061388-15

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 of the 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.

IC: **National Institute of Mental Health**
Title: **Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia**
PI: **Deanna L. Kelly**
Institution: **University of Maryland, Baltimore**
Grant No.: **5R01MH090071-04**

Risperidone is available generically and is 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 toward better tailoring and personalizing antipsychotic treatment, particularly for women who suffer from these problems.

IC: **National Institute of Mental Health**
Title: **Assessing Causality: Is Posttraumatic Stress Disorder Cardio-Toxic?**
PI: **Karestan C. Koenen**
Institution: **Columbia University Health Sciences**
Grant No.: **1R01MH101269-01A1**

Posttraumatic stress disorder (PTSD) is a pervasive and debilitating mental disorder in the U.S. population; 1 in 9 women will meet criteria for the diagnosis during their lives. PTSD, the sentinel stress-related mental disorder, has been declared "a life sentence" based on the belief that the disorder leads to a host of adverse physical health problems. The association between PTSD and coronary heart disease (CHD) has received particular attention, with observational studies suggesting PTSD contributes to early development of CHD, and also that mitigating CHD risk in this population might reduce overall burden of CHD. Despite consistent findings from these studies, whether PTSD causes CHD has not been established, and PTSD is not ranked in the American Heart Association (AHA) 2010 impact goals as a risk factor that requires attention. As a result, neither systematic surveillance nor treatment is provided persons with PTSD to reduce potential risk of developing CHD. Informed by these concerns, we propose 3 strategies to address if PTSD is causally related to CHD, using state-of-the-science approaches for inferring causality in observational data. First, we will apply innovative analytic designs not previously been applied in this research area, including consideration of effects when PTSD remits. Second, we will examine if PTSD influences both CHD onset and severity; to date, effects of PTSD on myocardial infarction (MI) severity has only been examined cross-sectionally. Third, evidence that PTSD affects CHD-related behavioral and biological pathways would offer further support for causation but a recent review noted, "mechanistic evidence on the progression of adverse cardiac outcomes in PTSD is lacking." PTSD is linked with CHD risk-related behavior and biomarkers. Because cross-sectional studies cannot test if such behaviors and biomarkers are vulnerabilities for or consequences of PTSD, longitudinal studies are needed. We propose the following Specific Aims: (1) To determine if PTSD influences risk of CHD onset and MI severity with conventional and marginal structural models; (2) To examine whether PTSD changes health behaviors; and (3) To identify if PTSD influences biological pathways associated with increased CHD risk. We will examine if new onset of PTSD among CHD-free women, produces changes in novel and conventional biomarkers associated with CHD risk. We will also explore using Mendelian randomization (MR) to test whether the relation between PTSD and CHD, health behaviors, and CHD risk markers is explained by shared genetic risk or reverse causality. Taken together, the proposed research moves forward not only our understanding of the relation between PTSD and CHD, but also the pathophysiology of PTSD in relation to health more broadly and has direct implications for population health.

IC: National Institute of Mental Health
Title: Specificity and Validity of Oxidative Stress Model of Chronic Fatigue Syndrome
PI: Dikoma C. Shungu
Institution: Weill Cornell Medical College of Cornell University
Grant No.: 5R01MH100005-02

Chronic fatigue syndrome (CFS) is a complex multi-system disorder, which is often misdiagnosed as a psychiatric illness. As a result, the diagnosis of CFS is highly controversial. Discovery of CFS-specific biomarkers that can differentiate the disorder from phenotypically similar psychiatric conditions, such as major depressive disorder (MDD), could thus have a profound impact, not only for how the disorder is generally perceived and managed, but also for the development of objective diagnostic tests, for identification of new therapeutic targets, as well as for advancing scientific understanding of CFS. Recently, using advanced magnetic resonance neuroimaging techniques and a standardized battery of clinical assessments in 15 patients with CFS, in 15 patients with MDD, and in 13 healthy controls, the applicants discovered strong experimental evidence, including a mean deficit of 36% in the most abundant antioxidant in living tissue, glutathione (GSH), increased ventricular cerebrospinal fluid (CSF) lactate, and decreased regional cerebral blood flow (rCBF) compared to controls, which suggested increased oxidative stress as a pathophysiological model of CFS. However, while highly promising and intrinsically consistent, both the validity and the specificity of this oxidative stress hypothesis for CFS remain uncertain, as (a) the essential findings of the study have yet to be replicated, and (b) the same types of abnormalities were found in MDD compared to controls. On the other hand, with comparisons revealing trend-level differences between CFS and MDD, the investigators hypothesized that limited sample size, coupled with the inherent clinical heterogeneity of the two disorders, likely limited the power of their pilot study to detect potential differences between the two disorders. Therefore, to address this potential limitation and to attempt objective differentiation of CFS and MDD—a daunting and continuing challenge—the investigators propose: (1) to replicate in larger cohorts the results of their pilot neuroimaging study that suggested the oxidative stress hypothesis of CFS; (2) to extend the support and evidence base for the model through measurements of several established markers of oxidative stress in plasma, urine, and CSF samples from all the subjects; (3) to correlate the resulting objective outcome measures with clinical indices of overall health and functional disability in all subjects; and (4) to attempt to decrease the inherent clinical heterogeneity in both the CFS and MDD groups through stratification or subtyping techniques based on clinical variables that are unique to each disorder, and then to compare the outcome measures between the resulting subgroups. The expectation is that this approach would identify subgroups of CFS and MDD patients between which significant differences in outcome measures exist that can enable objective differentiation of the two disorders, thereby establishing the outcome measures as bona fide diseases biomarkers, and supporting oxidative stress as a valid and specific pathophysiological model for CFS.

IC: National Institute of Neurological Disorders and Stroke
Title: Crowd-Coding in the Brain: 3D Imaging and Control of Collective Neuronal Dynamics
PI: Patrick O. Kanold
Institution: University of Maryland, College Park
Grant No.: 1U01NS090569-01

The cortex is a laminated structure that is thought to underlie sequential information processing. Sensory input enters layer 4 (L4) from which activity quickly spreads to superficial layers 2/3 (L2/3) and deep layers 5/6 (L5/6) and other cortical areas, eventually leading to appropriate motor responses. Sensory responses themselves depend on ongoing activity, i.e., spontaneous cortical activity, usually in the form of reverberating activity from within or distant cortical regions, as well as on the state and behavioral context of the animal. Receptive field properties of neurons can rapidly and adaptively be reshaped when an animal is engaged in a behavioral task, indicating that encoding of stimuli is dependent on task- or context-dependent state. Responses also depend on ongoing cortical dynamics in a lamina-dependent fashion and differ between the awake and anesthetized state. The intricate neuronal interplay between behavioral context, ongoing activity, and sensory stimulus underlying cortical representations is unknown. Specifically, we do not know how neuronal circuits shape these emergent dynamics within and between laminae, and we do not know which neurons encode which aspect of a sensory stimulus. One shortcoming of all prior studies of sensory processing is that only a few neurons are sampled, and thus information about the interactions between neurons and between neuron and global brain state is lacking. Here, we address these challenges by developing new in vivo 2-photon imaging technology that allows rapid imaging and stimulation in multiple focal planes and new computational and information theoretic techniques to extract network dynamics at the single neuron and population level. These measures go beyond paired measures and take synergistic interactions between neurons into account. We use these new techniques to investigate the 3D single cell and population activity patterns in the auditory cortex in mice. We investigate the influence of single neurons relative to the synergistic influence of specific groups of neurons (the crowd) on network dynamics and ultimately behavior of the animal.

IC: National Institute of Neurological Disorders and Stroke
Title: Integrative Functional Mapping of Sensory-Motor Pathways
PI: Michael H. Dickinson
Institution: California Institute of Technology
Grant No.: 1U01NS090514-01

The goal of the project team is to develop a robust, multi-lab research framework, enabled by large scale imaging, which will lead to principled integrative models of ethologically relevant behaviors that incorporate a detailed knowledge of individual cell classes. The specific neurobiological question that the team will address is how the brain integrates sensory information in order to guide locomotion in a particular direction. Our strategy is to systematically map and functionally characterize the neural circuits that underlie goal-directed locomotion, using the fruit fly, Drosophila, in order to exploit the convergence of powerful genetic, optical, behavioral, and analytical tools that are available in this species. The proposal focuses primarily on refining functional imaging approaches to map the activity of small brain regions and populations of individual neurons in intact, behaving animals while they respond to a

controlled panel of sensory stimuli. We have constructed a strategic plan consisting of seven interrelated research modules that create a flow for discovery that starts with functional imaging and ends with the development of integrative models for sensory-guided behavior. The goal of this proposal is to bring all research modules to the requisite level of maturity for future research. To achieve this goal, this project will develop robust, quantitative and high-throughput methods for: Functional 2-photon imaging using pan-neural drivers; ArcLight imaging using selected driver lines; functional 2-photon imaging using pan-neural drivers; circuit analysis of sensory motor pathways; and a plan for an integrative computational model of sensory-guided locomotion.

IC: **National Institute of Neurological Disorders and Stroke**
Title: **Mechanisms of Neural Circuit Dynamics in Working Memory**
PI: **Carlos D. Brody**
Institution: **Princeton University**
Grant No.: **1U01NS090541-01**

Working memory, the ability to temporarily hold multiple pieces of information for mental manipulation, is central to virtually all cognitive abilities. Working memory has been closely associated with multiple kinds of neural activity dynamics, such as persistent neural activity, activity ramps, and activity sequences. The neural circuit mechanisms of these dynamics remain unclear. This proposal will apply advanced technologies such as virtual reality, automated monitoring of behavior, in vivo microscopy, ontogenetic, and neural circuit reconstruction to solve fundamental problems in the understanding of working memory. The accumulation of evidence over time scales of seconds, a type of working memory critical for decision-making, will be used as a test bed for studying working memory. The proposal will build upon a rodent evidence-accumulation paradigm that allows quantitative, temporally precise parameterization of working memory and decision-making. The paradigm will be implemented with head-fixed rodents behaving in a virtual reality system (Aim 1), providing mechanical stability that enables the use of 2-photon calcium imaging to observe neural activity related to working memory in the neocortex, basal ganglia, and cerebellum (Aim 3). Brain activity will also be perturbed using ontogenetic to probe the roles of brain regions and specific cell types in the formation and stabilization of memory (Aim 2). Finally, we will develop methods for probing the roles of cell types and connectivity in working memory through correlative serial electron microscopy and light microscopy, as well as imaging of population responses to ontogenetic stimulation of single cells or groups of cells (Aim 4). This three-year project will produce a catalog of the types of neural circuit dynamics that are related to working memory across many brain regions. In subsequent years, this catalog will be mechanistically investigated by the anatomical and physiological methods developed in Aim 4. The long-term goal of this project is to arrive at a complete, brain-wide understanding of the cellular and circuit mechanisms of activity dynamics related to working memory. The understanding is expected to take the form of a new generation of models containing cognitive variables distributed across brain regions, as well as models that explicitly represent neural circuit dynamics. This achievement will be a crucial step toward a mechanistic understanding of the neural basis of cognition.

IC: National Institute of Neurological Disorders and Stroke
Title: The Role of Patterned Activity in Neuronal Codes for Behavior
PI: John H. R. Maunsell
Institution: University of Chicago
Grant No.: 1U01NS090576-01

A key aspect of brain function is how the activity of neuronal populations encodes information that is used to guide behavior. A longstanding model system to understand population coding is the visual cerebral cortex, because its structure and anatomy are well understood, and because visual stimuli can be presented to subjects with high levels of temporal and spatial control. Thousands or more neurons fire action potentials in response to a single visual stimulus, and an important open question is how this population response carries information—how the detailed timing and pattern of these spikes across neurons is decoded to guide behavior. Because it is known that genetics controls the identity and morphology of neurons and influences which other neurons they form synaptic partners with, it appears likely that the precise details of which neurons in a population fire spikes is vitally important for behavior. But surprisingly, past experimental work hints that the primary quantity governing neuronal coding is the total number of spikes or average firing rate across a population, making the precise timing and spatial distribution of those spikes less important. Theoretical work shows that either type of code can be supported by the cortex and that the type of code used may even vary from one behavioral task to the next. However, it has not been possible to definitively determine how cortical population codes are used for behavior because of the inability to change the activity of neurons in a patterned fashion. In this project, we will use two-photon ontogenetic stimulation to activate patterns of neurons in behaving animals to understand the details of how population codes control behavior. This work is made possible by the combination of optical wave front-shaping methods to control the size and shape of a two-photon optical focal volume, and psychophysical behavioral methods in mice that allow precise quantification of animals' perceptual performance when neuronal patterns are stimulated. We will use two-photon patterned stimulation to replay naturally occurring population responses to determine if they have special meaning to the animal, perhaps because those patterns are determined by essential synaptic connections. By using patterned stimulation to vary the activity correlation between neurons, we will also test whether previously-observed pairwise correlations, which measure the relationship between the firing activities of two neurons, are an important part of the neuronal code. In achieving our goals we will produce a new technology for stimulating neurons in the brains of behaving animals with single-cell specificity that can be adapted to explore neuronal dynamics in a wide range of animal models and behaviors.

R56 Program

IC: National Heart, Lung, and Blood Institute
Title: Sex Differences in Myocardial Ischemia/Reperfusion Injury
PI: Arthur P. Arnold
Institution: University of California, Los Angeles
Grant No.: 1R56HL119886-01A1

Among all cardiovascular-related diseases, coronary artery disease still remains the leading cause of death in western countries. The incidence and progression of heart disease is markedly different in males and females, indicating that sex-biased factors can protect from disease. The long-term objectives of this project are to identify processes, regulated by sex chromosomes and gonadal hormones, that affect cardiovascular disease; to improve the understanding of endogenous mechanisms of disease; and to identify sex-biased protective factors that may become targets for therapies. The project utilizes novel mouse models, which have already provided new evidence for striking differences in the response of XX and XY mice to myocardial ischemia/reperfusion injury, independent of the gonadal sex of the mice. These novel models vary the number or type of sex chromosomes in mice that have the same type of gonad, and thus allow the first understanding of the differential effects of XX vs. XY chromosomes. XX mice show dramatically greater susceptibility to ischemia/reperfusion injury, relative to XY mice, and lower post-ischemic heart contractile function. The XX vs. XY difference is attributable to the number of X chromosomes, not the presence/absence of the Y chromosome. Thus, the X chromosome harbors factors that strongly influence ischemia/reperfusion injury in a dose-dependent and sexually biased manner. Aim 1 is to investigate the physiological and molecular mechanisms that account for the XX vs. XY difference using these mouse models by measuring heart functional recovery and infarct size, mitochondrial function, superoxide production, and protective signal transduction pathways. Aim 2 is to first identify a list of candidate X gene(s) responsible for the XX vs. XY difference, and then to test the role of specific candidate genes by manipulating their expression in vivo. Response to ischemia/reperfusion injury will be measured in mice with different doses of specific candidate X genes. Aim 3 is to manipulate the levels of adult gonadal hormones and type of gonad to understand how estrogens and androgens act on XX and XY mice to cause protection from ischemia/reperfusion injury. Response to ischemic insult will be measured as a function of hormonal level, sex chromosome complement, and age. Discriminating the hormonal vs. chromosomal consequences of differences between females and males will provide an essential foundation for understanding factors that protect from ischemia/reperfusion injury, with an eye toward harnessing the protective factors to develop novel therapies.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Mechanisms of Macrophage Activation and Function in Scleroderma
PI: Patricia A. Pioli
Institution: Dartmouth College
Grant No.: 1R56AR063985-01A1

Scleroderma is an autoimmune disease associated with vascular injury, fibrosis, and inflammation. Women develop scleroderma 7–12 times more often than men, suggesting

estradiol may be involved in disease development and/or progression. There is no known cure for scleroderma and current treatments are limited. Progress in the development of therapies to combat scleroderma has been hampered by a lack of knowledge of the pathophysiology that underlies this disease. We recently reported that miR-125b, a microRNA aberrantly expressed in scleroderma patients, regulates activation of NF-κB. NF-κB is a master regulator of pro-inflammatory cytokines associated with disease activity in scleroderma. We hypothesize that aberrant regulation of miR-125b in scleroderma leads to enhanced activation of NF-κB and pro-inflammatory. We propose to test the following hypotheses: NF-κB cytokine production. The goal of this proposal is to determine how activation is dysregulated in scleroderma macrophages and to evaluate how modulation of miR-125b alters inflammation associated with this disease 1. That NF-κB activation differs between MØs derived from scleroderma patients vs. healthy controls. Activation of NF-κB contributes to pro-inflammatory cytokine production characteristic of scleroderma. Experiments in this aim will elucidate effects on transcriptional activation, DNA binding activity, and localization of components of the NF-κB signaling complex. 2. That aberrant expression of miR-125b results in inappropriate activation of NF-κB in scleroderma MØs. Our studies have shown that miR-125b inhibits expression of κB-Ras2, a negative regulator of NF-κB signaling. Aberrant expression of miR-125b has been reported in scleroderma patients. We will assess how aberrant expression of miR-125b in MØs derived from scleroderma patients affects NF-κB activation and pro-inflammatory cytokine production. 3. That estradiol differentially modulates miR-125b expression and NF-κB activation in scleroderma MØs vs. healthy controls. This aim will elucidate how estradiol regulation of miR-125b in scleroderma MØs affects NF-κB activation and inflammation.

IC: **National Institute on Drug Abuse**
Title: **A Videoconferencing Tobacco Cessation Research Study (VICTORY)**
PI: **Sun Seog Kim**
Institution: **University of Massachusetts Boston**
Grant No.: **1R56DA036798-01A1**

Smoking rates among Korean women in the United States have substantially increased in the past decade. As a result, their smoking rate is about four times higher than that of all other Asian women and similar to that of the general U.S. female population. Nonetheless, they are reluctant to seek an in-person cessation treatment due to the strong cultural taboo against women who smoke in their native country. They prefer online and telephone interventions that they can access remotely without publicly disclosing their smoker status to other Koreans in the community. However, these interventions showed no significant treatment effect over self-help materials. With NIDA K23 funding, Dr. Kim the PI of the proposed study developed and tested an in-person Korean-culture tailored cessation intervention against a brief standard cessation intervention. The culturally tailored cessation intervention produced an excellent outcome in Korean women compared to the other condition (biochemically verified 12-month prolonged abstinence rates: 56% versus 0%). However, recruitment of the women was very challenging. Almost 50% of the women who agreed to participate did not come for the baseline assessment versus 20% of the men. Exit interviews with the women who participated in the study helped us understand the conflicting desires: they valued most the client-and-therapist relationship and for this, they wanted to "see" the therapist. Yet, they preferred to have the therapist remotely so that the person may not have an acquaintance with their Korean neighbors. They suggested that videoconferencing counseling be a good alternative as other researchers have found in different

populations the same treatment outcome as that in in-person counseling. Therefore, we propose a 2-arm randomized controlled trial (RCT) to test a videoconferencing cessation intervention against a telephone cessation intervention. A total of 90 Korean women will be recruited and randomized at a ratio of 1:1 either to the video or to the telephone arm. Both arms will have the same eight weekly sessions of a 30-minute culturally tailored cessation intervention plus 8 weeks of nicotine patches. The study has three specific aims: (1) Determine the feasibility and acceptability of a videoconferencing culturally tailored cessation intervention for Korean American women; (2) Establish a preliminary effect size of the videoconferencing culturally tailored cessation intervention on a 3-month prolonged abstinence rate compared to telephone counseling of the same intervention; and (3) Refine the intervention manual and intervention fidelity procedures for use in a full scale RCT of a videoconferencing smoking cessation intervention. The study findings will prepare the PI for a larger RCT to evaluate the efficacy of a videoconferencing cessation intervention compared to a telephone intervention in Korean and other Asian American women.

IC: **National Institute on Drug Abuse**
Title: **Cost-Effectiveness and Efficacy of Computerized Therapy for Depression and Drug Use**
PI: **Suzette V. Glasner-Edwards**
Institution: **University of California, Los Angeles**
Grant No.: **1R56DA036718-01A1**

The objective of this research is to improve treatment for cannabis dependent adults with comorbid major depression by augmenting depression pharmacotherapy with an innovative, integrated computer-assisted strategy combining the techniques of cognitive behavioral therapy and motivational enhancement therapy (CBT/MET) to promote relapse prevention skills, reduce cannabis use and depressive symptoms, and improve psychiatric treatment adherence. In 2007 the applicant received a Career Development Award to study an integrated CBT/MET intervention for the treatment of substance users with comorbid major depression in a primary mental health care setting. Results show that (a) cannabis dependence is among the most frequently observed addictive disorders among depressed adults in this setting; (b) integrating CBT/MET with psychiatric treatment for depression produces significant reductions in depressive symptoms and facilitates reductions in cannabis use that are comparable to those observed in psychosocial intervention studies targeting cannabis dependence. To extend this model of evidence-based psychotherapy implementation for depressed cannabis users receiving usual care (TAU) in a primary psychiatric care setting to a computer-based platform, the specific aims of this research are: (1) To conduct an RCT among 195 depressed, cannabis dependent adults receiving TAU, comparing computer-assisted, integrated CBT/MET (cICBT/MET) and addressing cannabis use and depression, relative to therapist-delivered integrated CBT/MET (tICBT/MET) and TAU alone in improving cannabis use, depression, psychiatric treatment adherence, and health care outcomes; (2) To determine the cost-effectiveness of cICBT/MET; and (3) To examine neurobehavioral predictors and mechanisms of action of cICBT/MET, including impulsivity, operationalized by delay discounting, and self-efficacy. We hypothesize that cICBT/MET will yield superior clinical outcomes relative to TAU in reducing substance use, improving depressive symptoms and psychiatric treatment adherence, and reducing health service utilization during and after treatment. Moreover, we expect that cICBT/MET will be less costly and at least as effective as cICBT/MET. Further, we expect that cICBT/MET will have a

direct effect on psychological variables that are recognized mechanisms of change in CBT and MET, and these changes will be associated with cannabis use and depression outcomes. By providing support to maximize psychiatric treatment adherence, coupled with coping skills to prevent relapse, cICBT/MET may provide a promising, cost-effective, and easily deployable strategy for the treatment of depressed cannabis users.

IC: **National Institute on Drug Abuse**
Title: **Creatine Monohydrate Supplementation in Methamphetamine-Using Females**
PI: **Perry Franklin Renshaw**
Institution: **University of Utah**
Grant No.: **2R56DA027135-03A1**

Methamphetamine (MA) use is a significant public health concern for which there are no FDA-approved treatments. This proposal is a competing renewal of DA027135, a clinical trial of CDP-choline for MA users. That study found that female MA users have decreased brain phosphocreatine (PCr) levels, compared with both male MA users and female healthy controls. Following up on this key translational finding, preliminary data collected at our site suggests that when administered to female MA users, creatine monohydrate supplementation is associated with increased brain PCr, N-acetyl aspartate (NAA), and gamma-aminobutyric acid (GABA). Clinically, creatine was associated with decreased depression and anxiety symptoms. It may also reduce MA use, measured by urine drug screens. This proposal follows expert recommendations to target cognitive enhancement and neuronal repair in developing pharmacotherapies for stimulant addiction. Decreased brain PCr concentrations, measured by 31P magnetic resonance spectroscopy (31P-MRS), are associated with poorer depression outcomes. Female MA users have increased rates of depression, and more severe depressive symptoms than males. Because negative mood is associated with MA craving, depression may contribute to the risk of relapse. Creatine supplementation increases brain PCr and levels in human studies and animal models, thereby helping maintain neuronal bioenergetics, and mitochondrial energy production. MA use is associated with decreased brain NAA, and MA also alters the glutamine-glutamate-GABA system. Sustained abstinence from MA is associated with increased NAA, indicating some degree of normalization of neuronal function. Notably, increasing GABA-ergic activity has been shown to reduce MA self-administration, and to block both the development and reinstatement of MA-triggered conditioned place preference. Upregulation of GABA also improves MA-induced cognitive deficits. In our preliminary study, our neurochemical findings included: (1) A significant relationship between the glutamine/glutamate ratio and lifetime amount of MA use; and (2) Increased NAA and GABA concentrations following 8 weeks of creatine supplementation in female MA users. The glutamine/glutamate ratio is important for neuronal/glial viability, as mitochondrial function is tightly coupled with glutamine-glutamate-GABA metabolism. Thus, the proposed study implements 1H-MRS to measure NAA, GABA, and the glutamine/glutamate ratio, as complements to our key 31P-MRS finding of decreased PCr in female MA users. In summary, in women with MA use disorders, creatine is a hypothesis-generated intervention aimed at restoring neurochemistry, reducing depression and anxiety symptoms, and improving cognitive function. Thus, we propose a placebo-controlled clinical trial of creatine, paired with a translational multinuclear spectroscopic neuroimaging study, for females with MA use disorders.

IC: National Institute on Drug Abuse
Title: Imaging Data Re-analysis for Cocaine Addiction
PI: Ze Wang
Institution: University of Pennsylvania
Grant No.: 1R56DA036556-01A1

Cocaine addiction is a brain disorder that takes a large societal and economical toll in the United States. Although neuroimaging has been increasingly used to assess neural substrates critical for drug addiction by examining brain activity in response to drug or drug cues, much less attention has been paid to spontaneous brain activity (SBA) in the absence of an exogenous stimulus. In fact, SBA is the major component of the whole brain activity that accounts for most of brain energy consumption, and is inevitably altered by the chronic and substantial neurobiological interference of cocaine addiction. Assessing SBA may therefore provide a versatile biomarker of disease progression or treatment effects. However, SBA still remains new to cocaine addiction with only two papers published to date reporting the seed-based resting functional connectivity difference in cocaine dependent brain. The use of blood-oxygen-level-dependent (BOLD) fMRI to assess SBA represents a major research activity that has seen an intensive period of growth recently. A large number of BOLD fMRI-derived SBA patterns have been demonstrated, and many of them appear to be modulated by disease states, carrying a great potential for drug addiction study as well. However, those patterns are generally based on relative measures, providing no quantitative information for clinical applications. AIM 1 of this study is to derive a quantitative measure for characterizing the temporal fluctuations of SBA based on our recent pilot investigations. We will evaluate the measure using synthetic data and thousands of normal subjects' data from the 1000 Functional Connectomes Project. AIM 2 is to identify SBA alterations in cocaine dependent brain. Our center has acquired resting BOLD fMRI data and resting arterial spin labeling (ASL) perfusion fMRI data from a large cohort of cocaine patients, providing an opportunity to investigate SBA questions that were not covered in the original data collection project. We will reuse those data to find both the temporal fluctuation changes and magnitude changes of SBA in cocaine patients as reflected by the proposed quantitative SBA measure and regional cerebral blood flow (CBF) measured by ASL MRI. Moreover, we will assess the functional connection network-wise alterations in the cocaine-addicted brain. Finally, we will (AIM 3) explore the utility of SBA (including the temporal dynamics and magnitude and the functional connection network properties) for predicting clinical outcomes including drug craving and relapse to cocaine use. The feasibility of the proposed aims is evidenced by the substantial preliminary investigations. The broad technical impact of this project is that the resulting quantitative temporal SBA measure will benefit not only addiction study, but also to the general resting fMRI-based SBA research in normal and clinical populations. The clinical impact of this project is that it will offer the first evidence that cocaine addiction is associated with altered temporal SBA and resting CBF and the entire functional connectivity network. It will also provide information about SBA-based craving and relapse to drug use prediction.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Community-Clinic Partnership to Promote Physical Activity in South Asian Women
PI: Namratha R. Kandula
Institution: Northwestern University at Chicago
Grant No.: 1R56DK099680-01A1

South Asians (SAs) make up a quarter of the world's population and are one of the fastest growing racial/ethnic minority groups in the United States (U.S.). Our data, and others, have found that SAs are some of the least physically active adults in the U.S. and may require special considerations when designing and implementing PA programs. SAs also manifest greater visceral adiposity, insulin resistance, and a significantly higher prevalence of DM, at a lower BMI, compared to other racial/ethnic groups. Regular PA has been shown to decrease visceral adiposity, improve insulin sensitivity, and prevent DM, even in the absence of weight loss; thus, PA may be especially important to prevent or delay the onset of DM in SA populations. Facilitating and promoting PA interventions for the growing SA population could lead to a substantial impact on their DM risk. Yet there is almost no research on how best to adapt evidence-based PA interventions for U.S. SAs. Our prior community-based participatory research, conducted in SA communities with a high proportion of recent immigrants who have limited English proficiency and limited access to health care, found that SA women, in particular, are not being reached by current PA interventions. SA women reported little PA and even had difficulty defining exercise. Although 75% of the women were sedentary and overweight/obese, they did not recognize these as risk factors for DM. Lack of knowledge about benefits of PA, cultural and linguistic isolation, concerns about modesty, and rigid gender roles were strongly influencing SA women's PA. Despite these barriers, SA women were willing to participate in exercise if it could be done in women-only classes, with their children, and in a trusted community setting. In partnership with Chicago's SA community, we used this formative data, community input, and a social determinants framework to develop an innovative PA intervention. The intervention includes community-based exercise classes that engage SA women and their children in moderate intensity aerobic PA and resistance exercises through culturally acceptable activities. During the proposed 2 year-study, we will work with community partners to pilot-test healthcare-based identification of SA women at high risk for developing DM followed by delivery of a culturally-salient PA intervention in a community-based setting, via a 2-arm randomized design, and examine the intervention's feasibility (recruitment, retention, and program adherence) and initially efficacy on HbA1c. Secondary outcomes are fasting plasma glucose, biomarkers associated with insulin resistance, components of the metabolic syndrome, PA, and psychosocial processes. A process evaluation will be used to understand participants' and interventionists' perceptions of the intervention and its implementation. Study results will provide essential data for planning a larger-scale efficacy trial to reduce DM risk in SAs via community-based PA interventions. Importantly, the proposed study's community-participatory approach will use a fundamental structure that is generalizable and could be replicated in other high-risk, vulnerable populations.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Probiotic Analgesia for Pelvic Pain
PI: David J. Klumpp
Institution: Northwestern University
Grant No.: 1R56DK102807-01

Pain is poorly managed in chronic pelvic pain, so new analgesic strategies are urgently needed. Our long-term goal is to harness the potential of probiotics to develop new probiotic analgesics for treating the pelvic pain of interstitial cystitis/bladder pain syndrome (IC). We previously examined the molecular basis that discriminates the symptomatic response to uropathogenic E. coli (UPEC) from the lack of response to E. coli clinically associated with asymptomatic bacteriuria (ASB). We have now accumulated compelling preliminary data demonstrating that E. coli-based probiotics alleviate both acute and chronic pelvic pain in clinically relevant murine models that recapitulate key aspects of IC. We hypothesize that the analgesic activity of E. coli-based probiotics results from acting on three receptors involved in bladder pain signals, Toll-like receptor 4 (TLR4), transient receptor potential cation channel subfamily V member 1 (TRPV1), and chemokine C-C motif receptor 2 (CCR2). These mechanistic studies will define the analgesic ligands of probiotic E. coli and define the roles for each receptor in mediating pelvic pain in murine models of IC. These studies are highly innovative, and we are unaware of other groups studying analgesic probiotics for chronic pelvic pain. This project will thus result in a new mechanistic understanding of probiotic analgesics and provide critical pre-clinical data to drive these probiotics into clinical trials for IC.

IC: National Institute of Environmental Health Sciences
Title: Toxicokinetics and Metabolic Disrupting Actions of the Flame Retardant Mixture FM
PI: Heather B. Patisaul
Institution: North Carolina State University
Grant No.: 1R56ES022957-01A1

Obesity rates in the US have reached epidemic proportions. Although lifestyle factors are clearly primary contributors, fetal metabolic reprogramming by environmental chemicals collectively called "obesogens" has been hypothesized to exacerbate obesity risk. Data collaboratively generated by the three co-PIs have identified the newly introduced fire retardant mixture Firemaster® 550 (FM 550) as an emerging contaminant in US homes and that (in rats) perinatal exposure to FM 550 results in obesity, and hallmarks of metabolic syndrome including altered exploratory behaviors, disrupted glucose sensitivity and cardiac hypertrophy. There is pressing need to assess the toxicity of FM 550 because it is at least the second most common fire retardant used in residential furniture and baby products with ubiquitous exposure in the US, yet its potential toxicological effects are not well characterized. Working as an interdisciplinary, multi-PI team, comprising an environmental chemist, a neuroendocrinologist, and an endocrine pharmacologist, we submitted an R01 application to test the hypothesis that FM 550 is an obesogen, and perinatal exposure induces hallmarks of metabolic syndrome (e.g., hypertension, type-2 diabetes, and cardiovascular disease) via metabolic reprograming. To strengthen the R01 application and generate additional data required to address reviewer concerns, work in this R56 application will (1) characterize the toxicokinetics of FM 550 in female rats (pregnant and non-pregnant) to specifically assess the potential for fetal transfer; and (2) characterize the hallmarks

of metabolic disrupting and behavioral effects of FM 550 (one dose) in exposed offspring of both sexes. Importantly, whether or not the increase in body weight (identified as sexually dimorphic in the parent R01) observed in our pilot study is accompanied by increased food intake and/or changes in overall activity will be determined. These are key markers of metabolic reprogramming and will thus help address the central hypothesis of the parent R01 that FM 550 is an "obesogen" and can predispose exposed offspring to metabolic disease. Examining phenotypic sex differences is a fundamental feature of this application, and the data will ultimately be used to inform future work (and a specific aim of the R01 application) exploring the sex specific mechanisms underlying adipogenesis and the metabolic disrupting activity of FM 550, its components, and primary metabolites. Understanding the contributions of each FM 550 component to an obesogenic phenotype is critical because some have large volume applications as plasticizers in a wide variety of consumer products (e.g. polyvinyl chloride (PVC), circuit boards, hydraulic fluids, adhesives, nail polish). Collectively the proposed studies will contribute to our long term efforts to secure R01 funding for this work but also provide new knowledge required for evaluating potential human health effects of developmental FM 550 exposures including fate and transport in tissues, obesogenic potential of the mixture and its individual components across a wide-dose range, sex-specific mechanism of action, and the possible long-term metabolic health consequences of early life exposure in both sexes.

IC: **National Institute of Mental Health**
Title: **Corticotropin-Releasing Factor/Serotonergic Interactions**
PI: **Rita Valentino**
Institution: **Children's Hospital of Philadelphia**
Grant No.: **2R56MH058250-16**

Stress has been implicated in diverse psychiatric diseases including posttraumatic stress disorder, depression, anxiety, and substance abuse. One link between stress and these psychiatric disorders is corticotropin-releasing factor (CRF), the neuropeptide that orchestrates the stress response. In response to stress CRF regulates activity of the dorsal raphe (DR)-serotonin (5-HT) system, a system that has been implicated in stress-related psychiatric disorders. CRF has opposing inhibitory and excitatory effects on DR-5-HT neurons through CRF1 and CRF2 receptors, respectively. Low levels of CRF such as those released during acute stress initiate CRF1-mediated inhibition of 5-HT neuronal activity, and this is associated with the promotion of escape from shock and active coping in response to swim stress. A history of stress causes a cellular redistribution of CRF receptors in the DR such that CRF2 is recruited to the plasma membrane. This switches regulation of the DR-5-HT system from CRF1-mediated inhibition to CRF2-mediated excitation and promotes learned helplessness and immobility. A working hypothesis of this research is that stress-induced redistribution of CRF receptors in DR neurons is a cellular mechanism that underlies stress-induced impairments in cognition and social behavior, and that this is determined by sex and coping style. Stress-related psychiatric disorders are more prevalent in females, but our knowledge of CRF regulation of DR-5-HT function is based solely on studies using male rats. Therefore, both males and females will be used in these studies. Aim 1 will characterize CRF effects on female DR-5-HT neuronal activity and determine whether the stress-induced CRF receptor redistribution that occurs in male DR also occurs in females. Aim 2 will use resident-intruder stress as a social stress model that has a limited duration and causes CRF receptor redistribution in a subpopulation of vulnerable rats. Using this stressor, the role of CRF receptor redistribution in DR neurons in stress-induced

cognitive and social impairments will be assessed in male and female rats. Aim 3 will use male and female CRF-overexpressing mice as a genetic model of chronic stress and determine whether this condition causes CRF receptor redistribution in DR neurons that translates to changes in forebrain 5-HT and effects on behavior and cognitive function. Our past work characterized regulation of the male rat DR-5-HT system by CRF1 and CRF2 receptors and identified stress-induced CRF1/CRF2 redistribution as a cellular mechanism by which stress can impact this system to produce maladaptive psychopathology. Here, we address the role of sex differences in this cellular mechanism, its impact on cognitive processes that are dysfunctional in mood disorders, and the potential for genetic elevations of CRF, as have been proposed to occur in stress-related psychiatric disorders, to produce the same cellular and behavioral consequences.

Research Enhancement Awards Program

IC: National Cancer Institute
Title: A Pooled Analysis for Risk Factors of Triple Negative Breast Cancer
PI: Huiyan Ma
Institution: City of Hope/Beckman Research Institute
Grant No.: 1R03CA188549-01

Triple negative breast cancer (TNBC) is the breast tumor subtype that is negative for the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). Due to its aggressive nature and the lack of effective targeted therapies, patients with TNBC generally have a poorer prognosis than patients with the most common breast cancer subtype, luminal A (ER+ or PR+, HER2-). The overall 5-year survival rate for TNBC patients is at least 10% lower than that for luminal A patients. Furthermore, TNBC tends to strike premenopausal black women more frequently than others. Our long-term goal is to better understand the etiology of TNBC so that we can develop targeted approaches that reduce its occurrence on a population-wide scale. Gene expression studies indicate luminal A tumors are associated with ER signaling, whereas the majority of TNBCs are characterized by a "basal-like" molecular profile, typically overexpressing genes involved in cell proliferation and differentiation. Based on the clinical and molecular differences between TNBC and luminal A, we hypothesize that the risk profiles for these two subtypes are likely to be different. Previous studies have shown that established hormone-related risk factors for breast cancer overall (e.g., reproductive factors) are associated with luminal A. However, the TNBC risk profile remains vague due to the small number of TNBC cases in the majority of published single studies, and the limited risk factor data available for published collaborative or pooled analyses. The objective of this proposal is to identify risk factors for TNBC, compare their contributions to the likelihood of developing TNBC and luminal A, and determine if race or menopausal status modifies any overall main effect for TNBC or any heterogeneity detected between TNBC and luminal A. We have access to existing data collected by three large population-based case-control studies of women aged 20–64 years. The data include case participants' ER/PR/HER2 status and detailed information about various exposures for case and control participants. These studies will supply us with both a large number of TNBC cases (n = 566) and detailed information for an extended list of risk factors, which are not available in most previous studies. Factors of interest are 10 known and suspected risk or protective factors identified when breast cancer was considered as a single disease. They include menstrual/reproductive history, oral contraceptive use, menopausal hormone therapy use, body size measures and their changes over time, race, breast cancer family history, recreational physical activity, alcohol consumption, cigarette smoking, and prenatal factors. The large sample of TNBC cases, the extended list of potential breast cancer risk factors, and the variety of study participants with respect to race (white, black) and age (pre- and post-menopausal), all provide the resources needed to carry out this study. Successful completion of this project will provide new insight into the etiology of TNBC, which could lead to novel targeted approaches to the prevention of TNBC on a population-wide scale.

IC: National Cancer Institute
Title: Does Stanniocalcin Predict Late Breast Cancer Recurrence, or Is It a Fish Story?
PI: Timothy L. Lash
Institution: Emory University
Grant No.: 1R21CA185932-01

Advances in the effectiveness of breast cancer screening and treatment have reduced the breast cancer mortality rate over the last decades. These advances come from avoided recurrences but also from delayed recurrences. The success of chemotherapy, endocrine therapy, and radiation therapy is typically measured by a reduction in the risk of recurrence in the first five years after breast cancer diagnosis. Many recurrences, however, occur late; that is, more than five years after diagnosis. These recurrences erupt from single dormant cells or micro-metastases where tumor cell growth has been balanced by tumor cell death. How does a single cell, or a small colony of cells, survive for more than five years in a hostile microenvironment that, at least at the outset, often includes hypoxic climates induced by cancer therapies? One likely explanation is that tumors with the capability to recruit stanniocalcin are more likely to survive in this setting and to recur five or more years after diagnosis. Stanniocalcin is a hormone first discovered in bony fish, where it regulates the concentration of calcium at the gills. In humans, nerve cells, fat cells, heart cells, ova, and other long-lived cells recruit stanniocalcin as a survival strategy when they face hypoxic stress, helping them to live in sometimes-harsh conditions by uncoupling proton transport from glycosylation in the mitochondria. Preliminary human evidence and in vitro studies show that tumor expression of stanniocalcin is a marker of recurrence risk, and particularly late recurrence risk. We propose, therefore, to use an existing biobank from ~ 1,700 breast cancer patients (841 with recurrence and 841 matched controls) linked to complete clinical data and long-term follow-up for recurrence to investigate whether stanniocalcin expression is a specific marker for late recurrence risk. We will determine whether breast cancer patients with late recurrences were more likely to have had primary tumors that express stanniocalcin than breast cancer patients with early recurrences. We will also determine whether the tumor cells of those with late recurrence are more likely to have retained or acquired the ability to express stanniocalcin than the tumor cells of those with early recurrence. If we find that stanniocalcin is a specific marker for late breast cancer recurrence, we will seek new research support to validate the result in a second breast cancer cohort and in a colorectal cancer cohort, and to investigate drugs to disrupt the pathway. There is no specific marker for late recurrence risk. A marker that predicts when a recurrence will occur, rather than whether a recurrence will occur, would change the clinical paradigm for cancers with substantial late recurrence risk. It would allow personalization of recurrence screening strategies, development of low-toxicity prophylactic therapies that begin when the late recurrence risk rises, and personalization of existing adjuvant therapies with regard to time from diagnosis. This R21 high-risk, high-reward project will initiate a program to identify markers of late recurrence risk and strategies to reduce or ameliorate that risk.

IC: National Cancer Institute
Title: Molecular Mechanism of Oncogenic Programming by Histone Demethylase GASC1
PI: Zeng-Quan Yang
Institution: Wayne State University
Grant No.: 1R21CA175244-01A1

The long-term goal of this application is to elucidate the fundamental mechanism by which dysregulation of the histone demethylase, GASC1 (Gene Amplified in Squamous Cell Carcinoma 1, also known as JMJD2C and KDM4C), contributes to tumorigenesis, and to lay a foundation for the development of this protein as a new therapeutic target against breast cancer. The GASC1 gene was originally cloned from an amplified region at 9p24 in esophageal cancer cells. Later studies demonstrated that GASC1 is amplified in approximately 15% of breast cancers with overexpression more prevalent in aggressive, basal-type breast cancer. The GASC1 protein is a key member of histone demethylases that play an essential role in regulating chromatin architecture and gene expression, and is implicated in tumorigenesis. GASC1 mainly catalyzes demethylation of tri- and di-methylated forms of histone H3 lysine 9 (H3K9me3/me2) epigenetic repressive marks. However, the molecular mechanisms by which GASC1-dependent chromatin regulation translates to oncogenicity and cancer progression remain poorly understood. Intriguing preliminary evidence indicated that GASC1 is significantly enriched at target gene promoter regions, and that recruitment of GASC1 to specific genomic loci requires the GASC1 Tudor and Plant Homeo Domains (PHD). Studies indicate that the Tudor and PHD domains have the potential to bind H3K4me3 active marks at promoter regions. Importantly, we demonstrated that GASC1 target genes are involved in multiple signaling pathways and biological processes, including critical genes such as the S-phase kinase-associated protein 2 (SKP2), which participates in ubiquitination. The central hypothesis of this application is that GASC1 is recruited to gene promoter regions containing H3K4me3 active marks via its histone-binding domains, and the subsequent demethylation of H3K9me3/me2 repressive marks induces the transcription of a set of key ubiquitination pathway genes that ultimately promote tumorigenesis. Based on this hypothesis, strategies that selectively alter the GASC1 histone recruitment hold great promise as targeted therapies for aggressive, GASC1-amplified breast and esophageal cancers. In this application, two specific aims will be pursued. In Aim 1, we will elucidate the molecular mechanism and structural details of GASC1 that mediate its recruitment to promoter regions of target genes. In Aim 2, we will determine how GASC1 impacts the histone methylation status and expression of target genes responsible for mediating GASC1's role in breast tumorigenesis in vitro and in xenograft animal models. Significantly, the proposed research will fundamentally increase our understanding of the mechanisms by which GASC1 is recruited to genomic loci and how genetic amplification of GASC1 alters epigenetic programming and triggers downstream oncogenic pathways in cancer. These aspects have translational implications in the development of GASC1 mechanism-based therapies to target a wide range of cancers, particularly GASC1-amplified basal breast cancer.

IC: **National Cancer Institute**
Title: **Searching for New Risk Variants in Known Breast Cancer Risk Loci in Asians**
PI: **Jirong Long**
Institution: **Vanderbilt University**
Grant No.: **1R03CA176757-01A1**

Genetic factors play an important role in the etiology of breast cancer, a complex, multifactorial disease. To date, genome-wide association studies (GWAS) have discovered approximately 67 common genetic susceptibility loci for breast cancer risk. However, with the exception of a few loci, all others were identified initially in studies conducted among women of European ancestry. Among the 67 index SNPs reported to date, only about a half of them could be directly replicated in Asians. Given differences in genetic architecture across different ethnic populations, we hypothesize that different risk variants may exist in Asian-ancestry populations in some of the loci in which the index SNPs were not replicated in Asians. Multiple studies have shown that imputation based on the 1000 Genomes Project data provides better chance to identify novel risk variants than that based on the HapMap data since data in the 1000 Genomes Project have much denser SNPs, especially low allele frequency SNPs, and a larger sample size. Over the past few years, we have genotyped ~ 9,400 breast cancer cases and controls of Asian ancestry using Affymetrix 6.0 SNP arrays. We propose to impute data for these samples using the most recent 1000 Genomes Project data as reference to evaluate 10 breast cancer loci in which the index SNPs were not replicated in Asians. Promising SNPs will be further investigated in an independent set of 8,400 cases and controls of Asian ancestry. With strong methodology and a very cost-efficient study design, we anticipate that novel genetic variants will be identified in these loci in Asian ancestry populations. These newly identified variants could significantly improve our understanding of breast cancer genetics and biology and could be used for cancer screening and risk assessment aimed at identifying high-risk women for targeted breast cancer prevention.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Treating First Trimester Gestational Diabetes: A Randomized Controlled Trial**
PI: **Hilary Alpert Roeder**
Institution: **University of California, San Diego**
Grant No.: **1R03HD074826-01A1**

The primary aim of the proposed research is to demonstrate that promoting a normoglycemic intrauterine milieu in women with gestational diabetes (GDM) diagnosed in the first trimester of pregnancy by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria (fasting plasma glucose [FPG] 92–125 mg/dL) will decrease the accumulation of fetal white adipose tissue and development of infant/child obesity during the first year of life. This project: Treating First Trimester Gestational Diabetes: A Randomized Controlled Trial is built upon the hypothesis that pregnant subjects with GDM randomized in the first trimester of pregnancy to strict glycemic control and pharmacotherapy as needed will have less fetal adiposity and adverse neonatal outcomes than those who receive the diagnosis of GDM but do not initiate care until the third trimester. In the proposed study, 280 women meeting the above

criteria for GDM at 15w0d gestation will be randomized to either first trimester or third trimester treatment. Each group will have diabetes education, initiate blood glucose monitoring, begin pharmacotherapy as needed (per established protocol), undergo growth ultrasounds, and antenatal testing. The first trimester arm will receive the above interventions immediately upon diagnosis of GDM whereas the third trimester arm will receive only routine prenatal care until 28 weeks, at which time they will begin education and treatment. Both groups will be treated identically from 28 weeks until delivery. The primary outcome, neonatal fat mass will be calculated based on length, weight, and skinfold thickness within 48 hours of delivery. Additionally, neonates born to mothers in both arms will be followed for 12 months after delivery in order to determine if weight-for-length differs between first trimester and third trimester treatment of GDM. Our secondary outcome will be adherence to the Institute of Medicine guidelines for gestational weight gain. In the 2013 NIH/NICHD GDM Consensus Conference, the panel was concerned about adopting criteria that would increase prevalence of GDM (i.e., first trimester treatment) without first demonstrating improved outcomes. The results of this proposed trial, utilizing the IADPSG paradigm, will allow us to fill key research gaps; this is the first prospective trial to evaluate the IADPSG recommendations for screening and diagnosing GDM in the first trimester. Findings from this research will quantify the maternal and neonatal benefits and harms of treating women with GDM from early pregnancy. Additionally, the cohort of neonates that will result from this study can be followed into childhood to evaluate whether first trimester treatment has benefits beyond those anticipated at birth and may decrease the long-term incidence of obesity and diabetes.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Minimally Invasive Laser Treatment of Female Stress Urinary Incontinence**
PI: **Nathaniel M. Fried**
Institution: **University of North Carolina at Charlotte**
Grant No.: **1R15DK099774-01A1**

Over 6.5 million women in the U.S. suffer from Stress Urinary Incontinence (SUI), and yet only 200,000 women (3%) seek surgical intervention. The need for general anesthesia, prolonged recovery time, fear of incisions, and concerns about treatment failures are just some of the reasons behind patient hesitation to seek SUI therapy. As a result, the remaining women afflicted with SUI use disposable absorbable products with an estimated cost of billions of dollars to cope with, but not cure, their symptoms. Recently, radiofrequency (RF) energy has been used for transurethral thermal shrinkage and micro-remodeling of the endopelvic fascia as a nonsurgical treatment for SUI. The main limitation of RF energy is its limited tissue penetration depth, and hence, the need to invasively insert multiple RF needles into the submucosal tissue for thermal remodeling. We propose to develop a less-invasive alternative procedure for treatment of SUI using deeply penetrating near-infrared laser energy in combination with applied contact cooling of the tissue surface, delivered through an endoscopic laser probe as a transvaginal approach to SUI treatment. The technique of delivering laser energy in combination with applied cooling has been exploited with great success in cosmetic dermatology applications. However, this technique has not yet been extended to other applications where targeting of deeper tissue structures is necessary. Our preliminary studies in a variety of soft tissues have demonstrated, both ex vivo and in vivo, that targeting and thermal alteration of subsurface tissues can be achieved using a laser in conjunction with contact cooling of the tissue surface, preserving 1–2 mm of the tissue

surface from thermal necrosis. We hypothesize that for treatment of SUI, the vaginal mucosa can be completely preserved while the submucosal tissue is thermally remodeled, using an endoscopic laser probe with integrated cooling. We propose to design and test an endoscopic laser probe for minimally invasive transvaginal thermal treatment of female stress urinary incontinence. This project will involve (1) experimental measurements and computer simulations of optical and thermal parameters of tissues; (2) design of an endoscopic transvaginal laser probe for use in treating female incontinence; (3) optimization of the laser and cooling treatment parameters; and (4) pre-clinical evaluation of the endoscopic laser probe for thermal tissue denaturation, shrinkage, and remodeling in a short-term, chronic porcine model.

IC: **National Institute of Nursing Research**
Title: **RCT of a Tailored Walking Program To Reduce Stress Among Pregnant Women**
PI: **Cynthia L. Battle**
Institution: **Butler Hospital**
Grant No.: **1R01NR014540-01A1**

Depressive symptoms are prevalent among pregnant women and consistently linked with adverse outcomes for both women and infants, including higher rates of spontaneous abortion, preeclampsia, operative delivery, and postpartum depression. Infants of depressed pregnant women are more likely to be born pre-term, and experience more language and cognitive delays, anxiety disorders, and attention deficit/hyperactivity disorder. In spite of these risks, few interventions have been developed to reduce prenatal depressive symptoms. Because pregnant women are often reluctant to take antidepressants, the most available form of care, a pressing need exists to evaluate interventions that are efficacious in reducing symptoms and more acceptable and accessible to pregnant women. Increased physical activity has numerous advantages as a strategy to decrease symptoms of depression. Moderate intensity exercise is effective in lowering depressive symptom levels among individuals who are not pregnant. It is also inexpensive, safe, and associated with multiple positive health outcomes. The American College of Obstetricians and Gynecologists strongly recommends regular physical activity throughout pregnancy, yet, in practice, many pregnant women are unsure of how to safely adhere to this recommendation. Findings from our research indicate that a tailored, supported physical activity intervention would be acceptable to depressed pregnant women and would be preferable over pharmacotherapy. Plausible mechanisms exist by which increased physical activity may reduce depressive symptoms, including physiological, behavioral, and psychological factors. No study to date, however, has evaluated physical activity as an intervention for depressed pregnant women. Our team recently developed a gentle, 10-week, pedometer-based walking intervention designed for pregnant women, the Prenatal Walking Program (PWP), including detailed intervention manuals, interventionist training programs, and adherence scales. The program is designed to be low-cost and transportable for delivery in community settings. We evaluated PWP in an open trial and found evidence for the feasibility, acceptability, and safety of the intervention. In addition, participants reported significant reductions in depressive symptoms and functional improvements. The research plan for this R01 application includes a fully powered RCT to evaluate PWP in comparison with a perinatal-focused health education control (HEC) condition. 152 pregnant women will be randomized to PWP or HEC and will complete blind assessments at multiple points across pregnancy and postpartum. The primary aim is to examine whether the PWP group has greater reductions in depressive symptoms relative to HEC. In

addition, several key maternal health and functioning outcomes will be assessed, and infant neurobehavioral exams will allow for examination of group differences. Potential mechanisms will also be tested, including behavioral factors (behavioral activation, decreased avoidance), psychological factors (increased self-efficacy), and physiological factors (decreased inflammation, improved sleep).

Specialized Centers of Research on Sex Differences

IC: National Institute on Aging
Title: Sex-Specific Risk for Vascular Dysfunction and Cognitive Decline
PI: Virginia M. Miller
Institution: Mayo Clinic, Rochester
Grant No.: 5P50AG044170-03

Cardiovascular disease and cognitive decline are two related conditions disproportionately affecting men and women across their lifespan. This interdisciplinary program will utilize innovative tools imaging and diagnostic techniques to understand how changes in blood supply to the brain affect cognition in 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.

IC: National Institute of Arthritis and Musculoskeletal and Skin Diseases
Title: Sex Differences in Musculoskeletal Conditions Across the Lifespan
PI: Nancy E. Lane
Institution: University of California, Davis
Grant No.: 5P50AR063043-03

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 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; an epidemiologic study on the relation of sex differences in bone shape to occurrence, severity, and prognosis of osteoarthritis; a 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. Public Health Reference: This translational SCOR grant, "Sex Differences in Musculoskeletal Diseases Across the Lifespan," focuses on four musculoskeletal diseases or syndromes that differ by sex and include peak bone mass (a laboratory-based project), carpal tunnel syndrome (epidemiologic and observational), osteoarthritis of the knee (observational), and kyphosis (exercise intervention). Each project will carefully determine the sex differences in relation to the musculoskeletal diseases and inform preventive and clinical practices.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Bioenergetic and Metabolic Consequences of the Loss of Gonadal Function**
PI: **Wendy M. Kohrt**
Institution: **University of Colorado Denver**
Grant No.: **5P50HD073063-03**

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 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 I (clinical): Bioenergetic and Metabolic Consequences of the Loss of Ovarian Function in Women (PI: W. Kohrt); (2) Project II (preclinical): Effects of Pre-existing Obesity on Consequences of the Loss of Ovarian Function (PI: P. MacLean); and (3) Project III (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, 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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Birth, Muscle Injury, and Pelvic Floor Dysfunction**
PI: **John O. L. DeLancey**
Institution: **University of Michigan**
Grant No.: **5P50HD044406-13**

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 4 schools and 2 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 I, "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 II, "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 III, "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.

IC: ***Eunice Kennedy Shriver*** **National Institute of Child Health and Human Development**
Title: **Genes, Androgens, and Intrauterine Environment in PCOS**
PI: **Andrea Dunaif**
Institution: **Northwestern University at Chicago**
Grant No.: **5P50HD044405-13**

The NU SCOR explores the overarching hypothesis that genetic variation resulting in hyperandrogenemia produces the phenotypic features of the 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 I and II are clinical research projects, and Project III will utilize a novel non-human 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 I 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-β signaling, Wnt signaling, insulin signaling, gonadotropin action and extracellular matrix, as well as rare variants in genes in novel pathways. Project II 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 III will develop a novel non-human 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.

IC: **National Institute on Drug Abuse**
Title: **SCOR on Sex and Gender Factors Affecting Women's Health**
PI: **Kathleen T. Brady**
Institution: **Medical University of South Carolina**
Grant No.: **3P50DA016511-13S1**

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 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. Close collaboration with the MUSC BIRCWH program, 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 using emerging technology in closely aligned clinical and basic science projects. The overarching goals of the 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.

IC: **National Institute on Drug Abuse**
Title: **Sex Differences and Progesterone Effects on Impulsivity, Smoking and Cocaine Abuse**
PI: **Marilyn E. Carroll**
Institution: **University of Minnesota**
Grant No.: **5P50DA033942-03**

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) To 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) To 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 no pregnant 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.

IC: National Institute on Drug Abuse
Title: Yale-SCOR on Gender-Sensitive Treatment for Tobacco Dependence
PI: Sherry Ann McKee
Institution: Yale University
Grant No.: 5P50DA033945-03

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 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 inter-related 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. Our specific aims and objectives of the Yale-SCOR are to: Aim 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. Aim 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. Aim 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.

IC: National Institute of Diabetes and Digestive and Kidney Diseases
Title: Center for Neurovisceral Sciences and Women's Health
PI: Emeran A. Mayer
Institution: University of California, Los Angeles
Grant No.: 5P50DK064539-13

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 2 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 3 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 2 themes through 3 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 3 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 that can be identified by their responsiveness to a selective CRFIR antagonist.

IC: **National Institute of Diabetes and Digestive and Kidney Diseases**
Title: **Molecular and Epidemiologic Basis of UTI in Women**
PI: **Scott J. Hultgren**
Institution: **Washington University in St. Louis**
Grant No.: **5P50DK064540-13**

Antibiotic resistance is reaching a tipping point such that certain common infections with Enterococcus, MRSA, and E. coli are becoming untreatable. Developing anti-virulence drugs which target pathogenic nodes to disarm the pathogen so that innate defenses can eradicate it represents a hopeful strategy to develop new anti-infectives. In order to develop such preventive and therapeutic strategies, the molecular pathogenesis of sex-specific infectious disease processes must be better understood. Thus, it is critical to elucidate the molecular basis of host-pathogen interactions that result in persistence and/or the formation of reservoirs that seed recurrent infections and whether sex-specific differences alter the pathogenesis. Similarly, it is important to identify mechanisms by which a dysbiotic microbiota develops to predispose to an infection and the ramifications of sex differences on these processes and on host immune responses to invading pathogens and/or risk for downstream sequelae. Understanding the influence of hormones on host-pathogen interactions and differences in disease progression and therapeutic responses in females and males is also critical in order to gain a holistic molecular picture of pathogenesis. These factors are of particular interest in this SCOR as they relate to the urogenital tract, in which we have demonstrated host reservoirs and chronic persistent infections in female and male mouse models as well as modulatory effects of urogenital microflora on disease progression. In this proposal, we concentrate our efforts on the study of urinary tract

infections (UTI). UTI is a disease which: (i) primarily affects otherwise healthy females (50% of women will have a UTI); (ii) is associated with significant morbidity and economic impact, with over $2.5 billion spent annually on treatment; (iii) is becoming increasingly caused by antibiotic-resistant pathogens; (iv) is highly recurrent (25%–50% chance of second infection despite appropriate treatment for a first infection); (v) can become chronic (placebo studies show a 50% incidence of chronicity without antibiotic treatment); (vi) increases in frequency and potential for complications during specific stages of a woman's life, such as during pregnancy; (vii) can lead to complications, including sepsis and renal scarring in children, and is linked to preterm birth; (viii) affects males at the extremes of life (infants and elderly men); and (ix) represents a major complication in hospitalized patients. The objectives of our interdisciplinary team are to use an interwoven combination of clinical and basic research to better understand the epidemiology, pathophysiology and mechanisms involved in the initiation, progression, and outcome of UTIs. Project 1: We seek in this proposal to understand the complexity of host-pathogen interactions that determine the onset and progression of UTI. In Aim 1 we seek to elucidate bacterial mechanisms important in the formation of intracellular bacterial communities (IBCs) and the subsequent development of chronic cystitis. In Aim 2, we seek to analyze the correlation between IBC numbers during acute cystitis and propensity for chronic cystitis and to explore host epithelial mechanisms that are likely to restrict the development of IBCs. In Aim 3, we will utilize an innovative metabolomics approach to assess small molecules in urines collected from women with acute UTI who do and do not develop recurrence, and urines from pregnant women and male/female infants and animal studies. In Aim 4, in we will assess sex influences on UPEC pathogenesis, specifically the effects that co-inoculation of vaginal microflora with UPEC have on pathogenesis and disease outcome. Project 2: We will perform the first longitudinal study of its kind to investigate whether colonization by specific combinations of urogenital bacteria is associated with increased susceptibility of the pregnant host to acute or recurrent UTI or asymptomatic bacteriuria (ASB). Moreover, we will investigate whether these combined bacterial etiologies create a synergistic risk of preterm birth (PTB). In Aim 1, we will evaluate the effect of urogenital Group B Streptococcus (GBS) and bacterial vaginosis (BV) status on susceptibility to ASB and UTI in pregnancy. In Aim 2, we will interrogate the role of ASB recurrence in the persistent risk of PTB following acute bacteriuria, and in Aim 3, we will investigate polymicrobial synergy as a risk factor in bacteriuria-associated PTB. The completion of this study should inform new strategies to prevent urologic conditions and their complications in pregnancy. Project 3: We will investigate the hypothesis that sex- and age-specific differences in innate and adaptive responses to E. coli UTI exist and impact risk for recurrence. We will analyze serum and urine samples from male and female infants at the time of acute UTI and in convalescence, analyzing inflammatory cytokines, immune cell populations, sex hormones, novel biomarkers, and evidence of IBC formation compared to samples from control infants and from adult women (Aims 1 and 2). In Aim 3, we will use a surgical murine UTI model to corroborate host-response and other data obtained from our collected human samples in male and female mice, to test new hypotheses generated from work performed in Project I (e.g., bacterial and host mechanisms), and to study the effects of hormonal perturbation on the establishment of UTI, IBC formation and progression to chronic cystitis, and host immune responses. Admin Core: The objective of the Administrative Core is: (i) to oversee and coordinate interactions among the leaders and staff of the three proposed projects in order to achieve the overall SCOR program goals, (ii) to efficiently and professionally coordinate financial and scientific progress reporting to NIH, and (iii) to facilitate total program review and advice from our advisors.

IC: National Institute of Mental Health
Title: Prepubertal Stress, Windows of Risk, and Sex Bias for Affective Disturbance
PI: C. Neill Epperson
Institution: University of Pennsylvania
Grant No.: 5P50MH099910-03

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 (MOD) 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, MOD 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 premenstrum (premenstrual dysphoric disorder), the postpartum (onset/relapse bipolar disorder, MOD), 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 I & III) and aging (Projects II & III). In addition, mechanistic epigenetic studies will examine sex differences in response to stress during this sensitive window of brain maturation (Project III). 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.