Summaries of Co-Funded Research, FY 2012

NIH Office of Research on Women's Health

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Contents

National Cancer Institute

Title: **Definition of Microenvironment in Breast Cancer**
P.I.: **Mina Jahan Bissell**
Institution: **University of California, Berkeley, Lawrene Berkeley National Laboratory**
Grant No.: **CA064786-17**
Award: **$18,750**

One of the earliest manifestations of malignant progression is loss of tissue organization. This proposal continues to examine the hypothesis that architectural integrity is crucial for maintenance of normal breast function as well as for suppression of neoplasia. We have postulated that elucidation of a "signaling integration plan" that establishes and maintains polarity and structure within the acini and ducts of breast tissue will uncover prognostic and therapeutically-relevant markers of intermediary steps in malignancy. As such, we postulated and provided evidence that myoepithelial cells (MEPs) provide crucial structural and functional cues to luminal epithelial cells (LEPs) partly via production of, and signaling through, laminin-111 (Ln-1). We further postulated, and now provide additional evidence, that in traditional cell culture conditions, purified LEPs almost immediately develop a hybrid LEP/MEP phenotype acquiring aspects of MEP gene expression and in particular developing the tumor suppressor functions normally conferred in vivo by MEPs and an ability to make acini, which normally requires the presence of MEPs. Consequently, in order to make relevant models for the study of human LEP-MEP interactions we must identify the conditions that instruct these cell types to retain their original functions. Accordingly, we have developed new and versatile microenvironmental arrays (MEArrays) to probe how MEPs and LEPs become, and remain, determined. We now propose to expand our findings in 3 specific aims. We will specifically: 1- identify pathways that allow retention of MEP- and LEP- specific functions in culture using designer MEArrays and designer media. We then could probe the importance of desmosomal proteins and other regulatory molecules in addition to Ln-1 produced by MEPs, in how MEPs and LEPs interact to retain polarity, architecture and function. 2- complete the identification of Ln-1 signaling cascade components for mammary specific functions using inhibitory peptides, blocking antibodies, mutant cells and shRNA ablation in high throughput assays using Cellomics and other devices and designer 3D microenvironments. 3- identify and characterize central players and connections in the 'signaling integration plan' for structural integrity of acini using bioinformatics analysis of gene expression arrays, genome-wide methylation profiles and other changes in chromatin structure, identification of miRNAs affecting cellular architecture, and by positioning the new genes we identified using a unique 3D screen, on our integration map. Collectively these experiments address the importance of MEP/LEP interactions in maintenance of polar acinar structures in breast tissue, and could also provide a proof of principle for other tissues. Since loss of appropriate balance and/or integration of these signals leads to malignancy, our results will both advance

fundamental knowledge and yield novel markers for early diagnosis and therapeutic strategies to limit and/or reverse breast tumor progression.

Title: **P3K, Retroviral Oncogene, and Homolog of PI 3-Kinase**
P.I.: **Peter K. Vogt**
Institution: **Scripps Research Institute**
Grant No.: **CA078230-14**
Award: **$18,750**

The goal of this project is to achieve a molecular understanding of the oncogenicity of phosphatidylinositol 3-kinase (PI3K). The proposed work will use two basic approaches: (1) a genetic analysis of the oncogenic functions of p110¿, the catalytic subunit of PI3K, and (2) genome-wide interrogations for novel regulators and targets of PI3K. The genetic analysis will concentrate on the interactions between p110¿ and Ras as well as p110¿ and p85. These interactions are critical to the oncogenicity of p110¿; they are fundamentally changed in the cancer-specific gain-of-function mutants of p110¿. The p110¿ protein carrying cancer-specific mutations in the helical domain (E542K, E545K) has requirements for p85- and Ras-binding that are opposite to those of the kinase domain mutant (H1047R). The helical domain mutants depend on Ras-binding but are largely independent of p85-binding. The kinase domain mutant does not require Ras but needs p85 to be active. We plan to analyze mutants of p85 and of Ras in which specific functions are disabled for their ability to activate wild-type and mutant p110¿. This genetic analysis will advance our understanding of the molecular mechanisms by which cancer-specific mutations in p110¿ induce a gain-of-function and make the protein oncogenic. The genome-wide interrogations for regulators and targets will take advantage of two new technologies. (1) A screen of expression libraries in the yeast Saccharomyces cerevisiae. This is a lethality screen based on the fact that expression of PI3K is toxic to Saccharomyces cerevisiae. The observed growth defect can be rescued by the expression of negative regulators of PI3K. Using this screen, we have identified several novel suppressors of PI3K. We will characterize these regulators and define the signaling chains that connect them to PI3K. (2) The second technology is a kinome screen that uses the two universally conserved lysines in ATP pockets of kinases to tag ATP-binding proteins by covalent linkage to biotin. We have used this method to reveal PI3K-induced changes in the kinome and, during initial studies, have identified three growth-regulatory kinases that are differentially expressed in PI3K-transformed cells. The roles of these and additional PI3K targets identified by the kinome screen will be analyzed and determined.

Title: **Molecular Mechanisms of BRCA1-Dependent DNA Damage Response and Tumorigenesis**
P.I.: **Xiaochun Yu**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **CA132755-05S1**
Award: **$18,750**

BRCA1 is a nuclear polypeptide to suppress familial breast and ovarian cancers. Accumulated evidence suggests that BRCA1 participates in DNA damage response. However, the molecular mechanisms by which BRCA1 participates in DNA damage response remain elusive. Recently, we have identified two new BRCA1 partners, RAP80 and CCDC98. Both RAP80 and CCDC98 associate with BRCA1 BRCT domain and participate in DNA damage response. Functionally, RAP80 and CCDC98 facilitate BRCA1's translocation to DNA damage sites. To search for the signals that recruit this BRCA1 complex to the DNA damage lesions, we have found that BRCA1-associated protein RAP80 recognizes ubiquitinated histone H2A and H2B. And both histone H2A and H2B are further ubiquitinated following DNA damage. In addition, we have identified two biallelic missense mutations and one truncation mutation of RAP80 gene in breast and ovarian cancer cells, suggesting that RAP80 could be another breast and ovarian tumors suppressor in BRCA1-dependent pathway. Thus, we hypothesize that recognition of ubiquitinated histone by RAP80 is the molecular basis that loads BRCA1 to DNA damage sites, which regulates proper DNA damage response, protects genomic integrity and prevents breast and ovarian tumor development. We propose following experiments to examine our hypothesis. Aim1: To examine the molecular mechanism by which RAP80 and CCDC98 target BRCA1 to DNA damage lesions. Aim2: To examine the functional defects of RAP80 mutations in BRCA1-dependent DNA damage response. Aim3: To examine the role of RAP80 in tumor prevention. In summary, studies outlined here will not only reveal the molecular mechanism by which BRCA1 participates in DNA damage response, but also identify the functional partners of BRCA1 in tumor suppression.

Title: **Low-Dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction**
P.I.: **Melanie R. Palomares**
Institution: **Beckman Research Institute of City of Hope**
Grant No.: **CA140245-03**
Award: **$18,750**

Low-dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction Mantle radiation has been a cornerstone of HL treatment; however, female survivors of HL treated with mantle irradiation before age 30 have a 20- to 55-fold increased risk of developing breast cancer (BC)—a risk that is comparable to that of BRCA mutation carrierrs. Surgical prophylaxis is very effective in reducing the risk of BC, but such invasive strategies are not suitable for all women. Pharmacologic interventions exist, but only tamoxifen is approved for use in young women who have not yet reached menopause. Standard-dose tamoxifen (20 mg daily) is associated with undesirable side effects, but recent studies have laid convincing groundwork that tamoxifen at lower doses may be similarly efficacious in reducing BC risk with fewer side effects. We hypothesize that tamoxifen administered at a lower dose (5 mg daily) would be both an efficacious and safe non-surgical risk reduction intervention for female adult survivors of HL diagnosed during childhood or as a young adult. Thus, using a Phase IIb randomized, double-blind, placebo-controlled trial of low-dose tamoxifen (5

mg daily) in long-term female HL survivors treated with chest radiation, we aim to 1) Determine the impact of a two-year course of low-dose tamoxifen on well-established surrogate biomarkers of chemopreventive efficacy; 2) Establish the safety and tolerability of low-dose tamoxifen in this population; and, as an exploratory aim, 3) Examine the modifying effect of several well-defined demographic and clinical characteristics associated with radiation-related BC risk on the risk:benefit ratio from this intervention. Eligible subjects who provide informed consent will be randomized to 5 mg per day of tamoxifen versus placebo for two years. Outcomes will include several surrogate biomarkers of efficacy, including mammographic breast density (MBD, primary endpoint), breast cytomorphologic and proliferation measures, and insulin growth factors. Subjects will be carefully followed for safety and tolerability using patient-reported outcomes as well as lipid profiles, clotting factors, and markers of bone turnover as objective endpoints. Risk modifiers that will be examined include age, menopausal status, prior hormone use, body mass index, personal history of benign breast disease, and family history of cancer, as well as chest radiation dose, age at exposure, and latency from chest radiation. A sample size of 127 per arm will be able to detect a 20% reduction in MBD with low-dose tamoxifen relative to placebo with 80% power. We have identified over 900 potentially eligible subjects within our consortium of five institutions that have well-developed infrastructure to follow childhood cancer survivors long-term, thus demonstrating that we will have a sufficiently sized pool to draw the eligible patient population from and complete the study. At completion of this study, we hope to identify a well-tolerated risk reduction option for HL survivors that are at high risk for developing BC. Low-dose Tamoxifen in Hodgkin Lymphoma Survivors for Breast Cancer Risk Reduction Public Health Relevance: Survival from Hodgkin lymphoma (HL) is excellent, but chest radiotherapy (RT) has been a cornerstone of treatment, and women with HL exposed to chest RT when they are young have a 20- to 55-fold increased risk of developing breast cancer (BC). Tamoxifen reduces the risk of BC by 50%, but at the cost of some undesirable side effects, while more recent studies suggest that lower dose tamoxifen may be similarly efficacious in reducing BC risk with fewer side effects. We believe that tamoxifen administered at 5 mg daily would be an ideal non-surgical risk reduction intervention for female HL survivors exposed to chest RT at high risk for BC; therefore, we plan to test this hypothesis in a Phase IIb clinical trial.

Title: **PET-MRI for Assessing Treatment Response in Breast Cancer Clinical Trials**
P.I.: **Thomas E. Yankeelov**
Institution: **Vanderbilt University Medical Center**
Grant No.: **CA142565-03S1**
Award: **$18,750**

We propose to develop integrated high field (3T) magnetic resonance imaging (MRI) and positron emission tomography (PET) methods for assessing the effects of molecularly targeted anti-angiogenesis and cytoxic treatments in breast cancer clinical trials. Our goal is to provide the breast cancer community with practical data acquisition and analysis protocols that facilitate the translation of advanced imaging technologies into patient

management and clinical trials. Dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted MRI (DW-MRI) can report on vascular status, tissue volume fractions, and cellularity, while fluorodeoxythymidine PET (FLT-PET) can report on cell proliferation. We propose to combine these MRI and PET data to provide anatomical, physiological, and molecular assessments of the response of breast tumors to novel anti-angiogenic and cytoxic treatments in clinical trials. To accomplish these goals we will pursue the following specific aims: 1. We will develop high field breast MRI protocols that measure tissue cellularity and vascularity. We will then develop methods for the rigorous registration of these MRI measures with quantitative PET characterization of cell proliferation. We will develop the algorithms and software architecture necessary for synthesizing the imaging data with (traditional) clinical data to assisting in clinical decision making. 2. In an ongoing Phase II study we will employ DCE-MRI, DW-MRI, and FLT-PET to assess the degree of tumor response after one and two cycles of Carboplatin and nab-Paclitaxel with or without Vorinostat in HER2-negative primary operable breast cancer. 3. In our planned Phase II study we will employ DCE-MRI, DW-MRI, and FLT-PET to assess the degree of tumor response after one and two cycles of neoadjuvant cisplatin, paclitaxel and the TOI inhibitor everolimus in patients with triple negative breast tumors. As the anti-cancer agents employed in these clinical trials are implicated in apoptosis and/or inhibition of cellular proliferation and/or inhibition of angiogenesis, we hypothesize that changes in metrics of cellular proliferation and vascularity, when merged with traditional clinical biomarkers, will provide significantly more accurate predictions on patient response than traditional methods of tumor response including RECIST. RELEVANCE: We propose to develop integrated magnetic resonance imaging (MRI) and positron emission tomography (PET) methods for assessing the effects of molecularly targeted treatments in breast cancer clinical trials. We hypothesize that the synthesis of imaging metrics reporting on vascularity, cellularity, and cell proliferation will provide predictive measurements of tumor response to treatment in appropriately selected clinical trials. Our goal is to provide the breast cancer community with practical data acquisition and analysis protocols that facilitate the translation of advanced imaging technologies into patient management and clinical trials.

Title: **Understanding and Preventing Breast Cancer Disparties in Latinas**
P.I.: **Beti Thompson**
Institution: **Fred Hutchinson Cancer Research Center**
Grant No.: **CA148143-03**
Award: **$18,750**

Breast cancer is the most common cancer among Hispanic women in the United States (US). The incidence of breast cancer among Hispanics (83.5 per 100,000) is lower than that among non-Hispanic Whites (147.3 per 100,000); however, as Hispanic women adopt the practices of mainstream US culture, their risk for breast cancer increases. Further, Hispanic women are at increased risk for breast cancers with poor prognosis. The overarching theme of this PSO application is to understand and prevent pre-cursors of breast cancer and to reduce breast cancer morbidity and mortality among Latinas. This

will be done at multiple levels and will engage researchers across several disciplines. Projects have been carefully designed to contribute understanding to and preventing breast cancer in Latinas. It is the lonq-term goal of this PSO application to understand the antecedents of breast cancer in the Latina population, to understand the types of breast cancer found in the Latina population, and develop and implement a comprehensive program of screening to increase the opportunities for early breast cancer detection among Latinas. Our short-term obiectives are to: 1. Increase breast cancer screening among age-eligible Latinas; 2. Understand the processes by which ancestry, BMI, inflammation, and breast cancer are related in Latinas 3. To understand aspects of the etiology of poor prognosis breast cancers by identifying risk factors related to triple negative (TN) and HER-2-overexpressing (H2E) tumors, which are more commonly found in Latinas compared to non-Hispanic whites 4. To understand the role of ancestry in breast cancer antecedents and incidence among Latinas. 5. To explore expression of genes involved in tumor-related pathways signaling. This application is committed to a comprehensive multi-level approach to reducing health disparities. Its projects range from the biologic and genetic to the social context within which people live. Through its four projects and cores, the proposed Center will cover a myriad of aspects of breast cancer, from biological processes and genetic pathways to individual determinants and social determinants of breast cancer.

Title: **Assisted Reproductive Technology and Risk of Childhood Cancer**
P.I.: **Barbara Joan Luke**
Institution: **Michigan State University**
Grant No.: **CA151973-02**
Award: **$18,750**

Use of assisted reproductive technology (ART) has risen steadily in the United States during the past two decades due to several reasons, including childbearing at older maternal ages and increasing insurance coverage. Studies have reported significantly higher risks of adverse perinatal outcomes in assisted—versus spontaneous—conception pregnancies, including an excess of prematurity, low birthweight, and birth defects. ART and/or infertility may influence the incidence of other conditions with prenatal origins, such as childhood cancer. In addition, the prevalence of imprinting disorders such as Beckwith-Wiedemann and Angelman syndromes is elevated among children conceived by ART; some of these disorders, in turn, drastically raise the risk of several embryonal cancers that occur in early childhood. Several cohort, case-control, and case-series studies of assisted reproduction and childhood cancer have reported null results, although all were limited by small sample size and could not differentiate specific cancer types. One study that focused specifically on hepatoblastoma found that use of infertility treatment or assisted reproduction was associated with a nine-fold increased risk of disease. Using the resources of the Society for Assisted Reproductive Technology (SART) and the birth and cancer registries in 20 States and New York City, we propose to conduct the largest study to date of ART and childhood cancer risk. SART maintains an ongoing national database of programs that provide ART services in the United States as mandated by the federal Fertility Success Rate and Certification Act of 1992 [PL 102-493]. As of 2006,

the latest year of data available, this included comprehensive data (including identifiers sufficient for linkage) on 138,198 ART cycles from 483 clinics resulting in 41,343 pregnancies and 54,656 infants for a single year. We propose to link the data from the SART database from 2004-2013 to the birth and cancer registries of 20 states and New York City, including the five states with the highest numbers of ART births (California, New York, Illinois, New Jersey, and Massachusetts), to create a cohort of approximately 30 million children, including over 467,000 conceived by ART to evaluate the association between assisted reproduction and the risk for childhood cancer. The specific aim of this study is to compare the incidence of childhood cancer in children with assisted conception to that in the general population.

Title: **Feasibility of Community-Based Tampon Self-Sampling To Prevent Cervical Cancer**
P.I.: **Elizabeth H. Fontham**
Institution: **Louisiana State University Health Sciences Center New Orleans**
Grant No.: **CA157263-01A1**
Award: **$200,000**

Medically underserved women are generally at higher risk for many health problems including cervical cancer. Solutions can often be found by utilizing resources within the community. An academic-community partnership has been formed to develop a novel approach to screening for cervical cancer. High risk types of human papillomavirus (HPV), 16, 18 and others, are etiologically linked to cervical cancer. HPV can be detected from samples obtained from self-swabbing of the vagina, urine testing, or insertion of tampons. These methods could be performed in the community or at home by women, which is useful for the group of women not visiting the gynecologist to receive recommended testing. This study will compare the effectiveness of home-based self sampling screening for cervical cancer with conventional Pap testing in a community-based setting. Given the ease of home use, it is hypothesized that home-based tampon testing for HPV DNA will be equal or superior to the annual Pap testing. For such home sampling to be effective, it must be: (1) used at least as much as current referral rates to the gynecologist; (2) acceptable to the woman as a means to prevent cervical cancer; (3) able to be performed at home; and (4) able to identify those women at risk for developing cervical cancer. The specific aims of this project are to: compare compliance with a home-sampling tampon HPV test to compliance with clinic Pap testing; assess a high risk population's acceptance of home use of a tampon for HPV testing in general and compared to traditional clinically administered Pap testing; assess a high risk population's ability to correctly follow instructions for home tampon sampling for HPV testing; and assess the accuracy of the home administered tampon HPV results. In order to achieve these aims, a group of women will be asked to administer the tampon sampling at home and return via mail. Another group will have conventional Pap testing for comparison. Surveys of satisfaction will also be conducted.

Title: **Roles of EGFR and miR-143/miR-145 in Western Diet-Promoted Colonic Tumorigenesis**
P.I.: **Bruce Marc Bissonnette**
Institution: **University of Chicago**
Grant No.: **CA164124-01A1**
Award: **$150,000**

While Western diets are implicated in increased colon cancer risk, molecular underpinnings of these dietary effects remain largely unknown. The azoxymethane (AOM) and Apc+/min mouse models mimic many features of human colon cancer, including tumor promotion by Western diet. We showed that Western diet up-regulated ligands for epidermal growth factor receptors (EGFR). Furthermore, EGFR was required for tumor promotion. Several EGFR ligands are released from membrane-bound pro-ligands by the lipid-raft-associated metalloproteinase ADAM17. Our recent studies indicate that ADAM17 is down-regulated by microRNA-145 (miR-145), whereas K-ras, an EGFR effector is suppressed by miR-143. These co-transcribed miRNAs are down-regulated in human colon cancer. We recently showed that EGFR signals downregulate miR-143 and miR-145 in AOM and Apc+/min tumors. Furthermore, these miRNA reductions are necessary for EGFR mitogenic effects. Based on our data we hypothesize that ADAM17 up-regulation and miR-143 and miR-145 down-regulation play essential roles in Western diet-induced tumor promotion. We propose several aims to address this hypothesis: Aim 1: Elucidate the requirement for ADAM17 in diet-promoted colonic tumorigenesis. We hypothesize that ADAM17 inhibition or deletion will suppress diet-related tumor promotion. We will use 1a) the AOM model in conditional ADAM17-deleted mice; 1b) the Apc+/min model with a novel ADAM17 pharmacological inhibitor INCB3619 to dissect the role of ADAM17 in diet-promoted tumorigenesis; 1c) in vitro studies of lipid rafts to dissect fatty acid effects on ADAM17 in colon cancer cells. Aim 2: To determine contributions of miR-143 and miR-145 in diet-promoted colonic tumorigenesis. We hypothesize that loss of these miRNAs is necessary for diet-induced tumor promotion. We will employ Apc+/min mouse interbred with 2a) transgenic mice expressing villin-promoter regulated pre-miR-143 and pre-miR-145; or with 2b) miR-143 null mice or with 2c) miR-145 null mice to uncover the role of these miRNAs in diet-promoted tumorigenesis. In aim 2d), we will examine other miRNAs implicated in ADAM17 regulation and/or diet-related tumorigenesis, including miR-1, -31, -148, and -152. Aim 3: Determine the regulation of miR-143 and miR-145 by Western diet and tumorigenesis. We hypothesize that Western diet and malignant transformation suppress transcription, while neoplastic transformation also deranges processing. We will 3a) assess effects of ADAM17, diet and neoplastic stage on pri-, pre- and mature levels of miR-143, -145 in in vivo models; 3b) dissect EGFR and fatty acid effects on miR-143/-145 promoter activity using mutant deletions to identify cis regulatory elements; 3c) Determine proteins differentially co-associating with biotinylated miR-143 or miR-145 in murine processing-competent YAMC and processing-incompetent CT26 colon cancer cells to discover deregulated processing factors. Our proposal will clarify the role of ADAM17 and test a novel hypothesis that EGFR and these miRNAs form a self-amplifying loop that drives diet-promoted tumorigenesis.

Title: **Feasibility of Virtual Agent Cervical Cancer Education for Hispanic Farmworkers**
P.I.: **Kristen Jennifer Wells**
Institution: **University of South Florida**
Grant No.: **CA167418-01A1**
Award: **$100,000**

Latinas experience higher cervical cancer (CC) incidence and mortality when compared to the general population in the United States. Many Latinas lack access to health care and experience literacy, communication, and knowledge barriers that prevent them from obtaining CC screening. Patient navigator (PN) and other similar interventions have been implemented to increase CC screening rates; however, few have focused directly on the needs of Latinas. Interactive technological interventions, like embodied conversational agents (ECA), are currently used in other populations, settings, and for other health topics, but no known initiative has used culturally and literacy appropriate technology to deliver Spanish-language CC education as part of a PN intervention. This study aims to create and conduct a preliminary evaluation of a Spanish-language Virtual Patient Educator (VPE) multimedia application to augment a PN intervention for increasing CC screening rates among Latinas in a rural agricultural community. Using the Social Cognitive Theory, the proposed project will be conducted in 2 phases. In Phase 1, the research team will engage community members to develop a low literacy Spanish-language interactive multimedia application consisting of an ECA. Using theoretical principles and drawing from our formative research, the project team will design the VPE through systematic and technical processes. Ongoing feedback (usability testing) from members of the intended audience will be carried out to ensure that patients (users) can perform intended system tasks efficiently, effectively, and satisfactoril. Once usability testing is complete, a series of learner verification interviews will be conducted t assess initial suitability of the VPE. Since the VPE will be the first known Spanish-language ECA used to augment a PN intervention, it is important to see whether patients accept the VPE and whether it is feasible to conduct a study of patient navigation augmented by the VPE. In Phase 2, a preliminary evaluation of 2 methods of patient navigation delivery (with and without VPE) will be conducted with 60 participants who are not up to date with recommended CC screening according to American College of Gynecologists and Obstetricians' guidelines. Cluster randomization will be used to randomize patients to 1 of 2 PN intervention conditions: (1) PN; or (2) PN plus VPE (PN+VPE) using date of clinic as unit of randomization. The preliminary evaluation will examine the feasibility of recruitment, randomization, data collection, and acceptability of VPE application. Exploratory data will also be collected regarding the potential impact of PN+VPE on behavioral capacity and self-efficacy for obtaining CC screening, Pap test adherence, and satisfaction with care. The proposed project will advance our research towards the development of interactive technology interventions to disseminate health education to disparate populations.

Title: **International Pooling Project of Mammographic Density**

P.I.: **Valerie McCormack**
Institution: **International Agency for Research on Cancer**
Grant No.: **CA167771-01**
Award: **$49,267**

Women with a high percentage of fibroglandular tissue in their breast, as opposed to fatty tissue, have an increased breast cancer risk (up to 5-fold higher) in the subsequent 10 or more years. This attribute, known as mammographic density (MD), varies between women and can change within the same woman over time. Having both genetic and environmental determinants, between-country differences in MD may account for the over 6-fold international variations in breast cancer incidence rates. Only one study has investigated this to date, i.e. a US/Hawaii/Japanese comparison (Maskarinec et al. 2007). We aim to initiate a more widespread International Pooling Project of Mammographic Density to: (i) pool and obtain standardised comparable data on MD from countries spanning the breast cancer incidence range; (ii) describe international variations in overall and age-specific MD distributions and assess whether they are explained by individual-level risk factors for MD; (iii) quantify the extent to which international variations in MD correlated with corresponding breast cancer incidence rates and Pike's proposed model of breast tissue ageing; (iv) assess a range of MD metrics (absolute/relative/age-specific/cumulative); (v) continue and expand this pooled resource into the future. The International Pooling Project of Mammographic Density would be the first such initiative for MD, which could later be expanded to include new methods of MD measurement, imaging modalities and a broader range of determinants. Being led by the International Agency for Research on Cancer, we emphasize an international perspective for this marker, especially urgent as breast cancer is now the most common cancer in women in almost every country worldwide. If MD does underpin international variations in breast cancer incidence, the monitoring of MD-distributions would become an important early indicator of changes in breast cancer risk.

Title: **Using Technology To Promote Activity in Women at Elevated Breast Cancer Risk**
P.I.: **Lisa Anne Cadmusbertram**
Institution: **University of California at San Diego**
Grant No.: **CA168450-01**
Award: **$67,371**

Obesity (i.e., excess energy intake and inadequate physical inactivity) is associated with increased risk of breast cancer among postmenopausal women. Effective and practical intervention strategies are needed to address the high prevalence of excess weight and sedentary lifestyle in middle-aged and older US women. Although web-based interventions to promote a healthy lifestyle are common, no studies have tested the use of web-integrated physical activity meters for promoting behavior change in this population. By leveraging innovative technology-based approaches, researchers and physicians may be able to replace intensive physical activity interventions with low-cost alternatives. OBJECTIVE: To test the feasibility of using a web-based self-monitoring technology

(the FitBit) to promote physical activity among women at elevated risk for breast cancer (i.e., overweight/obese, inactive postmenopausal women). SPECIFIC AIMS: This pilot study proposes to use a 16-week randomized controlled trial of a novel intervention (FitBit activity monitor + training) vs. a pedometer to address the following aims: Primary aim: To investigate the effect of the FitBit-based intervention vs. provision of a pedometer on objective measures of physical activity and sedentary behavior. Secondary aim: To examine the acceptability and usage patterns of the device and website. METHODS: Fifty participants will be randomly assigned to receive (a) a FitBit monitor and training on use of the website or (b) a pedometer. The FitBit is a tiny physical activity tracking device that pairs with a website, wirelessly uploading activity data to provide the user with an easy-to-understand visualization of her daily activity patterns. Goal-setting features are used alongside simple graphs and charts to enhance self-monitoring of energy balance. Participants will be given a physical activity goal, trained in the use of the self-monitoring website, and asked to wear the FitBit clipped to their clothing every day for 16 weeks. The primary outcome will be change in MET-hours/day of physical activity, as measured by the ActiGraph GT3X accelerometer prior to randomization and at 16 weeks. Although this is a pilot study, we will have 80% power to observe an effect size of 0.7 at a significance level of $p<0.10$. Questionnaires will be used to measure intervention acceptability and direct data downloads will provide an objective assessment of usage patterns. CANCER RELEVANCE: Promotion of weight management and physical activity is an important aspect of breast cancer prevention because excess adiposity is associated with increased risk of post-menopausal breast cancer. As intervention research evolves, technology offers the potential for cancer prevention researchers to move away from costly traditional interventions toward easily disseminated interventions that can continue after the study has ended.

Title: **HPV Vaccine Development and Evaluation**
P.I.: **Allan Hildesheim**
Institution: **NCI Intramural Division of Cancer Epidemiology and Genetics Research Project**
Grant No.: **N261200100007**
Award: **$400,000**

ORWH has collaborated with the NCI on the development and evaluation of the prophylactic virus-like particle (VLP) human papillomavirus (HPV) vaccine that was discovered by investigators at the NCI. In the late 1990s, ORWH supported efforts to conduct animal studies and an early phase I human trial in the United States that were critical to demonstrating the potential for this vaccine. Subsequently, ORWH supported the multiyear, community-based randomized, phase III trial of the HPV vaccine conducted by NCI in Costa Rica. This is the only publically funded trial of an HPV vaccine. Results from the study in Costa Rica, which is ongoing, have shown that 1) the vaccine is highly effective at preventing new infections with HPV types 16 or 18, 2) the vaccine confers partial protection against HPV types phylogenetically related to HPV 16 or 18, 3) the vaccine does not help treat existing infections, 4) fewer than 3 doses of the vaccine protects as well as the full 3-dose series for at least 4 years, 5) levels of

antibodies achieved long-term following two doses (0 and 6 months) of the HPV vaccine are high and only slightly lower than those observed after three doses of the vaccine, likely explaining why fewer than three doses provided a high degree of protection , 6) the vaccine protects against HPV infection at the anus, 7) the vaccine protects against HPV infection in the oral cavity, 8) vaccine impact declines with increasing age at vaccination, 9) vaccination induces cross-neutralizing potential in sera of vaccinated individuals, and 10) modest levels of antibodies generated by natural HPV infection provide partial protection against re-infection. Efforts in Costa Rica are ongoing and completion of 10 years of follow-up of trial participants is expected within the next 4-5 years so that long-term effects of the vaccine (efficacy, safety and immunogenicity) can be fully evaluated. During the FY11-FY12 period, ORWH support enabled expansion of the work in Costa Rica to include 1) an assessment of vaccine efficacy at sites other than the cervix (anus and oral cavity) and 2) investigation of the immunological mechanisms/parameters that might explain why this vaccine is effective even when fewer than the recommended three doses are administered and against HPV types not included in the vaccine formulation.

Title: **Research and Studies on the Effects of Inflammation in Gall Bladder Cancer**
P.I.: **Ann Hsing and Jill Koshiol**
Institution: **NCI Intramural Research Project**
Grant No.: **N26100003**
Award: **$200,000**

Gallbladder cancer is one of the few non-gynecological tumors known to occur with higher frequency in women than in men. The highest rates of this cancer (particularly in women) are observed in Chile. Investigators in the Infections and Immuno-epidemiology Branch (IIB) are evaluating the feasibility of conducting a case-control study of gallbladder cancer in Chile to better understand the causes of this disease. As currently envisioned, the initial pilot effort will define whether such a study would be successful at identifying and enrolling cancer cases, controls with gallstones (an important precursor for this cancer) and controls form the general population. We are working with well established investigators in the region with a proven track record of conducting epidemiological investigations to maximize the likelihood of success. A case-control study of gallbladder cancer in Chile would permit us to elucidate the role of obesity (and metabolic syndrome more generally), diet, infections, immunological responses, and genetic susceptibility factors in the etiology of this tumor. This study could have important public health implications, since cholecystectomies are currently being recommended for women for the prophylaxis of gallbladder cancer in this high risk area. A better understanding of the causes of this disease could lead to the development of better and less aggressive preventative measures against this disease.

Title: **California Health Interview Survey**
P.I.: **David Grant**
Institution: **University of California, Los Angeles**

Grant No.: **N261200544000C**
Award: **$200,000**

California Health Interview Survey (The California Health Interview Survey (CHIS) is the largest and most comprehensive state health survey in the U.S. It provides valid local and state estimates for California. Conducted by telephone in English, Spanish, Chinese, Korean and Vietnamese, CHIS interviews a representative sample of over 40,000 adults in California households. Since its inception in 2001, NCI has supported cancer control items on CHIS, and ORWH provided funding for FY12. CHIS data are publicly released. CHIS data are widely accessible to policy makers, stakeholders and researchers via the AskCHIS calculator, public use data, and micro-data files (http://www.chis.ucla.edu/).

Title: **National Longitudinal Mortality Study**
P.I.: **Paul Sorley (NHLBI)**
Institution: **NHLBI, NIA, NCI, and Centers for Disease Control and Prevention/National Center for Health Statistics, in collaboration with the U.S. Census Bureau**
Grant No.: **0081-1998-005**
Award: **$200,000**

The National Longitudinal Mortality Study (NLMS) database is a population-based resource for studies of relationships between lifestyle factors, socioeconomic status (SES) and mortality. Advantages of the NLMS database compared to other large prospective studies include annual enrollment of nationally representative household samples with self-reported socioeconomic status. The study is designed to yield a sample reflecting the national population with respect to race, ethnicity and SES with precise estimates through weighting to adjust for under-sampling. ORWH contributed FY 2012 funding to update NLMS matches to the National Death Index through 2010. The updated match is an opportunity to advance understanding of factors affecting women's health and mortality experience in the United States. The NLMS Steering Committee includes representatives of three NIH Institutes: the National Heart Lung and Blood Institute, National Institute on Aging, and National Cancer Institute and CDC's National Center for Health Statistics and the Census Bureau. The Steering Committee facilitates research proposals from intramural and extramural investigators. More than 130 collaborators have used the dataset to publish over 70 journal articles in JAMA, British Medical Journal, Lancet, American Journal of Epidemiology, Archives of Internal Medicine, Cancer, Stroke, and the American Journal of Public Health. Articles have also been published in Demography, Ethnicity and Disease, Gender Medicine, Journal of Aging and Health, Journal of Health and Social Behavior, Journal of Rural Health, Psychological Medicine, and Social Science and Medicine.

Title: **DCEG/EBP Intramural—Follow-up of DES Cohorts**
P.I.: **Jessica Mills**
Institution: **Boston University**

Grant No.: 261201000128C*3
Award: $18,750

Since 1992, DCEG and other NCI investigators, along with collaborators from five field study centers, have been actively following diethylstilbestrol (DES) exposed and unexposed mothers, daughters and sons, and granddaughters for adverse health effects resulting from this exposure. As DES-exposed offspring are currently reaching the age when cancer rates begin to rise, it is important to continue to monitor long-term risk of cancer and other adverse health outcomes in this unique population. The study also provides a model for assessing a number of hypotheses that address concerns about prenatal hormonal influences on disease risk, both an intriguing area of science and an increasingly controversial environmental issue that affects a substantial proportion of the population.

To date the study has identified excess female breast cancer after age 40 that shows a dose-response effect, as well as increased risk for high-grade lesions of the cervix and vagina. Concern over other hormone-related cancers remains; though to date analyses have been limited due to small numbers of cases. In the sons, investigators observed an excess risk for urogenital anomalies and infertility, and a likely excess of testicular cancer. To examine the effects in the third generation (the daughters of the prenatally exposed daughters), investigators assembled a small cohort in 2000. Given their average age, there have been few relevant disease outcomes. However, investigators noted an elevated risk for infertility—though not statistically significant, this outcome was also seen in DES-daughters. In addition, there were three cases of ovarian cancer in the granddaughters, even though substantially less than one had been expected. While both of these observations remain difficult to interpret, they have added some urgency to expand the cohort and continue to follow-up.

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Title: **Pharmacotheraphy Evaluation Tools for Improving Breast Cancer Outcomes in Rural Appalachia**
P.I.: **Rajesh Balkrishnan**
Institution: **University of Michigan at Ann Arbor**
Grant No.: **CA168479-01**
Award: **$200,000**

Access to effective breast cancer care is a critical factor in Appalachia contributing to health disparities among this population. Poor adherence to adjuvant cancer treatment has been reported to increase risk of death and associated with increased medical costs in breast cancer. Patient medication use behaviors are critical to the cancer heath disparities in Appalachia, and research on essential medication use and quality in rural areas is scant. Data suggests that designing an effective intervention targeting determinants of access to cancer care in Appalachia will provide patients an opportunity to receive appropriate medical treatment to alleviate disparity in cancer morbidity and mortality. The major impact of this study will be the production of a concrete intervention design aimed at reducing cancer health disparities in Appalachia by targeting modifiable contributors such as accessibility of medical care, quality and quantity of pharmacological treatment delivery, and adherence behaviors and their determinants. The purpose of this application includes an innovative approach to model accessibility to cancer care resource influences guiding appropriate treatment delivery and medication use behaviors (persistence and adherence to prescribed treatment), and how such factors impact cancer survival. Our central hypothesis is that patients who are able to access adequate medical care are more likely to receive standard treatments and persistently follow recommendations which lead to better therapeutic outcomes (such as survival). The strategies proposed will address the following specific aims: 1) Assess the complexity of the relationship between access to cancer care resources and patient prescribed guideline appropriate for adjuvant cancer treatments, 2) Delineate the manner in which specific social, system-specific, and individual determinants of access to cancer care affect patient medication use behaviors of persistence and adherence, and 3) Model cancer survival as a function of patient and system specific dimensions of access to cancer care, prescribing guideline appropriate adjuvant treatment and medication use behaviors. This study will use a unique NCI-funded linked dataset of 7,566 patients with breast cancer assembled from cancer registries, Medicare and Medicaid Services (CMS) Medicare claims data, US Social Security Administration's Death Master File (DMF), American Medical Association (AMA) Master file for information on physician and practitioners, American Hospital Dictionary (AHD) for healthcare facility characteristics. We hypothesize that there are modifiable individual and health-system related factors that impact the patient's receipt

of optimal pharmacological treatment. The rationale for the proposed study is that, once medication access and utilization factors to which disparity in cancer survival can be attributed, are identified and accurately modeled, effective interventions targeting influential factors for breast cancer survival can be developed and tested in the same population and adapted to other populations burdened with similar inequalities, resulting in reducing health disparity in Appalachia and other regions.

Title: **Bedside to Bench—Molecular Epidemiology of Postpartum Involution of the Breast: Demonstration of Tools for Understanding Influences of Pregnancy on Breast Cancer Risk**
P.I.: **Mark Sherman**
Institution: **City of Hope**
Award: **$90,000**

Experimental and observational data implicate postpartum breast remodeling in the pathogenesis of early onset aggressive breast cancers (reviewed, J Mammary Gland Biol Neopl June 2009), a disease that disproportionately affects African Americans. Recent studies of animal models suggest that an inflammatory wound response related to remodeling promotes progression of in-situ to invasive cancer, and that this effect can be blocked by anti-inflammatory drugs (Nat Med 2011). In addition, our collaborator, Dr. Kathleen Arcaro, has developed immunomagnetic methods to isolate epithelial cells shed in milk and assess DNA methylation of tumor suppressor genes involved in breast cancer. Using this technique, she has preliminarily demonstrated detection of pregnancy associated breast cancers (AACR 2011).

This proposal would refine tools for studying women through the early postpartum period to understand the effects of pregnancy and lactation on the breast. These tools will include novel methods of sampling breast epithelial cells shed in milk and MRI imaging. We will preliminarily explore hypotheses related to specific candidate mechanisms and biomarkers that have been implicated in postpartum re-modeling or may predict breast cancer risk by comparing data from lower risk uniparous women, defined as younger or White, as compared to higher risk women, defined as older or African American. Bench aims will include: improved milk collection, fractionation and optimization of milk assays, including DNA methylation analysis and measurement of hormonal and inflammatory markers. Bedside aims include: collection of milk at two time points to assess molecular markers for comparison over time within subjects, and between subjects, stratified by race and age, and to assess a subset of the same subjects during this period by MRI at the NIH Clinical Center.

To pursue our aims, we will leverage a unique collaboration between CCR, extramural collaborators and NCI/DCEG investigators with broad interests in breast biology and cancer. The proposed collaboration will include: 1) Jane Balkam, R.N., Ph.D., an expert lactation consultant with the NIH Work Life program; 2) David Bluemke, M.D., Ph.D., Chief of Radiology at NIH who will develop MRI studies; 3) Kathleen Arcaro, Ph.D., a laboratory scientist at the University of Massachusetts who has developed methods to

isolate epithelial cells from milk for analysis of DNA methylation in tumor suppressor genes and will work with Dr. Sherman to optimize fractionation and assays and 5) DCEG investigators with interests in breast cancer epidemiology, including early life events, genetics, breast density, hormones and molecular pathology. Dr. Hewitt will work with Dr. Sherman to prepare cells for pathologic analysis, Dr. Faupel-Badger will evaluate hormone assay data, Dr. Gierach will interpret MRI data and provide epidemiological expertise and Dr. Meeker will perform telomere assays. Dr. Sherman will serve as PI and will lead the project, as well as providing expertise related to breast biology, pathology and molecular epidemiology. Dr. Arcaro, as extramural PI, will provide unique expertise on milk processing and performing DNA methylation assays on cells shed in milk.

National Eye Institute

Title: **Surveillance and Treatment of Community Newcomers and Travelers for Trachoma Control**
P.I.: **Sheila K. West**
Institution: **Johns Hopkins University**
Grant No.: **EY022584-01S1**
Award: **$40,000**

Infection with C. trachomatis has decreased substantially in trachoma endemic areas following repeated annual mass drug administration with azithromycin, although not as rapidly as anticipated. We propose to conduct a clinical trial to determine the added benefit for communities, which are now at low levels of infection, of a program to identify and treat new families who came after mass treatment, and travelers who return to the community, as they could be the source of re-emergent infection. The proportion of communities who are able to stop mass treatment will be compared in the group of communities randomized to mass treatment plus the newcomer treatment program compared to the communities randomized to mass treatment alone.

Title: **Broad Spectrum Molecular Therapy for Blinding Retina Disorders**
P.I.: **Jean Bennett**
Institution: **University of Pennsylvania**
Grant No.: **EY023177-02**
Award: **$150,000**

This proposal evaluates the translational potential of optogenetic therapy, an approach whereby visual function is achieved through the use of a molecular prosthesis that transmits its signals to downstream visual circuits. Studies in vitro and in vivo in animal models by our collaborators (and others) have demonstrated that light-activated chloride pumps or channels can be introduced into specific retinal cell types in diseased or atrophic retinas. There, these molecular prostheses can permit visual responses where before, there were none. The present program aims to address the knowledge gaps and

technical limitations relevant to development of optogenetic therapy in two different paradigms: 1) Physiologically optimized forms of Halorhodopsin (NpHR) will be used to activate function of failing cone photoreceptors after the rod photoreceptors have degenerated; 2) Optimized Channelrhodopsins (ChRd) will be used to confer light responsiveness to second order retinal neurons in degenerated retinas. We will design and develop the appropriate vectors, delivery strategies and outcome measures for each paradigm, will carry out the prerequisite preclinical safety and efficacy studies, and will bring one of the studies (NpHR) to clinical trial. In the process, novel strategies of altering the transduction characteristics of adeno-associated virus (AAV) will be developed, new surgical approaches which could be applied to human eyes will be devised, and sensitive, noninvasive, clinically relevant outcome measures will be defined. Simultaneous with development of the technology, we will evaluate the bioethics of gene therapy-mediated delivery of molecular prostheses in humans. This comprehensive program benefits greatly from the wisdom and experience of many talented collaborators and advisors and takes advantage of the infrastructure that the PI has already developed for ocular gene therapy translational research.

National Heart, Lung, and Blood Institute

Title: **Endogenous Cardiac Repair in Humans**
P.I.: **Kenneth Ber Margulies**
Institution: **University of Pennsylvania**
Grant No.: **HL089847-04S1**
Award: **$72,000**

Until recently, the heart has been viewed as a terminally differentiated organ with no capacity for new cardiac myocyte (CM) formation. This view appears to be incorrect, in that we and others have been able to isolate cardiac-derived progenitor cells (CDPCs) from human myocardium. Extending these results, our recent studies indicate that cells expressing the stem cell surface marker c-kit can be isolated from human hearts immediately after explantation and subsequently induced to differentiate into CM via short-term co-culture with neonatal rat ventricular myocytes (RVMs). Though we typically find more c-kit+ cells usually in failing vs. nonfailing hearts, the need to replace these failing hearts via transplantation highlights the inadequacy of native cardiac repair mechanisms. Based on these findings, our broad working hypothesis is that increased c-kit+ CDPCs in failing human hearts include both lineage-negative c-kit+ and c-kit+/CD45(dim-moderate) cells that are each capable of new myocyte formation in vitro. In this context, the objective of this proposal is to quantify and characterize these distinct subpopulations of stem/progenitor cells within human hearts with an emphasis on elucidating their functional capacity for replication and CM differentiation. Our first aim is to identify what types of stem/progenitor cells are present in normal and failing human hearts. We will define distinct stem/progenitor subpopulations based on immunotyping of disaggregated myocardial cells with fluorescence microscopy and flow cytometry and perform complementary studies in tissue sections from the same hearts to define their distribution. Our second aim is to characterize replicative capacity of the selected CDPC

subpopulations based on a combination of static assays (telomere length, telomerase activity and and p16INK4a expression) and functional assessment of proliferation rates. Our third aim is to characterize the cardiac myogenic potential of selected CDPC subpopulations derived from human hearts. These studies will define the rates and frequency of CM differentiation for sorted subpopulations under stardardized co-culture conditions, define whether cell contact is required for induction of CM differentiation by neonatal rat myocytes and identify secreted factors (chemokines or growth factors) that promote or augment rates of in vitro CM diffentiation in selected CDPC subpopulations. The clinical/therapeutic significance of this proposal is based on the premise that insights into the proliferative and cardiomyogenic potential of endogenous cardiac stem/progenitor cell subpopulations will promote progress towards therapeutic cardiac regeneration with or without cell therapy per se.

Title: **Avoiding Toxicity Associated with MTP Ablation**
P.I.: **M. Mahmood Hussain**
Institution: **SUNY Downstate Medical Center**
Grant No.: **HL095924-03S1**
Award: **$20,000**

High plasma lipids and lipoproteins are risk factors for various cardiovascular and metabolic disorders. An approach to lower plasma lipids is to inhibit apoB-lipoprotein biosynthesis, a process critically dependent on an endoplasmic reticulum (ER) resident chaperone, microsomal triglyceride transfer protein (MTP). MTP inhibitors decrease apoB-lipoprotein secretion and lower plasma cholesterol. However, they increase plasma aminotransferases, such as ALT and AST, indicating liver injury. We hypothesize that increases in plasma hepatic enzymes associated with MTP inhibition are due to increases in microsomal free cholesterol, induction of ER stress and cell death. We further hypothesize that reducing cellular free cholesterol along with MTP inhibition might reduce hyperlipidemias and avoiding toxicities associated with MTP antagonists. In the first aim, Alb-Cre-MTPfl/fl or MTPfl/fl mice will be fed T-0901317, a LXR agonist to induce free cholesterol efflux; lovastatin, a HMG Co-A reductase antagonist to inhibit cellular cholesterol biosynthesis; or WY14643, a PPAR945; agonist to enhance 946;-oxidation of fatty acids, for 3 or 24 weeks. In another group, 937;-3 fatty acids, PPAR945;/948; agonists, will be injected intraperitoneally to reduce hepatic triglyceride and free cholesterol. In addition, Alb-Cre-MTPfl/fl mice will be fed a western diet and then treated with T-0901317, lovastatin, WY14643, or &-3 fatty acids. Experiments will then be performed in C57Bl/6J mice fed a western diet and fed daily with MTP inhibitors. Additionally, they will be fed olive oil alone or with other compounds described above to determine if toxicities associated with MTP inhibitors can be avoided by these treatments. Outcome measurements will involve changes in apoB-lipoproteins and hepatic enzymes in the plasma; hepatic triglycerides, esterified cholesterol, and free cholesterol; quantification of candidate mRNAs and proteins involved in cholesterol and triglyceride biosynthesis, ER stress, as well as AST/ALT isoforms. These studies will show that toxicities associated with MTP inhibition can be avoided by reducing hepatic free cholesterol. The second aim is to test the hypothesis that release of hepatic enzymes

in the plasma is due to the induction of the ER stress and apoptosis. We will first demonstrate that MTP inhibition increases microsomal free cholesterol. Second, we will identify the ER stress pathways activated by MTP ablation/inhibition. Third, we will establish that MTP inhibition induces apoptosis. Fourth, a link between the ER stress and induction of apoptosis will be established. Fifth, importance of the ER stress pathways will be substantiated using ATF6-/-, CHOP-/- and Alb-Cre-Ire11fl/fl mice fed MTP inhibitors. Sixth, we will determine if induction of ER stress by tunicamycin increases plasma AST/ALT levels. At the completion of these studies, we will find out molecular mechanisms responsible for unwanted side effects associated with MTP therapy and suggest solutions to avoid these toxicities. These studies may lead to new therapeutic modalities for the treatment of various hyperlipidemias and have immediate potential for translational use.

Title: **Saturated Fat and Protein Effects on Atherogenic Dyslipidemia**
P.I.: **Ronald M. Krauss**
Institution: **Children's Hospital & Research Center Oakland**
Grant No.: **HL106003-02S1**
Award: **$200,000**

The overall objective of this project is to test the hypothesis that the effects of saturated fat (SF) on lipoprotein markers of cardiovascular disease (CVD) risk are influenced by food sources of dietary protein. There is growing epidemiological evidence that consumption of red meat is associated with greater incidence of CVD than either white meat or non-meat foods. Pathophysiological support for the validity of this association is provided by preliminary evidence from our group that a high beef diet has a more deleterious effect on lipoprotein measures of CVD risk than we have observed for mixed protein diets. Specifically, we have found that a high protein, high SF diet with a moderate red meat content selectively induces increases in intermediate density lipoproteins (IDL) and larger LDL particles that have been found to be much more weakly associated with CVD risk than smaller LDL. In contrast, a more recent study from our group has found that, with a similar intake of SF, high beef consumption results in a preferential increase in levels of small and medium sized LDL particles, both of which are strongly related to incident CVD. To date however, no studies have directly compared the lipoprotein effects of red meats with other food sources of protein in the context of both high and low saturated fat intake. We specifically hypothesize that increases in plasma levels of LDL cholesterol (C), and apolipoprotein (apo) B, induced by SF are greater when the major food source of protein is red meat rather than either white meat (poultry) or non-meat foods, and that this is due to increased levels of small and medium sized LDL particles. We therefore propose a clinical trial in which 180 healthy men and women will be randomized to high SF (15%) or low SF (7%) diet groups, and within each group, consume diets with equivalent amounts of protein derived from red meat, white meat, and non-meat sources for 4 wk each in random order. Our Specific Aims will test whether: (1) with high SF, the red meat diet, compared to the other food sources of protein, will result in higher levels of LDL-C, apoB, small and medium sized LDL particles, and total/HDL-C; (2) with low SF, dietary protein source

will not be related to any of these measurements; (3) with both the white meat and non-meat diets, increased LDL-C with high vs. low SF will be due primarily to increases in IDL and/or large LDL, whereas with red meat the additional increase in small and medium LDL will result in greater increases in apoB. In addition to these aims we will test for possible metabolic determinants of dietary effects on apoB-containing lipoprotein subclasses, including post-heparin plasma hepatic lipase activity, which is critical for production of smaller LDL, and LDL receptor activity as assessed in peripheral blood mononuclear cells, a system demonstrated to reflect physiologically relevant LDL receptor regulation. Finally, we will examine potential dietary influences on other metabolic biomarkers of CVD risk, including HDL subclasses and apoproteins, insulin sensitivity as assessed by HOMA-IR, measures of inflammation including CRP and multiple cytokines, and endothelial function using a non-invasive fingertip method.

Title: **Molecular Mechanism of Platelet Dense Granule Biogenesis**
P.I.: **Santiago Mauro Di Pietro**
Institution: **Colorado State University**
Grant No.: **HL106186-01A1S1**
Award: **$20,000**

Platelets play pivotal roles in both hemostasis and thrombosis. Platelet activation triggers secretion and the release of content from dense granules, a-granules, and lysosomes that in turn leads to the recruitment and aggregation of additional platelets and white cells. While impaired platelet function has been associated with disorders that manifest with moderate to severe mucocutaneous bleeding, excessive platelet aggregation is a major cause of morbidity and mortality due to its effect in myocardial infarction and stroke. In spite of the relevance of platelet dense granules for human health, little is known about their biogenesis. Therefore, our goal is to understand the molecular mechanism responsible for the biogenesis of platelet dense granules. Dense granules belong to a group of lysosome-related organelles (LROs). Formation of LROs involves two parallel protein transport pathways defined by Adaptor Protein-3 (AP-3) and Biogenesis of Lysosome-related Organelles Complex-2 (BLOC-2). AP-3 is an adaptor that selects proteins with specific targeting signals in early endosomes and packages them into vesicles for transport to LROs. BLOC-2 also localizes to early endosomes but its function is unknown. We have recently obtained preliminary evidence suggesting that BLOC-2 has adaptor-like properties but with the ability to bind new targeting signals in dense granule proteins, different from the signals recognized by AP-3. Moreover, we obtained substantial preliminary results indicating that five proteins are fundamental components and new players in the pathways to dense granules: two “molecular switches”, two novel proteins containing vesicle scission domains, and a molecular motor. These findings have opened new avenues to study the biogenesis of platelet dense granules. We propose to: (1) establish new in vitro and in vivo systems to study the biology of dense granules, (2) test the hypothesis that new dense granule targeting signals exist in dense granule proteins and that BLOC-2 is an adaptor that recognizes these signals and packages the corresponding proteins into vesicles destined for dense granules; (3) test the hypothesis that tissue specific “molecular switch” proteins recruit AP-3, BLOC-2, and other

ubiquitous components to endosomal membranes to specifically direct transport to dense granules; (4) test the hypothesis that new vesicle scission and molecular motor proteins mediate the formation and transport of vesicles loaded with dense granule membrane proteins to dense granules; and (5) test the possibility that numerous patients that present in the clinic with platelet type bleeding disease of unknown etiology may have deficiencies in these new molecular switches, scission, and molecular motor proteins involved in dense granule biogenesis.

Title: **Uterine-Specific Genetic Modification and Lymphangioleiomyomatosis**
P.I.: **Jose M. Teixeira**
Institution: **Massachusetts General Hospital**
Grant No.: **HL109935-02**
Award: **$50,000**

Lymphangioleiomyomatosis (LAM) is a rare disease primarily found in females and is characterized by a diffuse interstitial infiltrate of atypical smooth muscle cell lesions in the lung parenchyma resulting in airway restriction. The etiology of the disease is unknown but is thought to involve hormonal regulation because it usually presents between menarche and menopause. Additionally, LAM is often found in patients with mutations in tuberous sclerosis complex (TSC), suggesting that inactivation of TSC can contribute to its development. We are studying uterine development and associated pathologies by conditionally deleting and/or activating candidate genes in pathways critical for normal differentiation and function. We have created mice with uterine-specific leiomyomas (fibroids) by either constitutively activating ¿-catenin or by expressing a truncated allele of adenomatous polyposis coli (APC) and we have shown preliminary evidence that the leiomyomas develop as a result of vascular hemorrhaging and subsequent hypertrophic scarring. The Mullerian duct-derived internal female reproductive tract organs (uterus, oviduct, cervix, and cranial portion of the vagina) are the only structures from the bipotential mammalian embryo not found in males, suggesting that the hormonally responsive mesenchymal stromal cells of the uterus might be the source of the cells for pulmonary fibrosis and account for the female-specificity of LAM. We hypothesized that pulmonary LAM might be caused by uterine vascular pathologies that allow intravasation of uterine stromal cells that can subsequently lodge and proliferate in the lungs. Histological analysis of the lungs from our mouse models with uterine hemorrhaging and leiomyomas showed fibrotic lung plaques similar to that observed in human LAM that were also HMB45-, aSMA- and desmin-positive, markers for human LAM. We propose to investigate this hypothesis further with the following Specific Aims: (1) confirm that cells in the lung lesions are derived from the uterus, (2) determine whether uterine mesenchymal cells can be detected in peripheral blood, (3) test the hormone responsiveness of the smooth muscle cells in the lung lesions, and (4) assess the marker profile of lung lesions for comparison with human LAM. The results from these studies will lay the foundation for continued investigation of the triggers and signaling pathways involved in the development of the LAM lesions as well as provide an in vivo model system for preclinical studies of therapeutics targeting those pathways.

Title: **Premenstrual Syndrome and Risk of Subsequent Hypertension**
P.I.: **Elizabeth R. Bertone-Johnson**
Institution: **University of Massachusetts Amherst**
Grant No.: **HL115357-01**
Award: **$195,117**

Hypertension is one of the strongest predictors of cardiovascular disease (CVD) in women. Despite extensive knowledge of the etiology of hypertension and the availability of effective treatments, prevalence remains high. There is a substantial need for novel strategies to identify premenopausal women at high risk for hypertension who would benefit from early intervention to reduce their long term risk of CVD. Up to 20% of premenopausal women meet clinical criteria for premenstrual syndrome (PMS), a disorder characterized by moderate to severe luteal phase symptoms that substantially interfere with normal life activities and interpersonal relationships. The pathophysiology of PMS is complex, and factors including dysfunction of the renin-angiotensin-aldosterone system and vitamin D insufficiency likely contribute. Importantly, these factors have also been implicated in the etiology of hypertension. Thus, moderate to severe PMS may be predictive of increased risk of hypertension later in life, and may serve as an early sentinel of CVD risk. The proposed project will extend work completed during the Principal Investigator's current career development award (K01MH07624) to explore the relation of PMS with hypertension and blood pressure in two populations of women. First, we will determine prospectively if PMS occurring in the middle reproductive years is associated with subsequent risk of hypertension and changes in blood pressure over time. We have developed a prospective study of PMS nested within the Nurses' Health Study II (NHS2) cohort; to our knowledge, this is the only prospective epidemiologic study of women with PMS in existence. The NHS2 PMS Sub-Study includes 1257 women meeting established criteria for moderate to severe PMS and a comparison group of 2463 women without PMS. As of 2013, participants will have been followed for 24 years for incident hypertension and changes in blood pressure, and women with PMS will have been observed for up to 20 years following their PMS diagnosis. Second, we will determine if common PMS treatments and dietary and behavioral factors modify the association of PMS and blood pressure, and thus may provide opportunities for women experiencing PMS to reduce their risk of hypertension and CVD. Finally, using data from a second study of young adult women (n=375), we will determine if differences in blood pressure are already evident in women experiencing PMS in their late teens and early 20's. Data from both studies have already been collected, thus providing a cost-effective way to address these novel and important questions. IMPACT: This life course study will be the first to evaluate whether moderate to severe PMS may serve as an early sentinel of long-term health outcomes. It may help identify a population of women at high risk for hypertension who would benefit from increased screening and early intervention. Furthermore, it may lead to clinical trials of novels strategies for treating PMS, no only to reduce morbidity and improve quality of life in women with the disorder, but also to reduce their long-term risk of cardiovascular disease.

Title: **A Formative Examination of the Health and Safety of Female Firefighters**
P.I.: **Sara Anne Jahnke**
Institution: **National Development and Research Institutes, Inc.**
Grant No.: **HL119024-01A1**
Award: **$199,800**

Firefighters/EMS personnel are vital for public health safety, representing over two million individuals nationally. Because firefighters are required to respond to almost every domestic emergency, there is wide agreement that their health and readiness is of particular importance. Furthermore, a broad range of occupational exposures exist that negatively impact the health of firefighters. While the field of firefighter health has enjoyed growth over the past decade, the health of female firefighters remains largely unexamined. Similar occupational groups, such as the military, have developed focused programs to understand the unique work-related challenges to women's health; however, research in the fire service has remained relatively silent on the topic. This dearth of informatio likely contributes to the remarkably low rates of females recruited and retained by the fire service. While challenges such as harassment in the workplace have been identified as concerns for female firefighters, health concerns beyond emotional stress have received limited attention. Anecdotal evidence suggests that issues such as reproductive health, ill-fitting gear, and on-the-job injuries attributable to standard operating procedures and guidelines that do not accommodate differences in female characteristics are barriers to women serving as firefighters. The military, a similar population with regard to work task, environment, and a tradition of being primarily male, has been successful in making female health a priority through the development of a focused program of gender specific research. Despite significant cultural barriers, the armed forces have been successful in recruitment and retention of female personnel at a rate that far exceeds the US fire service. In this proposed project, we will use a multi-methods research design to examine health and safety issues among female firefighters. In addition, this study will identify factors which serve as barriers to recruitment and retention of women in the fire service. Unique strengths of this R21 developmental application include strong support from the largest national fire service organization focusing on women and an investigative team with a documented history of successful research on the health of firefighters. Research for this formative research will be conducted in three phases including: 1) focus groups with a national sample of female firefighters, and key informant interviews with male and female fire service opinion leaders; 2) key informant interviews with female firefighters who have chosen early retirement to determine barriers to retention among this population and 3) an epidemiological survey of a sample of female firefighters to determine current health status and health concerns across a number of domains. This innovative study is a critical step in addressing gender inequity of the US Fire Service and identifying areas of intervention and prevention for this understudied occupational group.

National Institute on Aging

Title: **SWAN: Study of Women's Health Across the Nation**
P.I.: **Joel S. Finkelstein**
Institution: **Massachusetts General Hospital**
Grant No.: **AG012531-19**
Award: **$75,000**

The Study of Women's Health Across the Nation (SWAN) is a multi-center, multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. The goals of the original RFA were to answer the following questions: How do hormones change with the menopausal transition? What factors affect the timing of the transition? What are the symptoms that accompany menopause and who is at risk? How do cardiovascular risk factors change with the transition and is there ethnic variation? What are the rates of bone loss with the transition? When does bone loss begin and what are the risk factors? What are the health consequences of menopause and who is at risk? SWAN is compiling the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based samples. SWAN is now poised to study the effects of these menopause-related changes on subsequent healthy aging and on age-related diseases in the post-reproductive period. SWAN I was first funded in September 1994 by the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the Office of Research on Women's Health (ORWH) in response to RFA AG-94-002, Menopause and Health in Aging Women. The first competing continuation of SWAN (SWAN II) was funded in 1999 and the second (SWAN III) in 2004. SWAN I, II and III have been supported by a cooperative agreement mechanism, with 9 funded components: 7 clinical centers, a central reproductive hormone laboratory (CLASS), and a coordinating center. A second central laboratory (MRL) was originally funded as a subcontract to the Coordinating Center (CC). In addition, a Core Repository of serum, plasma, and urine specimens and a DNA Repository were established in June 2000 under separate funding (U01 AG 17719, PI: Dr. MaryFran Sowers). For non-study-related reasons, site operations at New Jersey Medical School stopped in April 2004. The basis of this action was allegations made by two study employees who resigned abruptly. The SWAN PI and study coordinator were subsequently exonerated from these allegations. Please see Appendix 12 for a more complete report. The grant was transferred to the Albert Einstein College of Medicine in 2005. Since that time, the New Jersey PI and project director have worked tirelessly to overcome the obstacles to re-implement the study. As of June 1, 2008, a total of 155 women have successfully completed their clinic visit and five more visits are scheduled. We project that by the end of SWAN III, data will be available for 250 women. This has been very encouraging and thus Nanette Santoro, PI of the New Jersey SWAN site has been approved by the NIA to prepare a U01 application to cover further contacts for the Hispanic women. Please note that the SWAN IV project applications pertain to the remaining six sites only. Information relative to the New Jersey site is covered in the separate application submitted by Dr. Nanette Santoro. From over 16,000 women aged

40-55 years who were screened during 1995-1997, 3302 women aged 42-52 years were enrolled in SWAN's longitudinal cohort (approximately 450 at each of 7 clinical centers). They completed their baseline clinic visit during 1996-1997. Of the 3302 women enrolled, 1550 were Caucasian, 935 African American, 286 Hispanic, 250 Chinese, and 281 Japanese. A subset of 880 menstruating women was enrolled in the Daily Hormone Study (DHS) started in 1997, which is designed to examine cyclical daily hormone and symptom patterns during the menopausal transition.

Title: **Study of Women's Health Across the Nation—Coordinating Center**
P.I.: **Kim Sutton Tyrrell**
Institution: **University of Pittsburgh at Pittsburgh**
Grant No.: **AG012553-18**
Award: **$125,000**

The Study of Women's Health Across the Nation (SWAN) is a 7-center multi-ethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition. SWAN has amassed ten years of data about endocrinology of the transition and other factors relevant to midlife health and aging. As SWAN requests its fourth competing renewal, the study itself proposes to transition from a study of the menopause to a study of aging in women. The average age of participants at the beginning of the SWAN IV project will be 59 years (54 to 65) and SWAN IV will follow these women through the age range of 59 to 70. SWAN has the unprecedented capability to link the expansive biological, medical, social, behavioral, and demographic data it has collected during mid-life and the menopausal transition to the development of both positive and adverse health states in early oldage. The primary objectives of SWAN IV are to: 1) Characterize the endocrinology and symptomotology of the post-menopause (2 to 12 years after final menses); 2) Ascertain additional health outcomes (such as measured physical performance) that are relevant to the early old age range and that may be affected by the factors that we have studied in mid-life and 3) Understand the relations between the mid-life and menopausal transition experience of women and subsequent positive and negative health outcomes. To accomplish this, the investigators propose annual phone contact to closely track menopausal status, menopausal symptoms and selected health events. In addition, two in-person clinic visits are proposed to accomplish detailed physical measures of early disease. The major thematic areas of SWAN IV include 1) Physical Functioning; 2) Bone/Osteoporosis; 3) Cognitive Function/ Symptoms/ Mental Health and 4) Cardiovascular. New areas for SWAN include physical performance and osteoarthritis, history of major depression, and carotid wall thickness. SWAN will continue to monitor symptoms, cognition, cardiovascular risk factors, endocrinology, bone density and fractures. SWAN IV will advance our understanding of how modifiable risk factors related to the menopause transition are linked to sub-clinical disease measures and hard outcomes. This may lead to improved strategies for the primary prevention of disease in women. RELEVANCE: SWAN has compiled the most comprehensive characterization to date of the health and the physiologic and psychosocial changes of women from pre- to postmenopause in community based

samples. Of particular public health importance is that the continuation of SWAN will permit the study to increase understanding of the effects of these menopause-related changes on subsequent health and risk factors for age-related diseases.

Title: **Effects of Aging on Visual Memory: Neuroimaging Studies**
P.I.: **Roberto Cabeza**
Institution: **Duke University**
Grant No.: **AG019731-10**
Award: **$200,000**

Aging is associated with substantial deterioration of the visual system and associated sensory-perceptual processes. This decline in visual processing is a strong predictor of cognitive decline in healthy aging and of Alzheimer's disease. Yet, the effects of aging on visual processing and cognitive functions, such as memory, have typically been investigated independently of each other. Filling this void, the proposed neuroimaging studies focus on the interactions between age effects on visual and memory processes, and the brain regions mediating these processes. This significant goal is combined with an innovative multi-measure methodological approach which assesses age effects (1) on visual and memory performance using behavioral tests; (2) on brain activity in occipito-temporal, medial temporal, prefrontal regions using functional MRI (fMRI); (3) on the interactions among these regions using functional connectivity (fCON); and (4) on the integrity of the white-matter fiber tracts connecting these regions using diffusion tensor imaging (DTI). Most importantly, these different measures are directly linked to each other. The multi-measure approach is applied to three specific aims. Specific Aim 1 is to investigate the role of peripheral and top-down modulation deficits in visual memory impairments in older adults. Older adults show reduced activity and selectivity (dedifferentiation) in occipito-temporal cortex, which may reflect peripheral or top-down modulation deficits. Study 1 compares the effects of divided attention, which interferes with top-down modulation, and stimulus degradation, which mimics age-related peripheral visual deficits. Study 2 employs overlapping face-house stimuli to examine selective attention deficits. Specific Aim 2 is to investigate the role of perceptual and conceptual processing deficits in visual memory impairments in older adults. Conceptual processing enhances memory for meaningful visual stimuli such as objects but, when combined with perceptual processing deficits, can lead to false memories. Study 3 investigates age effects on conceptual vs. perceptual processing during the encoding of meaningful objects. Study 4 examines age effects on encoding leading to true vs. false memory for objects. Specific Aim 3 is to investigate the role of retrieval reactivation deficits in visual memory impairments in older adults. Visual memory depends not only on visual cortex activations during learning but also on visual cortex reactivations when visual events are remembered. Study 5 investigates age effects on the reactivation of memories for familiar faces and objects. Linking with Specific Aim 2, Study 6 investigates the reactivation of perceptual and conceptual representations. The proposed studies will be the first to systematically investigate the neural mechanisms of age-related visual memory decline. Their results will have direct implications for the development of treatments for memory decline in healthy aging. Moreover, given that visual memory

decline predicts Alzheimer's disease a decade before diagnosis, the results will also have implications for the early detection and treatment of this disease.

Title: **National Social Life, Health, and Aging Project**
P.I.: **Linda J. Waite**
Institution: **National Opinion Research Center**
Grant No.: **AG030481-05**
Award: **$200,000**

The primary objective of the National Social Life, Health and Aging Project (NSHAP) is to establish an innovative, high-quality dataset for use by researchers studying the relationships between social processes and health among older adults. Wave I obtained questionnaire and biomeasure data on a nationally-representative sample of 3,005 community-dwelling adults ages 57-85 in 2005/6. We propose to collect a second wave in NSHAP to obtain data on social networks and social support, marital and cohabitational relationships, attitudes, self-reported health and behavior, and cutting-edge biomeasures of physical function and health. The crucial contribution of Wave II will be in enabling analyses of trajectories; the availability to the community of scholars of such a broad-based, longitudinal data set will permit an examination of the health trajectories of older adults and inform new approaches to reducing morbidity and preventing disability and dysfunction as individuals age. We propose to revisit respondents four years after their initial interview. Using these data, we can describe and model the distribution of changes in health, well-being, social networks, social participation and social context. In each case, we shall examine the distributions both for the entire sample and within subgroups defined by key sociodemographic characteristics such as gender, race/ethnicity, and socioeconomic status. We also propose to augment the sample by interviewing the spouse/cohabitating romantic partner. These data will allow us to characterize the impact of marital and romantic relationships on health by examining the effects of one person's characteristics and behaviors on the health of the other. We will also analyze the partnerships themselves, and assess the relationship between characteristics of the partnership, such as support, closeness and mistreatment, and the health of each of the partners. In sum, we will explore our overarching hypothesis that older adults with strong functioning intimate relationships will show more positive (or less negative) health trajectories that those who have weaker relationships or lack such relationships altogether.

Title: **Menopausal Symptoms Initiative-Finding Lasting Answers for Sweats and Hot Flashes**
P.I.: **Andrea Z. LaCroix**
Institution: **Fred Hutchinson Cancer Research Center**
Grant No.: **AG032699-05**
Award: **$200,000**

The long-term objective of NIA's RFA-AG-08-004 entitled, New Interventions for Menopausal Symptoms (U01) is to accelerate progress in identifying effective remedies for vasomotor symptoms (VMS) in women going through the menopausal transition. We have created a network of scientists who are highly knowledgeable about the menopausal transition and experienced in the conduct of women's health trials to fulfill this mission. This Data Coordinating Center (DCC) application is being submitted in conjunction with the network entitled, The Menopausal Symptoms Initiative-Finding Lasting Answers to Sweats and Hot Flashes (MSI-FLASH). Our DCC will be jointly led by Andrea LaCroix and Garnet Anderson who have served together as Co-Principal Investigators of the Women's Health Initiative Clinical Coordinating Center (Seattle) for more than a decade. The MSI-FLASH network has five clinical sites located in Boston (Lee Cohen and Hadine Joffe, PIs), Indianapolis, IN (Janet Carpenter, PI), Oakland, CA (Barbara Sternfeld and Bette Caan, PIs), Philadelphia (Ellen Freeman, PI) and Seattle (Katherine Newton and Susan Reed, PIs). This multidisciplinary investigator group proposes five randomized controlled trials testing a range of behavioral, mind-body, hormonal and pharmacologic interventions to treat hot flashes. The specific objectives of the DCC are to: 1) Provide and coordinate all necessary leadership activities to facilitate collaboration and productivity among network scientists during all phases in the lifecycle of VMS clinical trials from hypothesis formulation to publication, dissemination, and data sharing; 2) Build upon 15 years of experience and well established human and operational resources to coordinate 5 or more multi-site randomized trials including support of protocol development, recruitment, intervention, data collection and management, and statistical analysis; and 3) Create the infrastructure to involve an expanded network of scientists from the US and worldwide to facilitate the development and use of common methodologies and measurements for VMS trials inside and outside of this trial network so that emerging new treatments for hot flashes can be rapidly identified and rigorously tested for efficacy and safety with comparable results.

Title: **The Role of Vascular Aging in Cognitive and Physical Function**
P.I.: **Lydia Bazzano**
Institution: **Tulane University of Louisiana**
Grant No.: **AG041200-01A1**
Award: **$300,000**

Maintaining optimal health, both physical and cognitive, throughout the aging process is critical to minimizing healthcare costs and morbidity and mortality associated with diseases of aging. The integrity of the vascular system is essential for healthy aging. Aging-related structural and functional disturbances in the macro- or microcirculation contribute the development of cognitive dysfunction and declining physical performance. Early life factors, from birth through childhood and adolescence, may play an important role in successful cognitive and physical aging via the aging of the vascular system. In the proposed study we will examine the role of vascular aging in maintenance of cognitive and physical performance by recruiting 1,257 participants in the Bogalusa Heart Study cohort who participated in cardiovascular risk factors examinations at least twice in childhood and twice again in adulthood. Participants will undergo cognitive

function testing, physical function assessments and vascular risk factor examination with noninvasive studies of vascular structure and function. Birth weight and childhood socioeconomic and risk factor data is available for all individuals. Longitudinal analysis will be used to examine the relationship of early life risk factrs to subclinical vascular disease markers, while linear models will be used to examine the role of vascular risk factors and subclinical markers in maintenance of cognitive and physical function. This study represents a unique opportunity because all vascular disease risk factors have been collected prospectively from early life to middle-age in this bi-racial (black/white), rural community, allowing for exploration of race and gender relationships with cognitive and physical function from mid-life. The proposed research will link vascular risk factors across the life span and subclinical vascular markers in early middle age with cognitive and physical performance in later middle age. In doing so, we will identify risk factors, timing and subpopulations for intervention that could reduce the incidence of cognitive and physical decline in old age and improve the rate of successful aging for persons across the nation.

Title: **Hypertension, Angiotensin Receptor Blockers, and Cognition: Effects and Mechanism**
P.I.: **Ihab M. Hajjar**
Institution: **University of Southern California**
Grant No.: **AG042127-01A1**
Award: **$200,000**

Hypertension is associated with cognitive impairment even in the absence of dementia. These vascular-related mild cognitive impairments are undetected and are commonly characterized by executive dysfunction. To date, no specific treatment is available for executive mild cognitive impairment which is associated with poor outcomes in hypertension. The PI has recently completed, with support from a K23 award, a preparatory pilot study (n=47) to test the feasibility, safety and effect size of candesartan, an angiotensin receptor blocker, compared to hydrochlorothiazide and lisinopril, in individuals with hypertension and mild cognitive impairment characterized by executive dysfunction. Our preliminary analysis which was recently accepted for publication in the Archives of Internal Medicine, suggests that, independent of blood pressure, candesartan is superior to other antihypertensives in preserving executive function. Candesartan was also associated with an increase in cerebral blood flow velocity that only reached significance in those with low flow velocity at baseline (n=23). We hypothesized based on these data to further test the effect of angiotensin receptor blockers on cognitive function by conducting a 1-year double blind randomized active-control trial of candesartan vs. lisinopril in 160 individuals with hypertension and evidence of mild cognitive impairment in the executive domain. The specific aims of this proposal are to investigate the effects of candesartan on executive function decline and on change in cerebral perfusion, cerebrovascular reserve and microvascular brain injury. We also aim at Identifying potential underlying mechanisms related to vascular structure and function by which candesartan may affect the cognitive and cerebrovascular outcomes. Participants will be recruited from the greater Los Angeles Area and evaluated at the

University of Southern California. Cognitive tests that assess executive function and other cognitive domains will be administered at baseline and 12 months after treatment. Neuroimaging which includes perfusion (continuous arterial spin labeling) and micro-structure (diffusion tensor imaging), carotid ultrasound (carotid intima-media thickness), and endothelial and vascular inflammatory markers will be performed at baseline and after 12 months of treatment. This trial will shed more light onto the potential therapeutic effects of angiotensin receptor blockers on executive dysfunction and related vascular brain injury. This project will also improve our understanding of the possible mechanisms of action of this class of antihypertensives.

National Institute on Alcohol Abuse and Alcoholism

Title: **Pharmacokinetics and Pharmacological Effects of Alcohol After Bariatric Surgery**
P.I.: **Marta Yanina Pepino**
Institution: **Washington University**
Grant No.: **AA020018-01A1**
Award: **$258,709**

Today, millions of Americans have had bariatric surgery, and given the magnitude of the obesity epidemic, it is anticipated that this number will continue to rise. Despite the numerous health benefits of these procedures, there is a growing concern with the development of alcohol problems after gastric bypass surgery. We believe that changes in alcohol pharmacokinetics and subjective responses to alcohol that occur as a result of the anatomical and physiological changes caused by upper gastrointestinal tract diversion might be an important mechanism responsible for the association between gastric bypass surgery and postoperative alcohol abuse. The current proposal will be the first study that will investigate the effects of gastric bypass surgery on subjective responses to alcohol and alcohol pharmacokinetic using validated methods and controlling for the important confounding effect of changes in body weight. Patients who will undergo gastric bypass surgery and a group of patients undergoing banding gastric surgery will be evaluated 3 times before and 3 times 9 m after surgery following identical procedures. Unlike after gastric bypass, the anatomy of the intestine/stomach is intact after gastric banding. Thus, gastric banding subjects will allow controlling for changes in alcohol metabolism and mood effects that could be caused by weight loss. Breath and blood samples will be taken before and at various times after a dose of alcohol (0.8 or 1.4 g/l of total body water) or non-alcoholic placebo control are consumed. Blood alcohol concentrations (BAC) will be determined by the gold standard technique of headspace gas chromatography and these concentrations will be compared with the BAC estimated from breath samples. Subjective ratings of alcohol effects will be measured by validated questionnaires extensively used in the field. The results from our study will lay the foundation for understanding the effect of gastric bypass and gastric banding procedures on alcohol kinetics and pharmacodynamics, which can help tailor counseling in patients undergoing these procedures and prevent alcohol misuse after surgery.

Title: **Ethanol-Induced Conditioned Partner Preference in Mice**
P.I.: **Ruth I. Wood**
Institution: **University of Southern California**
Grant No.: **AA020575-01A1**
Award: **$205,000**

Drinking behavior and social context are intimately intertwined, particularly among young adults. Peer relations can promote drinking. At the same time, alcohol consumption promotes social bonding, as in the popular concept of a "drinking buddy". Ultimately, to combat unhealthy patterns of social drinking, it is important to understand how ethanol shapes the neurochemistry of affiliative behavior. We have developed a mouse model of conditioned partner preference, and we have obtained pilot data to demonstrate ethanol (EtOH)-induced social preference in female mice. Conditioned partner preference is similar to conditioned place preference, but it incorporates social aspects of approach, recognition, and affiliation. This has relevance to drinking behavior in humans. In our pilot studies thus far, female mice prefer conspecifics with whom they have previously been intoxicated. There is a further interaction of EtOH and estradiol to promote social preference, since EtOH-induced partner preference is enhanced in estrogen-treated ovariectomized females (OVX+E) vs ovariectomized females without estrogen (OVX). The proposed studies will use C57Bl/6 female mice to extend our initial observations. Aim 1a will determine the range of EtOH doses which facilitate conditioned partner preference in OVX, OVX+E, and OVX+E females with progesterone. Aim 1b will examine sex differences in EtOH-induced conditioned partner preference by testing orchidectomized males with and without testosterone. Aim 2 will expand the conditioned partner preference model to test the effects of other drugs of abuse (amphetamines, morphine) on social bonding. Finally, Aim 3 will begin to explore underlying mechanisms for EtOH-induced conditioned partner preference. In this regard, pair bonding and affiliative behavior are sensitive to vasopressin mediated through the vasopressin V1a receptor. Furthermore, the vasopressin system is sensitive to both EtOH and estradiol. Aim 3 will test the ability of a V1a receptor antagonist to block EtOH-induced conditioned partner preference. Together, these studies represent an essential first-step to understand substance abuse and social bonding in mice.

Title: **Role of MSK1, ERa and Brf1 in Alcohol-Associated Breast Cancer**
P.I.: **Shuping Zhong**
Institution: **University of Southern California**
Grant No.: **AA021114-01A1**
Award: **$205,000**

Alcohol is the dietary factor, which is most consistently associated with breast cancer risk. This association involves the estrogen receptor (ER), which is over-expressed (ER+) in around 80% of breast cancer cases. Alcohol-association is more pronounced in ER(+) breast cancer cases than in ER(-) breast cancer cases, however, the molecular mechanism remains to be determined. Cancer cells have a consistent cytological feature of nucleolar

hypertrophy, where rRNAs are synthesized by RNA polymerases (Pol) I and Pol III. Pathologists have been using enlarged nucleoli as a diagnostic indicator of cell transformation and neoplasia. It indicates that transformation in situ is tightly linked to the deregulation of RNA Pol I and III gene transcription, because the size of the nucleolus reflects the levels of rRNA synthesis. RNA Pol III is responsible for the synthesis of a variety of untranslated RNAs, including 5S rRNAs and tRNAs. Deregulation of RNA Pol III-dependent genes (Pol III genes) would serve to enhance the translational capacity of cells, which is required to promote cell transformation and tumor development. Alcohol-induced deregulation of Pol III genes may be fundamental to the development of breast cancer. Our previous studies demonstrated that MAP kinases modulated Brf1 and TBP expression and Pol III gene transcription and mediated phosphorylation of histone H3 (H3ph). Our recent studies have demonstrated that ethanol activates MAP kinase and induces Pol III gene transcription through enhanced TBP and c-Jun expression by using cell culture and an animal model. Preliminary results have revealed that alcohol induces Pol III gene transcription in both normal breast and breast cancer cell lines. However, the induction in breast cancer cells (5-6 fold) is higher than i normal breast cells (2.5 fold). Further analysis indicates that the induction is ER dependent. The ER ligand, E2 (17b-estradiol) causes an induction (< 2 fold) of these genes, whereas ethanol works with E2 to create an additional increase (12 fold) in Pol III gene transcription, resulting i cell proliferation and transformation. Alcohol activated MSK1 (mitogen- and stress-activated protein kinase 1), a downstream component of MAP kinases, which mediates phosphorylation of histone H3 (H3ph) at serine 10 (H3S10ph) and serine 28 (H3S28ph) and modulates gene expression and cell transformation. Thus, we hypothesize that alcohol activates MSK1, which mediates H3ph. H3ph in turn upregulates Brf1 expression and Pol III gene transcription to enhance the protein synthetic capacity of cells, which can eventually lead to ERa-dependent breast cancer. This implies that the induction by alcohol may be an early event, contributing to the development of ER(+) breast cancer. By using cell culture and animal models, we will determine: 1) if alcohol-activated MSK1 mediates Brf1 expression and Pol III gene transcription, which in turn causes phenotypic changes, and if inhibition of MSK1 by its chemical inhibitor and shRNA or using a MSK KO mouse blocks alcohol-induced cell transformation and Pol III gene transcription; 2) if alcohol-induced H3ph modulates Brf1 and Pol III gene expression and cell transformation; 3) if alteration of ERa and Brf1 expression affects transcription of Pol III genes and if blocking Brf1 expression by its shRNA inhibits tumor formation in nude mouse upon administration of alcohol or alcohol plus E2. These studies are designed to determine the molecular mechanism of alcohol-induced deregulation of Pol III genes in the development of ER+ breast cancer. Investigating the effects of MSK1 and Brf1 shRNAs on tumor formation may provide a new approach to inhibit tumor growth. Our overall objective is to investigate the role of MSK1 and Brf1 in the alcohol-induced response that may be critically important in ER+ breast cancer development.

National Institute of Allergy and Infectious Diseases

Title: **Mechanisms of B Cell Responses in Autoimmune Disease**

P.I.: **Eugene William St. Clair**
Institution: **Duke University**
Grant No.: **AI056363-09**
Award: **$30,000**

This application is a competitive renewal of the Autoimmunity Center of Excellence (ACE) at Duke. Its research focus will continue to be modulation of B cell responses in autoimmune disease. The ACE will be under the leadership of Dr. E. William St. Clair, Professor of Medicine and Immunology. For the past 5 years, Duke has been a productive member of the ACE network, contributing new insights into the developmental pathways of B cells and the mechanisms of B cell directed therapy. The proposed ACE builds on these discoveries and will support 2 new basic science projects, 5 ongoing and 2 new clinical trials, and an Administrative Core, and continue to emphasize a strong and fluid integration between the bench and the bedside. Tedder and colleagues have recently found that a phenotypically unqiue subset of B cells secreting IL-10 (called B10 cells) serve as critical negative regulators during adaptive CD4+ T cells responses, and dramatically suppress Th1 immune responses and autoimmune disease in mice. For Basic Research Project 1, they will examine the hypothesis that antigen-specific regulatory B10 cells modulate autoimmune responses in mice and man and that they can be manipulated for therapeutic gain. A picture is gradually emerging about the precursors of self-reactive B cells in autoimmune disease. Kelsoe and coworkers in Basic Research Project 2 will investigate developmentally regulated expression of activated cytidine deaminase (AID) in human fetal and neonatal pre-, pro, and immature/transitional B cells and its relationship to the generation of self-reactive B cells in human autoimmune disease, potentially eludidating another pathway of B cell self-reactivity outside the confines of normal tolerance mechanisms. We propose two new clinical trials to investigate lymphotoxin-beta receptor fusion protein as a treatment for primary Sjögren's syndrome, and rituximab therapy for bullous pemphigoid. A Pilot Research Project is also proposed to engineer tetramers of self-antigen enabling the identification and characterization of self-reactive B cells, which will have implications for the goals of the clinical and other basic research projects. Overall, the Duke ACE will bridge these basic and clinical studies to advance our understanding of autoimmune disease. The B cell is a type of immune cell essential to autoimmunity. The goal of the proposed Autoimmunity Center of Excellence at Duke is to improve our understanding of the roles played by B cells in human autoimmune disease. The projects are designed to be highly integrative between the bench and the bedside, with collaborations between basic and clinical scientists. These studies may lead to better treatments. CLINICAL COMPONENT: Clinical Component (ST CLAIR, W) CLINICAL COMPONENT DESCRIPTION (provided by applicant): The Clinical Research Component of the Autoimmunity Center of Excellence shares with the Basic Research omponent an overall goal of advancing our understanding about the role of B cells in the pathogenesis of autoimmune diseases. This component will be directed by Dr. E. William St. Clair. During the past 5 years, the Duke ACE has brought 3 new clinical trial concepts to the ACE Steering Committee, resulting in 1 completed trial, 1 ongoing trial, and 1 protocol in development. We are also participating in 3 other ongoing ACE-sponsored clinical trials. Therefore, substantial clinical research activity will carry over to the next funding cycle. Our center is organized to support

clinical trials in rheumatology, dermatology, gastroenterology, hematology, and neurology. We have access to several large patient populations, including patiens with rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome, scleroderma, autoimmune blistering disease, psoriasis, inflammatory bowel disease, autoimmune hepatitis, anti-phospholipid antibody syndrome, and myasthenia gravis. Each of these disease areas has leadership from one or more physician-investigators with significant clinical trial experience, including an example of a productive inter-institutional collaboration. The physician leadership is supported by an ample infrastructure that provides clinical research space, infusion facilities, experienced clinical coordinators, and an Immune Monitoring Component. The Clinical Research Component aligns with the ACE at a thematic level, with substantial collaborations between basic and clinical scientists. To this end, the proposed clinical trial concepts will focus on B cell directed therapy. In one case, we propose to examine the clinical efficacy of lymphtoxin-beta receptor fusion protein in the treatment of primary Sjögren's syndrome, and have already secured commitment from the industry sponsor to provide study drug for this trial. The other application will investigate rituximab as initial therapy for bullous pemphigoid. The mechanistic studies for these proposed trials as well as current trials are highly integrated with the basic research projects. The Clinical Research Component will make a significant contribution to the ACE enterprise during the upcoming funding cycle. The Clinical Research Component will support clinical trials sponsored by the Autoimmunity Centers of Excellence in several disease areas, including rheumatology, dermatology, gastroenterology, hematology, and neurology. It has been productive during the current funding cycle, and has the capability, as shown in this application, to generate new ideas for clinical trials that can be translated into well-designed studies.

Title: **Epithelial Genes in Allergic Inflammation**
P.I.: **Gurjit K. Khurana Hershey**
Institution: **Cincinnati Children's Hospital Medical Center**
Grant No.: **AI070235-07**
Award: **$12,500**

Allergic disorders are a major global health concern affecting 150 million people worldwide. Recently, epithelial cells have emerged as central participants in the pathogenesis of allergic inflammation: (1) they interface with the environment and initiate the response to environmental triggers; (2) the mucosal epithelium in the lung, skin, and gut functions as a physical barrier against pathogens and environmental exposures including allergens; and (3) epithelial cells have been directly implicated in Th2 responses, serving as a critical interface between innate immune responses and Th2 immunity. The overall objective of these studies is to elucidate the mechanisms by which epithelial cells contribute to the pathogenesis of allergic disorders. The overarching hypothesis of this Center proposal is that epithelial cell genes play a central role in the pathogenesis of allergic disorders. This hypothesis will be tested by three integrated projects that use the Center for coordination and synergistic extension of the projects beyond the scopes and capabilities of the individual projects. This Center will provide

important insights into the genes and pathways that may be Important in epithelial driven allergic inflammation and provide a basis for the design of novel therapeutic strategies aimed at the epithelial surface, i.e. lung (asthma), skin (atopic dermatitis), or gut (food allergy or eosinophilic esophagitis). Furthermore, integration of data across projects will provide novel insights into a key question in allergy—What are the mechanisms underlying tissue specific disease manifestations of allergic inflammation? Each project in the Center is focused on distinct epithelial cell genes and their roles in allergic disorders. Project 1 will examine the association of epithelial genes with allergic diseases that target distinct mucosal surfaces. Project 2 will dissect the role of epithelial desmoglein-1 in the pathogenesis of the allergic disorder eosinophilic esophagitis. Project 3 will focus on delineating the mechanisms by which epithelial-derived IL-33 is regulated by trefoil factor 2 (TFF2) during the early innate immune events that initiate allergy and asthma; and better define the role of the TFF2/IL-33 pathway in the pathogenesis of allergic disorders.

Title: **Role of Unique ADP-Ribosylating Vacuolating Mycoplasma Pneumoniae Toxin in Asthma**
P.I.: **Joel Barry Baseman**
Institution: **University of Texas Health Science Center at San Antonio**
Grant No.: **AI070412-07**
Award: **$12,500**

The San Antonio Asthma and Allergic Diseases Cooperative Research Center (SA-AADCRC) represents a tightly focused, integrative and innovative effort to understand the role of Mycoplasma pneumoniae and its unique ADP-ribosylating and vacuolating toxin, designated Community Acquired Respiratory Distress Syndrome ToXin (CARDS TX) as important mediators of acute and chronic airway diseases, including new onset asthma and exacerbations, as well as persistent pulmonary dysfunction in children and adults. The basic science and clinical investigators who comprise the SA-AADCRC team share broad expertise and are highly collaborative. The SA-AADCRC's broad strategy of attack interlinks basic science and clinical research projects and cores. Project 1 uses the murine model and human materials to address fundamental questions on how CARDS TX induces asthma-like disease and exacerbates allergic pulmonary inflammation. Project 2 focuses on identifying CARDS TX ADP-ribosylating airway protein targets, delineating functionally important CARDS TX domains and essential amino acids that mediate CARDS TX binding to human surfactant protein A (SP-A) and airway cells, and generating antibody reagents that block/neutralize CARDS TX. Project 3 applies state-of-the-art biophysical techniques to uncover the structure and action of CARDS TX by using single crystal X-ray diffraction to determine CARDS TX three dimensional structure in the presence and absence of its cofactor NAD; neutralizing monoclonal antibody Fab fragments; and surfactant protein-A (SP-A). Clinical Core will collect human material from subjects with well controlled asthma, poorly controlled asthma and healthy controls and help in evaluation and follow-up of patient-related studies. Diagnostic Core will process clinical and experimental samples for diagnostic analysis by providing highly sensitive and specific diagnostic assays for rapid detection of M.

pneumoniae CARDS TX. Pathology Core will provide necessary biopsy and necropsy procedures, lung pathology interpretation, histochemical and immunocytochemical evaluations, and qualitative and semiquantitative histopathologicai analyses. Administrative Core will oversee all SA-AADCRC-related activities and coordinate interactions and collaborations between projects and cores. Therefore, the SA-AADCRC represents a network of collaborators/colleagues who continuously ask fundamental and translational questions about asthma, airway-related pathologies, immunopathogenesis, and M. pneumoniae/CARDS TX biology and virulence mechanisms.

Title: **Epithelial Barrier Programs in Asthma and Allergic Disease**
P.I.: **Michael J. Holtzman**
Institution: **Washington University**
Grant No.: **AI070489-07**
Award: **$12,500**

The overall goal of this AADCRC proposal is to define the role of the epithelial cell barrier in the pathogenesis of asthma and allergic disease and to use that information to prevent this type of disease. We combine expertise in airway as well as gut and skin epithelial cell biology, and we use cell and mouse models with high fidelity to directly translate our findings to humans. The AADRC therefore consists of three interrelated Projects that ask, first, how airway epithelial cells mediate effective antiviral defense under one condition but asthma under another (Project 1), second, how airway epithelial cells remodel towards an overabundance of mucous cells in post-viral and allergic asthma (Project 2), and third, how epithelial injury in the skin triggers the march from atopic dermatitis to asthma (Project 3). Each project addresses the respective question with a novel but overlapping molecular approach to mechanism and takes advantage of a breakthrough discovery to set a new scientific paradigm for the system under study. Thus, Project 1 unravels a new IFN signaling pathway that offers improved protection against viral infection and post-viral asthma and is specific to the airway epithelial cell barrier; Project 2 dissects a new pathway for autophagy proteins to support proper mucous cell function and prevent mucous cell metaplasia in the airway in a manner reminiscent of the intestinal epithelial barrier; and Project 3 defines a new TSLP production and secretion pathway that drives airway inflammation based on its expression in the skin epithelial barrier. Each Project is constructed so that the first aim will establish a basic pathogenic mechanism using cell and mouse models that are shared among projects and supported by the Cores for tissue and cell processing (Core C) and mouse models (Core D). In turn, each Project will conduct a second aim to validate and translate its findings using samples from children and adults with asthma and/or atopic dermatitis supplied by the Core for human subjects and data analysis (Core B). Sharing samples and overlapping scientific goals among projects create a synergistic program that can be coordinated by a common Administrative Core (Core A). Project and Core interactions are based on the overall principle that each Project begins with molecular hypothesis building in cell and mouse models and translates findings from these models to studies of humans with asthma and/or allergy. In each project, we aim to validate a clinically useful biomarker of the disease process and lay the groundwork for the future

development of biological and/or small molecular weight compounds that might influence the process as a therapeutic strategy.

Title: **Airway Inflammation and Airway Remodeling**
P.I.: **David H. Broide**
Institution: **University of California at San Diego**
Grant No.: **AI070535-07**
Award: **$12,500**

Airway remodeling is the term applied to the structural changes observed in the airway in asthma. Although current NIH guidelines recommend maintaining a goal of normal lung function in asthma, current therapeutic strategies do not specifically target airway remodeling as the cellular and molecular mechanisms that result in remodeling are not well defined and thus therapeutic targets are not well understood. Thus, there is an important need to identify mechanisms by which airway remodeling is mediated so that potential novel therapies could be directed at these pathways. In addition, characterization of these pathways could lead to the development of non-invasive blood or sputum biomarkers to identify, monitor, and perhaps subset, patients with asthma and remodeled airways. This UCSD AADCRC proposal will be directed by David Broide (Professor of Medicine) and include three projects (Broide, Croft, Zuraw) that will investigate mechanisms of airway remodeling in asthmatics exposed to allergen and rhinovirus common triggers of asthma. Thus, the overall hypothesis that will be explored in all three projects is that exposure to allergen triggers expression of inflammatory and remodeling pathways in allergic asthmatics that are exacerbated by exposure to respiratory viruses such as rhinovirus. The specific hypothesis that will be explored in each project and that will be driven by samples from asthmatics, is that the innate immune response (airway epithelium, macrophages, natural helper cells) play an important role in initiating and perpetuating the inflammatory and airway remodeling response to environmental triggers in allergic asthmatics. The three interrelated projects will focus on Innate inflammation and airway remodeling (Broide, Project 1), TNF-R family members, inflammation and remodeling (Croft, Project 2), and Epithelial GILZ inflammation and remodeling (Zuraw, Project 3) and be supported by Administrative Core A, and Asthma Clinical Core B, which will be a source of sputum, BAL, endobronchial biopsy, and blood samples from asthma and control subjects provided by investigators in Core B (Ramsdell, Harrell, and Thistlethwaite, UCSD; Proud and Leigh, University of Calgary; and Hamid, McGill University). An lOFM Core is also proposed as requested by the RFA.

Title: **Oklahoma Autoimmunity Center of Excellence**
P.I.: **Judith A. James**
Institution: **Oklahoma Medical Research Foundation**
Grant No.: **AI082714-04**
Award: **$30,000**

The Oklahoma Medical Research Foundation is home to outstanding clinical and basic science investigators who have research interests in the etiology and pathogenesis of autoimmune diseases and seek to identify novel therapeutics for more effective patient treatments. The scientific expertise, extensive clinical trial experience, access to geographically distinct patient populations, as well as unique patient registries, repositories and core technologies provide a solid foundation for the Oklahoma Autoimmunity Center of Excellence (ACE) application to which we have added a multidisciplinary team of clinical and basic science investigators. The focus of the Oklahoma ACE application is on expediting the translation of scientific discoveries in autoimmunity to clinical application in the diagnosis and treatment of systemic autoimmune diseases. To accomplish this, the Oklahoma ACE comprises two research projects, a proposed pilot research project, a Clinical Center (Joan Merrill, PI) and an administrative core (Judith James, PI). The research projects focus on thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and Sjögren's syndrome, which are also focuses of the Clinical Center. Multiple sclerosis, rheumatoid arthritis, pediatric arthritis, insulin-dependent diabetes, idiopathic thrombocytopenia and pediatric lupus are other key disease emphases of the Clinical Center. Two complimentary, but unique, research projects focus on understanding early events in the development of lupus autoimmunity and in defining targetable genetic associations in Sjögren's syndrome. The pilot project uses complimentary methods to address roles of elevated interferon activity in patients with TTP and a novel animal model of thrombocytopenia. In addition, two clinical trials are proposed; both of which enhance or build upon the basic science projects. The first studies efficacy and mechanistic affects of anti-IFN in select SLE patient subsets by applying a patient centric, dose optimization strategy. The second tests the efficacy and early MRI changes of a novel MEK1/MEK2 inhibitor in RA with additional mechanistic studies. The Administrative Core will provide leadership and management through acting on behalf of the Oklahoma ACE members within the ACE Network and NIH Program, ensuring fiscal responsibility for the ACE, and providing an educational foundation for a multi-disciplinary approach to autoimmune disease research. Thus, the Oklahoma ACE will unite Oklahoma-based clinical and basic science experts to facilitate access to unique patient populations for participation in clinical trials and to understand basic mechanisms of etiology and pathogenesis. The Oklahoma ACE brings together adult and pediatric rheumatologists, neurologists, endocrinologists, dermatologists, hematologists, dentists, ophthalmologists, geneticists, immunologists, molecular biologists, epidemiologists and biostatisticians to provide a multidisciplinary approach to discovering and applying novel therapeutics in systemic autoimmune diseases. Through strong basic science projects paired with clinical expertise the Oklahoma ACE will provide unique research and clinical opportunities to the ACE Network. CLINICAL COMPONENT: CLINICAL CENTER (Merrill, J) CLINICAL COMPONENT DESCRIPTION (provided by applicant): The Oklahoma ACE Clinical Center brings together disease-specific and interdisciplinary clinics in systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, thrombotic thrombocytopenic purpura, insulin dependent diabetes mellitus, pediatric SLE and juvenile inflammatory arthritis to forward translational research in autoimmunity. Patients from each of these disease populations are available and committed to participate in potential national ACE investigations. With adult and pediatric rheumatologists, adult

and pediatric endocrinologists, neurologists, hematologists, dermatologists, ophthalmologists and dentists, as well as basic scientists from various areas of immunology, molecular biology, genetics, epidemiology and biostatistics, our investigative team is poised to make basic advances regarding disease pathogenesis and to help translate these discoveries to the clinic. The Clinical Pharmacology program at OMRF will serve as the primary home for the SLE, RA, Sjögren's syndrome and TTP clinics. Currently leading or participating in more than 20 active clinical trials, this clinical center is accustomed to participating in clinical trials, managing confidential patient information, and providing multidisciplinary care. In addition, the Clinical Pharmacology space provides investigators access to state-of-the-art research tools directly adjacent to the patient care unit. Pediatric IDDM and rheumatology clinics are housed across the street at OUHSC and a large, community based multiple sclerosis clinic will participate for MS patient investigation. Joan Merrill, MD serves as the leader of our Clinical Center. She is the current medical director of the Lupus Foundation of America and a leader in SLE clinical trial development. She has served as the lead investigator on large, multi-site trials. Combining her extensive knowledge of clinical trial design and the known heterogenic presentation of SLE, she proposes to devise patient-centric clinical trials that use biomarkers of disease to optimize therapeutic doses. Our Clinical Center proposes two potential clinical concepts. Based upon our basic science investigation regarding pivotal roles for increased interferon activity in pre-clinical SLE, Sjögren's syndrome and potentially TTP, our first trial examines the efficacy and biologic impact of anti-INF alpha in SLE patients with arthritis and select dermatologic manifestations. The second trial proposes use of a first-in-class target of MEK1/MEK2 inhibition in RA to assess impact on MRI progression of disease and on select biomarkers. Both of these trials have mechanistic studies proposed to address key scientific questions regarding pathogenesis and response. The Oklahoma Autoimmunity Center of Excellence Clinical Center will provide interdisciplinary investigators with unique populations of well-characterized patients to participate in ACE network autoimmune disease clinical trials. With our rich Native American heritage and large rural populations, the patients provided by the Oklahoma ACE will be previously understudied and provide unique insights for therapeutic trials.

Title: **A Systems Biology Approach for Pediatric and Adult Autoimmune Diseases**
P.I.: **Maria Virginia Pascual**
Institution: **Baylor Research Institute**
Grant No.: **AI082715-04**
Award: **$30,000**

We propose to create an Autoimmunity Center of Excellence that will incorporate the efforts of clinicians, human immunologists (both basic and translational), physician-scientists with clinical expertise and research experience in autoimmunity, bioinformaticians, and geriomics/systems biologists. Together, the assembled group has an extensive background in clinical trials and a proven track record for merging basic and clinical science. This team is committed to bringing innovative treatments from the

laboratory bench to their patients' bedside. Within this collaborative setting, a systems biology approach is proposed to focus on both pediatric and adult autoimmune diseases. The goals of the Center are: 1) To assess the efficacy of novel targeted therapies, 2) To develop simple and robust biomarkers using state-of-the-art genomic approaches, 3) To understand the role of recently identified T cell subsets in disease pathogenesis, and 4) To assess antigen-specific responses in pediatric and adult autoimmune diseases. These projects will provide a better understanding of the pathogenesis of specific autoimmune diseases and allow us to develop a strategy to assess disease activity based on novel transcriptional markers as well as to identify autoantigen-specific immune responses. The Center will deliver: 1) Innovative clinical trials targeting specific cytokines in psoriasis & dermatomyositis. 2) Development of biomarkers for dermatomyositis, psoriasis, lupus and multiple sclerosis. 3) Identification of novel therapeutic targets in dermatomyositis. 4) Development of assays to test autoantigen-specific immune responses. 5) Development of a unique microarray database of human autoimmune diseases. CLINICAL COMPONENT (Cush, J) CLINICAL COMPONENT DESCRIPTION (provided by applicant): Baylor Institute for Immunology Research aims to bring together a distinguished team of clinical investigators to conduct cutting-edge clinical trials on specific autoimmune diseases. This unique group of investigators and clinicians has appointments at Baylor University Medical Center, UT Southwestern Medical Center, Texas Scottish Rite Hospital in Dallas and Northwestern University. These talented individuals have been enlisted from diverse programs with subspecialties in dermatology, rheumatology, neurology, pediatrics, and human immunology. They provide a set of inimitable resources for clinical trials and have a proven track record for merging basic and clinical science. Indeed, this team is committed to bringing innovative treatments from the laboratory bench to their patients' bedside. With such outstanding collaborative players, a systems biology approach is proposed here which investigates both pediatric and adult autoimmune disease. To this end, two Phase II randomized, double-blind, placebo-phase controlled clinical trials are proposed. The first trial investigates whether blocking IL-1 with Anakinra will result in objective disease improvement for patients with Juvenile Dermatomysitis. The trial design will demonstrate: 1) if the time to improvement for patients receiving Anakinra early in the study will be earlier than those who receive later treatment; and 2) if the proportion of patients improved at week 8 of the blinded phase will be significantly greater in the early treatment group. Mechanistic studies will utilize gene expression profiling assays to find a novel diagnostic test for JDM as well as disease activity measures and biomarkers to follow and predict patients' response to therapy. The second clinical project proposes to use a-IL-17 in patients with plaque psoriasis as well as psoriatic arthritis. Specifically, this study will assess the safety and efficacy of a-IL-17 in these patients and determine both the time to achieve endpoints of a PASI 75 or ACR20 and sustainability of such responses at 24 weeks. Associated studies will establish blood transcriptional markers to predict clinical responses in patients treated with a-IL-17, determine if transcriptional scores can be used to assess disease activity, and analyze the effect(s) of IL-17 blockade on B and T cell subsets. A dynamic team of clinical investigators assembled at BUR to conduct state-of-the-art clinical trials on autoimmune disease would be of great value and accelerate the process of bringing research from the laboratory bench to the bedside. This team proposes two

important trials that will assess a-IL-1 treatment in Juvenile Dermatomyositis and IL-17 blockade in psoriatic diseases.

Title: **Autoimmunity Center of Excellence (ACE) at Stanford**
P.I.: **Charles Garrison Fathman**
Institution: **Stanford University**
Grant No.: **AI082719-04**
Award: **$30,000**

The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune disease. The major theme of the Stanford Autoimmunity Center of Excellence (the Center) is the study of the regulation of CD4 T cells in pathogenesis and treatment of autoimmune diseases. The Center will support and be supported by other ACE groups across the United States; and will take advantage of Stanford's documented leadership in basic and clinical research, technology development, and education in clinical immunology. Success of the Center will be supported by the interrelationships previously established at Stanford among clinician scientists from multiple departments studying autoimmune diseases in multiple organs and tissues. The Stanford ACE will be composed of outstanding basic and clinical investigators from multiple disciplines at Stanford Medical School and proposes both a basic Research Project, centered on CD4 T cell unresponsiveness, and a translational Research Project to study a new T cell lineage (termed Th17 cells) that is characterized by the ability of these lymphocytes to secrete high levels of the proinflammatory cytokine interleukin-17 (IL-17). Proposed clinical research projects encompass three different autoimmune diseases [diffuse systemic sclerosis (SSc), psoriatic arthritis and systemic juvenile idiopathic arthritis (SJIA)] that afflict adults and children, as well as organ systems including joints, skin, blood elements, and blood vessels, and will both test efficacy of therapy and develop tests to characterize the mechanisms of action of these therapeutics. The proposed Pilot and Feasibility Project proposes a two year research plan in Systemic Juvenile Idiopathic Arthritis (SJIA) patients to identify and validate urine peptide biomarkers that predict (a) response to TNF inhibition; (b) response to IL-1 inhibition; and (c) impending disease flare. In addition, this proposal will provide other ACE groups access to cutting edge reagents and technology platforms for studying human autoimmune diseases, and dissemination of Educational Materials that can be used by other ACEs to teach clinical immunology concepts to high school, undergraduate, graduate, postgraduate, and clinical fellows and faculty. The Stanford ACE proposes to support integrated basic, pre-clinical and clinical research by proposing and then conducting basic and translational research into the mechanism of CD4 T cell unresponsiveness; two clinical trials that include novel therapies and mechanistic studies of these therapies for autoimmune diseases; and a pilot proposal that intends to develop new bi omarkers of disease. PROJECT 1A: Clinical Component (Genovese, M) CLINICAL COMPONENT DESCRIPTION (provided by applicant): Stanford University Medical Center (SUMC) has an extraordinary tradition of medical, translational, and basic science research. An outstanding array of resources, faculty, and facilities will be available to support the proposed ACE site at Stanford

University. This proposal brings together a skilled group of translational researchers with a track record of productivity in both laboratory and clinical research focusing on human autoimmune mediated diseases. Stanford has brought together various disciplines to demonstrate both accomplishment and ability to work together with the following fields represented: Adult Rheumatology, Dermatology, Pulmonary Medicine, and Pediatric Rheumatology. The projects chosen for this submission highlight the significant collaborations that exist between Rheumatology (Adult and Pediatric), Dermatology and Pulmonary Medicine. Both clinical trials projects explore dermatologic and rheumatologic manifestations of diseases such as Psoriatic arthritis and Systemic Sclerosis. Clinical Trial Concept 1: The use of an anti-IL-17 mab in the treatment of active Psoriatic Arthritis Primary Hypothesis: The proportion of patients achieving the ACR 20 response from Baseline to Week 14 among active Psoriatic Arthritis (PSA) subjects treated with IL-17 mab is larger than the proportion achieving ACR 20 response from Baseline to Week 14 among active PSA subjects treated with placebo Objectives: The goal of this study is to determine the safety and efficacy of a monoclonal antibody to lnterleukin-17 (IL-17 mab) in the treatment of PsA with active skin and joint disease. Clinical Trial Concept 2: The use of CTLA-4lg (abatacept) in subjects with diffuse systemic sclerosis Primary hypothesis: Given several lines of evidence supporting the role of activated T cells in affected skin, we hypothesize that inhibiting T cell activation may lead to significant clinical improvement in skin manifestations in patients with diffuse systemic sclerosis (dSSc), and that changes in tissue and blood autoantibody and cytokine profiles will be associated with clinical response. Objectives: The primary goal of this study is to determine the safety and efficacy of CTLA-4lg (Abatacept) for the treatment of cutaneous manifestations of dSSc RELEVANCE (See instructions): The Stanford ACE will support an integrated basic and clinical research program focused on tolerance induction and immune modulation to prevent or treat autoimmune (Al) disease. The Stanford ACE proposes clinical research projects that encompass three different autoimmune diseases (SSc, psoriatic arthritis and SJIA), and proposes to study the MoA of therapeutics for preventing or treating different Al diseases.

Title: **Nanoparticle Microbicides for Delivery of Combination Antiretroviral Drugs**
P.I.: **Kim A. Woodrow**
Institution: **University of Washington**
Grant No.: **AI094412-02**
Award: **$18,750**

Sexual transmission through the genital tract or rectal mucosa is the most common route for acquiring new HIV infections and accounted for ~70% of the 2.7 million people worldwide who became newly infected in 2007. A cure or effective vaccine that would contain the global spread of this epidemic is not expected in the near term, and new HIV infections continue to outpace advances made in treatment with antiretroviral drugs. There is consequently an urgent need to develop agents that can be applied topically to mucosal surfaces to prevent the sexual transmission of HIV. However, several large-scale clinical trials testing the efficacy of agents that disrupt the integrity of the viral envelope

(detergents) or prevent adsorption or fusion of the virus with its target cells (polyanions) have failed to protect against HIV infection. The success of highly active antiretroviral therapy (HAART) provides a paradigm for developing the next generation of microbicides, raising the possibility that a combination of potent and broadly active inhibitors that exhibit multiple and complementary mechanisms of action may be vastly superior to the delivery of single compounds. To fully realize the potential of these potent antiretroviral (ARV) drugs, the challenges of formulating and delivering compounds with markedly different chemical stability and aqueous solubility in a topical combination product must be overcome. This research plan is designed to evaluate nanoparticle-based vaginal drug delivery systems for HIV prevention. The experimental focus is to achieve protection against vaginal transmission of HIV-1 by topical delivery of a combination of antiretroviral drugs using mucus- and tissue-diffusing nanoparticle microbicides. This research would be the first to control the temporal and spatial co-delivery of a combination of antiretroviral agents that have different mechanisms of action against HIV-1 (Aim 1). If successful, our studies would be the first to determine the size range and penetration depth accessible for nanoparticulate drug delivery systems in the vaginal mucosa (Aim 2). Our proposed research will also provide valuable data on the transport, biodistribution, and pharmacokinetics of encapsulated and released antiretroviral agents that are administered topically to the vaginal mucosa using nanoparticle microbicides (Aim 3). Finally, we will conduct preclinical safety and anti-HIV efficacy studies to rapidly advance our nanoparticle-based microbicides to human safety and efficacy trials (Aim 4). The outcomes from our proposed research may highly impact the field of microbicide research for HIV and other sexually-transmitted infections.

Title: **Thermostable Vaginal Probiotic Microbicide**
P.I.: **Victor Bronshtein**
Institution: **Universal Stabilization Technologies, Inc.**
Grant No.: **AI094508-02**
Award: **$18,375**

Recently revised statistics show the number of individuals living with HIV at over 33 million worldwide, with 68% being in sub-Saharan Africa. Current HIV prevention methods, such as condom use, monogamy and abstinence, are not always feasible. The need for improved HIV preventative technologies remains urgent. The development of topical microbicides represents a new and exciting field in the prevention of sexually transmitted diseases. Of these, application of live probiotic bacterial microbicides (PBM) represents a promising preventative method. Our ultimate goal is to develop potent optimized multistrain thermostable and easily deliverable probiotic vaginal topical microbicides. To achieve this goal we will stabilize vaginal probiotics for long-term storage at high ambient temperatures and short term survival at temperatures required for quick dissolve film manufacturing (60¿C and above). The cornerstones of this proposal are: 1) Preservation by Vaporization (PBV)—an innovative, patent pending method of dry-stabilizing probiotics bacteria and other fragile biologicals at high ambient temperatures, and 2) Quick-dissolve thin film technology that is being optimized to deliver conventional vaginal microbicides. The strategy can be described briefly as, to

occupy the vaginal epithelium and provide a long lasting protective environment against HIV, BV, and STI acquisition small (10-50 ¿m) glassy sugar particles containing PBV vaginal probiotic bacteria will be formulated into thin films which utilize a water soluble polymer base. Thin films offer a unique delivery platform which has a number of advantages over other dosage forms. In a recent study comparing women's preference between films, tablets and ovules, the film dosage form was shown to have greatest acceptability among women studied. We believe that women will prefer using a vaginal film over other potential methods of probiotic microbicide delivery especially if a long-acting effect of the bacteria colonizing vaginal epithelium allows for less frequent use. Biologic properties of PBM after long-term storage at ambient temperatures will be characterized using cell culture models of vaginal and cervical epithelium.

Title: **The Semen Enhancer of HIV Infection as a Novel Microbicide Target**
P.I.: **Stephen Dewhurst**
Institution: **University of Rochester**
Grant No.: **AI094511-02**
Award: **$18,750**

We will also test whether our lead molecules have efficacy in a cervical explant model for HIV-1 infection, and whether they have a synergistic or additive effect on the ability of other candidate microbicides to inhibit HIV-1 infection in the presence of semen. In the final Aim, we will assess the toxicity and inflammatory effects of the most promising candidate molecules, using beneficial Lactobacillus strains and cervical explants. The R33 phase will culminate with an evaluation of the safety and tolerability of the most promising compound in the rabbit vaginal irritation (RVI) model. The overall goal of these studies is to carefully determine whether small molecules that target SEVI have potential utility as a novel class of microbicides.

Title: **Designing Optimal Microbicide Delivery Integrating Rheology and Acceptability**
P.I.: **John Edward Hayes**
Institution: **Pennsylvania State University**
Grant No.: **AI094514-02**
Award: **$18,750**

This year perhaps 2.5 million people will be added to the approximately 35 million already infected with HIV/AIDS, 50% of whom are women. Topical microbicides offer these women a means to prevent sexually transmitted infections (STIs), including HIV. However, in addition to concerns about the biological efficacy of current microbicides, user acceptance of and adherence to their use is suboptimal. It has been estimated that a single microbicide with even limited efficacy could prevent millions of new HIV cases annually. The design of vaginal microbicide dosage forms has challenged formulation scientists. Safe and efficacious products are necessary, but not sufficient to assure

adherence. User acceptability depends both on the physical properties of the material and behavioral factors. Constraints that drive acceptance must be identified and addressed early in development. The acceptability of the product to women must be evaluated preclinically. We propose the rational preclinical design and development of a dosage form that delivers an immediate efficacious dose of active pharmaceutical ingredient (API) followed by the slow release of API over a period of 1-3 days to maintain efficacy. This dosage form can be thought of as a temporal vaginal ring/diaphragm that releases API(s) as it slowly erodes away. These products will be an adaptation of current softgel capsule technology. However, unlike current gelatin capsules, we will develop a range of non-gelatin capsules varying in shape and firmness (texture). Human perceptual data will be assessed throughout and guide the design process. Carrageenan will be used for the development of heat-stable softgels that, unlike current gelatin capsules, will not melt in tropical environments. The two-phase nature of softgels ('ovules') will permit the inclusion of a second component. Our R21 goals provide for proof-of-concept of this new delivery system, and the R33 goals will optimize both acceptability and biophysical functionality. The R33 will also explore potential higher-order functionality, like mucoadhesion or delivery of probiotics. Here, we propose a new microbicide delivery system, designed to overcome both biological (insufficient HIV neutralization) and behavioral (poor acceptability and adherence) deficiencies of current products. By designing formulations that function for optimal efficacy and optimal use (acceptability / adherence), microbicides produced via these methods are likely to have a greater impact on the HIV/AIDS pandemic than those currently in the development pipeline. Also, by developing a methodology for design of vaginal products where multiple factors (shape, texture, size, and multi-stage delivery) play a central role, we increase the options women have in microbicide use. Critically, our product type is flexible—allowing for multiple textures, sizes, shapes and antiviral strategies—to accommodate a range of user preferences.

Title: **Mucosal Tissue Explants as Surrogates for in vivo Efficacy of Microbicides**
P.I.: **Carolina Herrera**
Institution: **University of London, Imperial College of Science, Technology and Medicine**
Grant No.: **AI094515-03**
Award: **$18,750**

The HIV microbicide field is dependent upon testing in non-human primates (NHPs) as the only relevant model to study infection. However, the predictive accuracy of NHP studies of efficacy in humans has not been validated and as such the economic value is unknown. Hence, refinement of this model and development of a novel correlate of efficacy in humans that will reduce the potential use of NHPs is key for the global progress of microbicides and specifically of the Microbicide Innovation Program's mission. This proposal addresses these issues by testing the hypothesis that ex vivo tissue explant cultures can provide a potential surrogate of in vivo efficacy through measurement of intra-tissular drug pharmacology and ex vivo infection/protection. This

will be investigated using combined expertise in modeling mucosal tissue infection and measurement of antiretroviral (ARV) drug pharmacokinetics and pharmacodynamics in tissue. The proposal will focus on a reverse transcriptase inhibitor, PMPA (tenofovir), and an entry inhibitor, maraviroc, used alone and in combination as candidate microbicides. In the R21 component of the proposal we will demonstrate the robustness of our ex vivo explant models for analysis of pharmacological parameters and ex vivo infection independently of the origin (human or NHP) and the type of mucosa (cervicovaginal or colorectal). This will be investigated through two Specific Aims: 1) to define ex vivo pharmacological dose-responses (pharmacokinetics and pharmacodynamics) in human and rhesus macaque mucosal tissue explants; 2) to define whether the viral backbone affects pharmacological correlates of activity. The next step of our proposal in the R33 component will involve validation of the model as a surrogate for prediction of in vivo efficacy of ARV drugs as vaginal and colorectal microbicides. Here the two Specific Aims are: 3) to assess whether activity of drugs titrated in vivo can be predicted with ex vivo challenge models: 4) to correlate ex vivo and in vivo protection and drug dosing in NHPs. The iterative design of the overall proposal will allow us to assess correlates between intra-tissular pharmacological dosing and efficacy at all levels: tissue type, origin of tissue, route of dosing and challenge, and nature of experiment (ex vivo, in vivo). These correlates will define conversion factors of microbicides efficacy between the NHP model and in humans, which will be key for the rational development of existing and future candidate microbicides.

Title: **Mucus Penetrating Particles for Rectal Microbicides**
P.I.: **Justin S. Hanes**
Institution: **Johns Hopkins University**
Grant No.: **AI094519-02**
Award: **$18,750**

For reliable protection against STD transmission, rectal microbicides must be formulated in a way that will deliver the active agent to all the surfaces that are susceptible to infection. These include the entire rectum as well as a large fraction of the colon (due to peristaltic stirring of colonic contents). Colorectal surfaces are columnar epithelia that are mechanically and osmotically fragile, and are highly susceptible to STD transmission. Although continuous mucus secretion by these susceptible surfaces helps protect against trauma and pathogens, this continuously secreted mucus also poses a significant barrier against effective delivery of microbicides to the epithelial surface. Recently we developed novel mucus penetrating nanoparticles (MPP) that can overcome this barrier and provide sustained, well-distributed delivery of drugs to mucosal surfaces. Our hypothesis is that MPP will significantly increase the protective efficacy of rectal microbicides by achieving more uniform and complete colorectal distribution, sustained drug activity, and thus longer duration and more complete protection compared to drug delivered in gels (free drug) or drug delivered in conventional nanoparticles, CP, that adhere to mucus and fail to penetrate mucus barriers. In the R21 phase, we will determine optimal MPP properties for penetration of mouse colorectal mucus, and we will characterize the uniformity of MPP distribution and retention times in the mouse

colorectum compared to CP and free drug. We will then prepare drug-loaded biodegradable and biocompatible MPP that provide sustained release of antiviral drugs (valacyclovir for HSV and UC-781 for HIV). We will deliver these MPP in both a rectal enema format and a rectal lubricant gel format since both formats are frequently used for enhancing rectal intercourse. Moreover, an enema may deliver MPP to large regions of the colon unlikely to be reached by a gel. The key milestone for the R21 phase will be development of valacyclovir-MPP and UC-781- MPP that provide more complete and persistent coverage of the rectal epithelial surface, with minimal toxicity, compared to CP formulations or free drug. In the R33 phase, we will extensively test these MPP formulations for safety and protective efficacy in our mouse/HSV rectal model and in the hu-BLT-SCID mouse/HIV model (via a subcontract with Dr. J. Victor Garcia-Martinez at UNC).

Title: **Development of an HIV-1 Entry Inhibitor Pre-drug as a Microbicide**
P.I.: **Min Lu**
Institution: **University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School**
Grant No.: **AI094555-02**
Award: **$18,750**

With no vaccine in sight, there is an urgent public health need to develop an effective topical microbicide that can reduce the number of new HIV-1 infections in women. The potential role of virus-cell fusion inhibitor-based microbicides in preventing mucosal transmission of HIV-1 has been clearly identified. However, none of the reported gp41 fusion inhibitors has made significant progress toward clinical trials. HIV-1 infection requires fusion of the viral and cellular membranes, driven by association of two heptad-repeat regions in the gp41 ectodomain to form a highly stable six-helix bundle structure. Whereas this postfusion motif comprising native N36 and C34 peptides has no inhibitory activity, the isolated peptides inhibit HIV-1 entry by binding to their cognate sites on gp41. Our goal in this MIP VI application is to develop an inexpensive, potent, structured ‘pro-drug’ form of the N- and C-peptide fusion inhibitors that exhibits significant microbicidal activity upon use in situ. Our development effort will be based on preliminary data obtained with a truncated six-helix bundle that inhibits in vitro infection by primary HIV-1 isolates with low nanomolar IC50 values. We propose a comprehensive, interdisciplinary approach that combines high-resolution structural determination, recombinant protein production and mutagenic analyses, virology, and animal model efficacy studies. In this project we seek to conduct in vitro and in vivo preclinical and animal model-based research intended to facilitate the development of new HIV-1 gp41 peptide fusion inhibitor as a practical microbicide. The Specific Aims are: 1. To optimize and identify HIV-1 peptide fusion inhibitors for development as a vaginal microbicide. (a) To identify and incorporate specific amino-acid residue substitutions that optimize both potency and solubility of fusion inhibitor peptides. (b) To develop and optimize robust procedures for the large-scale bacterial expression and purification of select fusion inhibitor peptides. (c) Investigate the mechanisms of

resistance to peptide inhibitors so as to avoid eliciting resistance. 2. To characterize the specificity, potency and toxicity of optimized peptide fusion inhibitors and their in vitro synergistic interactions with the CCR5 inhibitor CMPD167 and the entry inhibitor BMS-378806. (a) Determine the virucidal activity of optimized fusion inhibitor peptides against a diverse set of primary HIV-1 isolates. (b) Evaluate their toxicity, immunogenicity and drug stability in the rabbit model. (c) Study antiviral synergy in vitro in order to make rational predictions for lead inhibitor combinations for in vivo efficacy testing. 3. To test the effectiveness of the fusion inhibitor peptides to protect against mucosal HIV-1 infection. (a) Characterize the specificity and potency of effective peptide inhibitors in an in vitro model of HIV-1 infection of human cervical and vaginal tissue. (b) Use the NOD/SCID-hu BLT mouse vaginal transmission model to assess the in vivo potency and breadth of activity of highly effective peptide inhibitors alone and in combination with the small-molecule CCR5 inhibitor CMPD167 and the small-molecule entry inhibitor BMS-378806.

Title: **Cervical/Vaginal Mucus and Microbicides**
P.I.: **Thomas Hope**
Institution: **Northwestern University at Chicago**
Grant No.: **AI094584-02**
Award: **$18,750**

To develop a functional microbicide it is critical to know how it will interact within HIV in the context of the female genital tract. This is a critical issue as previous clinical trials have indicated that microbicides do not function as expected in the presence of semen. Likewise, other factors, such as cervical/vaginal mucus, might also modulate microbicide function. To date, little is known about how HIV interacts with these fluids and how the interaction of these fluids changes the local environment. Even less is known about how microbicides interact with HIV within this milieu. For example, the vehicle delivering the microbicide might interact with the biological fluids of sexual transmission to either increase or inhibit HIV acquisition or microbicide potency. The Hope laboratory has recently developed methods that allow the transport of HIV with cervical and cervical/vaginal mucus to be analyzed and quantified. These studies have revealed that mucus can perturb HIV transport and is pH sensitive. At acidic pH, as is found in the lactobacilli influenced environment of the vaginal vault, HIV transport is greatly reduced. At neutral pH, such as when semen is introduced into the system, HIV transport is reduced 10-15 fold relative to what is observed in media (water). Additionally, we have found, but not yet published, that virus-binding antibodies can further reduce transport in neutral pH cervical mucus. These antibodies do not need to be neutralizing as any antibody binding to the virus can decrease virus transport. Semen also contains mucins and other components that have the potential to alter HIV transport as we have observed in cervical mucus. How HIV is transported within semen and how this changes when mixed with mucus or microbicides is not defined. How this process influences HIV transport and interaction with mucosal barriers is not understood. In the first phase (R21) of this proposal we will define how HIV is transported in semen alone and mixed with mucus and/or microbicide vehicles such as carbopol gel and hydroxy ethyl cellulose

(HEC). In the second phase (R33) of this proposal we will extend our studies into the environment of the rhesus macaque female genital tract to determine how biological fluids and microbicide vehicles alter the way that virus interacts with the mucosal barriers of this environment and how these changes can increase or decrease SIV acquisition. These studies will lead to a better understanding of how virus interacts with biological fluids and how these interactions might alter microbicide efficacy.

Title: **Pathophysiologic and Therapeutic Mechanisms of Aspirin Exacerbated Respiratory Disorders**
P.I.: **Joshua A. Boyce**
Institution: **Brigham and Women's Hospital**
Grant No.: **AI095219-02**
Award: **$12,500**

This Proposal for support of an Asthma and Allergic Disease Cooperative Research Center (AADCRC) grant is focused on the mechanistic basis of aspirin-exacerbated respiratory disease (AERD), a distinctive clinical syndrome that accounts for a disproportionate percentage of individuals with severe asthma and recurrent nasal polyps. AERD is associated with both characteristic clinical reactions to ingestion of nonselective inhibitors of cyclooxygenase (COX), persistently elevated generation of the cysteinyl leukotrienes (cys-LTs), especially during reactions to aspirin, and selective airway hyperresponsivness to leukotriene E4 (LTE4), the most stable and abundant of the cys-LTs. We have discovered a molecular pathway through which LTE4 induces pulmonary inflammation (requiring P2Y12 receptors and platelets) and vascular leak (requiring a putative novel LTE4 receptor, GPR99). We have also discovered that leukocytes from individuals with AERD display a defect in expression of COX-2 and COX-2-dependent generation of prostaglandin E2 (essential to maintain homeostasis in AERD), and that this reverses with desensitization to aspirin. We have also found that platelets and leukocytes from individuals with AERD lack the EP2 receptor for PGE2. A team of highly accomplished investigators with complementary skills will apply cellular, molecular, and whole animal strategies, combined with a proof-of-concept clinical trial to determine the cellular and molecular basis for these findings, their relevance to disease pathophysiology, and their amenability to therapy. Project 1 (J. Boyce, PI) focuses on the physiologic and functional consequences of EP2 receptor deficiency, and determines its epigenetic basis. Project 2 (Y. Kanaoka, PI) will verify the identity and function of GPR99 and determine its susceptibility to desensitization and its requirement for downstream effectors (platelets, P2Y12, and thromboxane) to elicit physiologic responses. Project 3 (E. Israel, PI) will determine the efficacy of P2Y12 antagonism on the severity of clinical reactions to aspirin, and the mechanism by which aspirin treatment restores COX-2-dependent PGE2 generation. The coordination of the AADCRC is enhanced by an administrative Core.

Title: **Host and Viral Determinants of Infant and Childhood Allergy and Asthma**

P.I.: **Ray Stokes Peebles**
Institution: **Vanderbilt University Medical Center**
Grant No.: **AI095227-02**
Award: **$12,500**

The long term objective of this application is to define the relationship between infant respiratory syncytial virus (RSV) infection and the host response that enables asthma inception. There is abundant evidence that children who experience severe RSV bronchiolitis during infancy are at greater risk for developing asthma later in childhood; however the host and viral determinants of severity of illness are not fully defined. Also unknown is whether mild RSV-induced illness in infancy may protect against the subsequent development of childhood asthma. In Project 1, we utilize the ReSPIRA (Respiratory Study for Protection of Infants from RSV to Asthma) cohort of 2000 infants to focus on host immune responses to RSV infection and the subsequent risk of recurrent wheezing and childhood asthma. Specifically, in Project 1 we will a) establish the relationship between the host phenotypic response to RSV infection in the first 6 months of life and the risk of recurrent wheeze and asthma, and b) identify the host genetic and immune response determinants of the RSV infection phenotype that affect the development of early childhood wheezing and asthma following RSV infection. In Project 2, we will focus on the contribution of specific RSV strains to early childhood wheezing and asthma development. RSV strains isolated from the ReSPIRA cohort will be genotyped and clinical parameters such as bronchiolitis severity score, as well as mediators of the host immune response measured in respiratory secretions will be studied to determine how RSV genotypes impact the host response. In Project 3, we will utilize a mouse model of RSV infection to examine the role of the prostaglandin 12 (PGI2) on airway dysfunction of an RSV strain (01/2-20) that has been associated with severe infant bronchiolitis and which induces airway pathology in the mouse. We previously reported that PG12 and signaling through its receptor (IP) is a critical determinant of severity of illness in RSV strain A2 infection. This project will determine the role of host PGI2 in RSV airway pathogenesis and also determine if a PGI2 analog currently used in the treatment of human disease is a target for RSV bronchiolitis. Further, in Project 3, we will use RSV strains isolated from ReSPIRA in Project 2 to determine the generalizability of PGI2 as a therapeutic target.

Title: **Airway Inflammation and HLA-G in Asthma**
P.I.: **Steven R. White**
Institution: **University of Chicago**
Grant No.: **AI095230-02**
Award: **$12,500**

Our program seeks to clarify cellular and molecular mechanisms that lead to chronic asthma in order to identify novel, more effective therapies. We concentrate on immune mechanisms that underlie chronic airway inflammation with a clear focus on one immune tolerance molecule, the class I major histocompatibility complex protein human leukocyte antigen (HLA)-G, that we believe has an important role in modulating airway

inflammation that is critical to chronic asthma. The key premise of our AADCRC proposal is that understanding the role of HLA-G will lead to new and better therapies to alleviate the suffering caused by asthma. To this end we propose three highly integrated and related projects: in Project 1, we will examine the presence and regulation of expression of HLA-G in asthmatic airways and in the airway epithelium, and relate presence to asthma severity and to the expression of regulating microRNA. We will examine the regulation of HLA-G expression by key Th2 cytokines such as IL-13 that are important to chronic asthma and relate expression back to airway cytokine concentrations in chronic asthma. In Project 2, we will exploit naturally occurring genetic variations in HLA-G and its LILRB receptors to understand how signaling through HLA-G and its receptors regulate the transition of CD4+ lymphocytes to the Th2 phenotype in mild/moderate asthma and to the Th17 phenotype in severe asthma. This project also will examine how genetic variation in the LILRB receptors modulate the effects of HLA-G on both T cell phenotype and on the SHP1 and SHP2 signaling pathways that modulate airway smooth muscle hypertrophy in chronic asthma. In Project 3, we will elucidate mechanisms that account for the higher risk of asthma among children of asthmatic mothers compared to children of non-asthmatic mothers. Using HLA-G as a model of the interactions of genotype and asthma status in mother and child, we will identify differentially expressed genes and the mechanisms for their differential expression in airway epithelium, CD4+ T cells and airway smooth muscle in subjects with chronic asthma. To complete these projects, each will interact with a robust Patient Recruitment and Data Analysis Core that will recruit 100 carefully phenotyped and genotyped asthmatic subjects and additional control subjects, and collect blood and airway biological specimens to be used in each project through a Lung Biological Specimens Core that will provide analytical and long-term storage. We believe that our current levels of productivity and collaboration combined with new, exciting and cutting-edge questions in this proposal will allow us to be successful in achieving our overall goal—identifying novel therapeutic targets for chronic asthma.

Title: **T Cell Effector and Regulatory Mechanisms in Asthma and Food Allergy**
P.I.: **Andrew D. Luster**
Institution: **Massachusetts General Hospital**
Grant No.: **AI095261-02**
Award: **$12,500**

The Massachusetts General Hospital/Harvard Medical School AADCRC entitled T cell effector and regulatory mechanisms in asthma and food allergy seeks to gain a better understanding of the role of allergen-specific effector and regulatory T cells in determining the physiological response to an allergen at mucosal surfaces. It is becoming increasingly clear that the net outcome of an inflammatory response is the balance of allergen-specific effector T cell activity and opposing regulatory T cell activity. Antigen-specific effector and regulatory T cell numbers and activity are in large measure determined by the outcome of allergen-loaded dendritic cell (DC) interactions with antigen-specific T cells. The MGH/Harvard AADCRC will explore the balance of

effector and regulatory activity in asthma and food allergy and the ability of tolerogenic DCs to affect this balance. The Center will focus on two allergic conditions relevant to the mission of the NIAID, namely allergic asthma and food allergy, and utilize two clinical models [endobronchial segmental allergen challenge (SAC) and oral immunotherapy (OIT)] as a foundation for its studies. Project 1 focuses on the role of antigen-specific effector and regulatory T cells in determining airways inflammation and airways hyper-reactivity by correlating the numbers, phenotype and function of these cells in allergic asthmatics (AA) and allergic nonasthmatics (ANA) using innovative imaging techniques; Project 2 focuses on correlating the numbers, phenotype and function of these same T cell subsets with clinical outcomes of milk allergic patients undergoing milk OIT; and Project 3 focuses on the ability of tolerogenic DC therapy to manipulate the balance between these two opposing T cell populations in favor of regulatory T cells and tolerance in both asthma and food allergy. The three interrelated projects will be supported by Cores that will recruit, enroll and characterize allergic subjects for SAC and OIT, provide MHC class II tetramers to specifically identify and study allergen-specific T cells, and perform sophisticated transcriptome phenotypic analysis on T cell and DC subsets. The goal of this Center is to understand the balance of effector and regulatory allergen-specific T cell activity that determines clinical disease in asthma and food allergy and to establish the utility of using tolerogenic DCs to manipulate this balance to induce allergen-specific tolerance. This would pave the way for new therapeutic approaches to treat these and other allergic diseases.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Title: **Role of B Cells and DCs in Lupus Pathogenesis**
P.I.: **Mark J. Shlomchik**
Institution: **Yale University**
Grant No.: **AR044077-15A1**
Award: **$200,000**

Breaking T cell tolerance is arguably a critical step in the pathogenesis of SLE. Activated T cells provide help to autoantibody-secreting B cells and also infiltrate target organs. Therefore it is important to identify how, where and when such T cells are activated and how this is maintained. In fact, the latter is critical because any therapy will have to interrupt ongoing disease. Lupus-prone mice lacking B cells from birth have markedly reduced disease and much less T cell activation. This suggested that B cells are upstream in T cell activation and also that they would be good therapeutic targets. However, in lupus mice B cell depletion was difficult to achieve using standard anti-CD20 mAb and effects, particularly on T cell activation, were not striking. Similarly anti-CD20 failed to show clinical effect in SLE patients, though anti-BLyS did. These findings raise the question of what the role of B cells really was in ongoing disease, and whether, if efficient depletion were possible, would T cell activation and disease be reduced. They also suggested that other cell types such as DCs could be as or more important both for initiation and propagation. In this proposal we will use genetic approaches to target key

cells and molecules-including deletion during disease rather than from birth-in order to unravel the complex interplays of disease mechanisms in vivo. To this end, we recently deleted cDC and pDC in lupus-prone MRL.Faslpr mice from birth. Surprisingly, we found little effect on T cell activation in secondary lymphoid tissue (SLT), but there were striking reductions in nephritis and skin disease, decreased proteinuria and longer survival. These data suggested that DCs might be required to activate T cells in target tissues-a novel role rather than to initiate activation, as might have been assumed. We propose a new model in DCs have non-redundant roles in tissue infiltration in lupus but that B cells are the most upstream APC in SLT. To address this model, we will first deplete both B cells and DCs during ongoing disease, rather than from birth. This will validate DCs as therapeutic targets and help resolve the controversial role of B cells. We will also distinguish the roles of cDCs from pDCs, as whether pDCs are important for SLE has not been tested experimentally. Second, to understand how B cells and DCs might be activating T cells, we will block APC function by deleting MHCII from each. Further, we will investigate the role of ICOS signals, which are linked to lupus in a number of ways, including emerging data that ICOS specifies T follicular helper (TFH) and T extrafollicular helper differentiation, cells that help autoreactive B cells. We also have exciting preliminary data that ICOSL on DCs specifically is required to promote infiltrating T cells in kidney, and that such cells express Bcl6 and thus may be related to TFH. To further investigate the roles of ICOS signals, we will specifically delete ICOSL on B cells and on DCs. Together these experiments-organized around Aim 1 focusing on B cells and Aim 2 focusing on DCs-will test our model; determine if B cells/DCs or both are important as APC; validate B cells, cDCs, and pDCs as therapeutic targets; and elucidate the role of ICOS signals in the development of pathogenic T cells.

Title: **Osteoarthritis Initiative**
P.I.: **Michael Nevitt**
Institutions: **University of California, San Francisco (coordinating center); Ohio State University; University of Pittsburgh; University of Maryland; Memorial Hospital of Rhode Island**
Grant No.: **AR022258, 26820120031C*1**
Award: **$650,000**

Knee osteoarthritis (OA) is the most common cause of disability in adults. The "Osteoarthritis Initiative (OAI): A Knee Health Study" is a nationwide research study that will help researchers gather more information about the physical changes that occur prior to the onset of arthritis symptoms or before OA gets worse. The purpose of this study is to examine people who have knee OA or are at high risk for knee OA; information will be used to better understand how to prevent and treat knee OA Knee OA causes more health problems and medical expenses that any other form of arthritis. Symptoms of OA can range from stiffness and mild pain to severe joint pain and even disability. Previous research has shown that certain factors, such as knee pain, prior knee injury or knee surgery, OA of the hand, or obesity, may lead to knee OA. The OAI is a multicenter, observational study of knee OA that will collect information on potential biomarkers for OA and trends in OA onset and progression. The OAI will recruit and

follow participants who have knee OA or are at high risk for developing knee OA for at least a four-year period at one of four clinical centers. Blood and urine collection, magnetic resonance imaging (MRI), and X-rays will be completed at each of four annual follow-up visits. A questionnaire and physical examination at screening will assess for risk factors for the development and progression of knee OA. Levels of knee pain and physical disability will be assessed at study start and at each of the follow-up visits by questionnaire and examination.

Title: **Predictors of Pregnancy Outcome in SLE and APS**
P.I.: **Jane E. Salmon**
Institution: **Hospital for Special Surgery**
Grant No.: **AR049772-10**
Award: **$200,000**

Pregnancy complications in women with the antiphospholipid syndrome (APS) and/or SLE include recurrent miscarriage, preeclampsia, placental insufficiency, and intrauterine growth restriction (IUGR). The mechanisms leading to placental and fetal injury in vivo are incompletely understood and treatment remains sub-optimal. We have identified complement as an early effector in pregnancy loss and/or IUGR associated with placental inflammation in a mouse model of APS and shown that complement activation causes the release of anti-angiogenic factors and abnormal placental development. The PROMISSE Study (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) is a first-time effort to translate our novel findings in mice to humans and determine if elevations of complement split products predict pregnancy complications in patients with antiphospholipid (aPL) antibodies and/or SLE. In the first 4 years of this prospective, observational study of pregnant patients grouped and analyzed according to the presence or absence of aPL antibodies and preexisting SLE, we have enrolled 342 pregnant patients in 7 centers, obtained detailed medical and obstetrical information monthly, and serially collected plasma, serum, DNA, RNA, and urine. Preliminary data suggest that elevated levels of complement activation products antecede and predict poor fetal outcome, consistent with our hypothesis that complement is a proximal mediator of fetal loss and IUGR. We propose to increase our target sample size from 400 to 700 pregnant patients to maintain study power given lower than expected outcome rates, and to leverage the infrastructure and rich collection of patient data and samples by expanding the array of biomarkers and scope of adverse pregnancy outcomes. Specifically, in Aim 1 we will determine whether elevations of split products generated by activation of complement pathways predict poor fetal and/or maternal outcome in patients with aPL antibodies and/or SLE and, in Aim 2, whether the balance of circulating angiogenic and antiangiogenic factors predicts preeclampsia or delivery of IUGR infants. In Aim 3, a new direction, we will use the PROMISSE cohort to affirm in humans our recent findings in mice, that certain anti-DNA antibodies cross-react with N-methyl D- aspartate receptors (NMDAR) and cause neuronal death with ensuing cognitive and behavioral impairment. We propose to quantitate anti-NMDAR antibody levels throughout pregnancy in PROMISSE SLE patients and test the hypothesis that in utero exposure to maternal anti-NMDAR

antibodies alters behavior and cognitive development in offspring by evaluating cortical function tasks in 12 month and 3.5 year old children. This competitive renewal and extension of the PROMISSE Study provides an outstanding opportunity to translate knowledge from mouse models to patients, define pathogenic mechanisms, identify predictors of poor pregnancy outcome in APL and/or SLE, and define novel therapeutic targets to prevent such outcomes.Patients with systemic lupus erythematosus (SLE) and/or antiphospholipid (aPL) antibodies are at increased risk for miscarriage, preeclampsia and fetal growth restriction—major causes of maternal, fetal, and neonatal morbidity and mortality in the US and worldwide—whose etiology and mechanism remain unknown and for which therapy is limited. In addition to causing placental dysfunction, maternal autoantibodies may also directly impair fetal brain development. Identification of biomarkers that predict poor pregnancy outcome in these patients will elucidate mechanisms of disease, define targets for treating patients, and generate clinically applicable indicators to permit initiation of interventional trials in patients at greatest risk for pregnancy complications.

Title: **Sex-Specific Movement Differences in Young Adults with and Without Hip Pain**
P.I.: **Cara L. Lewis**
Institution: **Boston University**
Grant No.: **AR061690-01A1**
Award: **$184,162**

Acetabular labral tears are an increasingly recognized source of hip pain in young adults, especially females, and have been linked to the premature development of hip osteoarthritis (OA). Recently, femoroacetabular impingement (FAI) has been implicated as a cause of labral injury and OA. In FAI, hip pain occurs in the presence of a structural abnormality of the acetabulum or femur which results in early contact between the bones during hip flexion and internal rotation. Current treatment for FAI includes surgical procedures to resect or reorient the femur or acetabulum or both. While structure does contribute to hip pain, increasing evidence suggests that movement patterns may also play an important role. The long-term goal of this line of research is to improve treatment for hip pain, especially in young adults, which will prevent or slow the progression of chondral damage and thereby reduce the need for hip arthroplasty. The purpose of this project is to assess the movement patterns of people with FAI compared to people without hip pain and to test for sex- and limb-specific differences in these patterns. Identification of differences in movement patterns which may contribute to hip pain can improve non-invasive treatment for people with hip pain. To test for these differences, we will assess movement patterns using kinematic data collected during movements including walking, stepping down, supine straight leg raise and prone hip extension on subjects with FAI and subjects without hip pain. We hypothesize that subjects with FAI will display movement patterns which are closer to their end-range hip motion than subjects without hip pain. We believe that these movement patterns contribute to a subject's hip pain. We also hypothesize that females with FAI will display different movement patterns than males with FAI. We anticipate this sex difference in movement

patterns because there is an unequal distribution of the structural abnormalities among females and males, and because a sex effect has been noted in other lower extremity injuries (e.g. ACL tears, patellofemoral pain). Furthermore, as subjects often have unilateral pain despite bilateral structural abnormalities, we hypothesize that subjects with FAI will display different movement patterns of the painful hip than the unimpaired hip. The knowledge gained from this research has the potential to redirect treatment for people with FAI by identifying sex-specific movement patterns which could be targeted by inexpensive and non-invasive therapeutic interventions. It also could be used to develop prevention programs focused on neuromuscular retraining.

Title: **NIH Osteoporosis and Related Bone Diseases-National Resource Center**
P.I.: **NIAMS (coordinating center)**
Institutions: **NIAMS, in cooperation with NIA, NICHD, NIDCR, NIDDK, ORWH, and HHS/OWH**
Grant No.: **268200800001C*42**
Award: **$50,000**

The National Institutes of Health (NIH) Osteoporosis and Related Bone Diseases ~ National Resource Center, a part of the U.S. Department of Health and Human Services, provides patients, health professionals, and the public with an important link to resources and information on metabolic bone diseases, including osteoporosis, Paget's disease of the bone, and osteogenesis imperfecta. The NIH National Resource Center is dedicated to increasing the awareness, knowledge, and understanding of physicians, health professionals, patients, underserved and at-risk populations (such as Hispanic and Asian women, adolescents, and men), and the general public about the prevention, early detection, and treatment of osteoporosis and related bone diseases.

National Institute of Biomedical Imaging and Bioengineering

Title: **Steroid-Based Contrast Agents for Magnetic Resonance Imaging of Endocrine Disease**
P.I.: **Thomas J. Meade**
Institution: **Northwestern University at Chicago**
Grant No.: **EB014806-01**
Award: **$250,000**

The objective of this research proposal is to develop a series of steroid-based magnetic resonance imaging (MRI) contrast agents to facilitate molecular characterization of the status and function of steroid receptors in hormone-dependent disease and development. The ability to detect the location of cell receptors and their concentration throughout a living organism is of vital importance as it allows for further understanding of cell signaling mechanics. Progesterone and estrogen are steroid hormones that bind to their receptors and function as a transcription factors in the nucleus. A non-invasive means of

determining the hormone receptor status of hormone-dependent tumors and benign lesions could assist with treatment options, identification of the size and exact location of the tumor, and provide additional tools when traditional imaging strategies miss or confuse lesions of the breast and uterus. Unlike fluorescence and optical microscopy, MRI is not limited by depth or transparency of the specimen. MRI does not use ionizing radiation or radioactivity like positron emission tomography (PET) and X-ray/CT, and it allows for 3D reconstructions and high resolution imaging over time without the need to sacrifice the organism. It is the hypothesis of this grant proposal that gadolinium(III) conjugated hormone-based contrast agents can target and accumulate in hormone receptor positive cells to non-invasively image receptor status. Our preliminary studies have identified gadolinium (Gd)-conjugated progesterone derivatives as compounds capable of traversing the cell membrane, binding to progesterone receptors, initiating gene transcription, and enhancing contrast in mammalian tissues and tumors imaged in vivo using magnetic resonance, the most promising of which is termed "ProGlo". This proposal focuses on the application and expansion of ProGlo to enhance the imaging of steroid receptor tumors and tissues in vivo. AIM 1. To synthesize and test a series of CAs that targets the estrogen receptor. Estrogen-based contrast agents will be designed and synthesized with varying polarities, charges, and water solubilities that will selectively probe membrane bound receptors or receptors located inside the cells and tumors. AIM 2. To investigate if hormone receptor disease of the breast and uterus can be classified as receptor positive using functional hormone MR agents. AIM 3. To chemically modify CAs to enhance in vivo relaxivity and reduce toxicity by developing and testing bio-orthogonal, water-soluble, and multi-chelated hormone CAs. Steroid receptors have emerged as attractive targets for molecular imaging due to their role in promoting the growth of breast and uterine lesions. This proposal will develop steroid contrast agents that could provide a molecular profile of hormone receptor status in cells, validate responsiveness to therapy, and improve diagnoses. Functional contrast agents will provide valuable tools for use in humans and for immediate use in animal models of hormone receptor dependent development and disease without the need to euthanize the animal thereby increasing knowledge about developmental biology, disease etiology, and progression.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Title: **A Collaborative Workshop Across the Scientific Disciplines**
P.I.: **Sally T. Hillsman**
Institution: **American Sociological Association, Inc.**
Grant No.: **HD010988-01**
Award: **$10,000**

It is well-recognized in the scientific community that data-driven, scientifically rigorous tools are needed to stimulate and enhance efforts to use the talents of all our citizens, including underrepresented minorities and women. There is an additional need to look beyond individual efforts to begin to pursue a system-based analysis. This workshop

proposes to address the recommendation from a 2008 National Institutes of Health (NIH)-supported (additional funding provided by the National Science Foundation (NSF)) leadership retreat, "Enhancing Diversity in Science: A Leadership Retreat on the Role of Professional Associations and Scientific Societies," regarding the need to establish a common standard for measuring and evaluating success of diversity-enhancing programs. The workshop further addresses the need to establish a more comprehensive and cohesive effort needed to track the many and various efforts of government (federal, state, and local), foundations, universities, scientific societies, and professional associations. Systematic data collection would allow possible answers to broad and important questions such as: To what extent research training should be supported collaboratively? What are the best practices that could be adapted that would allow for a maximum increase on the return on investment?

Title: **Perioperative Pelvic Floor Rehab: A Randomized Trial**
P.I.: **Holly E. Richter**
Institution: **University of Alabama at Birmingham**
Grant No.: **HD041261-12**
Award: **$25,000**

The University of Alabama at Birmingham (UAB) is seeking to successfully compete in the third cycle of the NICHD sponsored Pelvic Floor Disorders Network. As a part of this important research infrastructure we have demonstrated our credible, productive, multidisciplinary clinical approach to the evaluation and treatment of women with pelvic floor disorders including urinary and fecal incontinence as well as pelvic organ prolapse. We have substantially contributed to the Network activities by participating at all levels of clinical trial design, implementation, recruitment, intervention implementation, retention and scientific reporting. We have reported outcomes and implication for care of these research initiatives at national and international scientific meetings and we are committed to continuing these activities. Through this application with its concept proposal, we wish to highlight our ability and commitment to continue these meaningful research activities. Current common treatment options for fecal incontinence (Fl) include behavioral therapy consisting of pelvic muscle exercises, diet and defecatory strategies and surgical approaches including anal sphincter repair, artificial bowel sphincter and as a last resort, colostomy. A significant proportion of women with Fl, however, do not gain benefit from behavioral therapy or sphincter repair yet do not wish to undergo colostomy. As the population of post-reproductive women continues to increase, it is imperative to study other treatment options that improve quality of life for this condition. An existing modality called sacral neuromodulation (SNM, Interstim®) has been FDA approved and utilized for the treatment of refractory urge incontinence. Two small randomized trials and several cohort studies have shown efficacy of sacral neuromodulation for the treatment of refractory Fl (although it is not yet FDA approved for this indication). We propose a randomized trial to credibly characterize the effect of SNM on Fl episodes, symptom specific quality of life, effect on other pelvic floor symptoms, sexual function, predictors of response, adverse events, cost effectiveness and the role of biomarkers in optimal and suboptimal responses to this treatment. This information will allow us to

more effectively individualize treatment for women with this condition. RELEVANCE: In order to improve on the care and individualized treatment for women with pelvic floor disorders, it is important that a credible research program exists that helps guide provider care. The Pelvic Floor Disorders Network (NICHD) performs such research and we are competing to continue to participate in this important initiative. As a part of this application, we propose a concept describing a randomized trial of sacral neuromodulation for the treatment of women with fecal incontinence refractory to current standard of care treatments. This exciting new treatment modality may help a cohort of women with diminished quality of life.

Title: **Pelvic Floor Disorders Network—Duke University Clinical Site**
P.I.: **Anthony G. Visco**
Institution: **Duke University**
Grant No.: **HD041267-13**
Award: **$25,000**

Pelvic floor disorders research at Duke University Medical Center (DUMC) is sophisticated and comprehensive with committed investigators addressing issues of great importance to women. DUMC has a tradition of excellence in clinical care, training and research in pelvic floor disorders and includes one of the nation's first accredited fellowship programs in the field. DUMC offers detailed evaluation and treatment in a high-volume, multidisciplinary setting that serves as a tertiary referral center for women across the southeast US. Each of the five Duke urogynecology investigators is fellowship-trained with expertise in both surgical and non-surgical management of urinary incontinence (Ul), pelvic organ prolapse (POP), fecal incontinence, and defecatory dysfunction. Last year, our Division cared for more than 1550 new patients and performed more than 400 surgical procedures for Ul and 270 for POP. Our patient population is 80% Caucasian, 15% African American, 2% Asian and 2% Hispanic, from both suburban and rural communities with stable care and follow-up patterns. DUMC is the hub of a multidisciplinary team of outstanding collaborative investigators in urogynecology, urology, colorectal surgery, gastroenterology, maternal-fetal medicine, physical therapy and epidemiology. DUMC offers a wide range of diagnostic resources: multi-channel urodynamic testing, video urodynamics, cystoscopy, defecography, pelvic MRI, endoanal ultrasound, and needle electromyography. During the current PFDN cycle, DUMC-initiated three active RCTs: 1. Anticholinergic vs Botox RCT (ABC, Dr. Visco, currently enrolling), Interstim vs Botox RCT (ROSETTA, Dr. Amundsen, full protocol), and a RCT evaluating transvaginal mesh for prolapse repair (Dr. Weidner, mini-protocol planned for fall of 2010. DUMC has consistently been a high recruitment site across a wide range of non-surgical and surgical studies with unparalleled retention rates. We have proven our ability to support and successfully complete large-scale, multi-centered investigations through our robust clinical practice and exceptional research infrastructure. Accordingly, Duke University Medical Center is well equipped and uniquely qualified to continue as a valuable and productive member of the Pelvic Floor Disorders Network. RELEVANCE: Female pelvic floor disorders represent a major public health burden given their high prevalence, impairment of quality of life, and

substantial economic costs. As part of the Pelvic Floor Disorders Network, Duke University Medical Center is committed to actively participating in innovative clinical trials aimed at improving the evaluation and treatment of pelvic floor disorders through high-quality, high-impact clinical research.

Title: **Pelvic Floor Disorders Network**
P.I.: **Charles William Nager**
Institution: **University of California at San Diego**
Grant No.: **HD054214-07**
Award: **$25,000**

The objectives and aims of this application are for the San Diego site to continue its work In the Pelvic Floor Disorders Network (PFDN). The unique strength of our application is our proven two site model, which combines the strengths of 7 academic investigators at both a tertiary medical center and a large volume HMO. We would like to provide leadership, continuity, innovation, academic expertise, a captured diverse patient population, and a proven research infrastructure to the network. We have a track-record of being the top 2 recruitment in surgical trials for pelvic floor disorders and we want to continue that into the third cycle of the PFDN. As noted in the RFA, "In many cases, clinicians caring for women with pelvic floor disorders have adopted principles of care and surgical techniques before rigorous, objective, controlled evaluation has taken place. New devices and techniques have had a dramatic influence on surgical practice...". Our study addresses this concern. Vaginal mesh is probably the most controversial topic in pelvic floor disorders and a strong argument can be made that the PFDN is the best group to study it. A growing-trend of women is seeking uterine sparing surgery for prolapse and a growing trend of gynecologists and urologists are managing uterine prolapse with vaginal mesh kit procedures. Our proposed randomized trial of uterine sparing, grafted vaginal apical suspension vs. traditional hysterectomy with native tissue suspension addresses the very important question of whether it is necessary to remove the uterus to treat uterine prolapse. This proposed study recognizes the role of new devices and techniques that are changing our care of women with pelvic floor disorders. Our comprehensive outcome measures should allow us to answer whether these new uterine-sparing, apical vaginal procedures are reasonable alternatives to conventional vaginal hysterectomy and native tissue suspension. RELEVANCE: Our site's participation in the next cycle of the PFDN should allow successful network recruitment for surgical trials. Uterine prolapse is a very common pelvic floor disorder and we should determine the best vaginal surgical treatment for this condition. This proposed research study will answer whether uterine-sparing procedures are reasonable alternatives to hysterectomy for this condition.

Title: **Cleveland Clinic Clinical Site**
P.I.: **Matthew Barber**
Institution: **Cleveland Clinic Lerner College of Medicine**
Grant No.: **HD054215-07**

Award: $25,000

The goal of the Pelvic Floor Disorders Network (PFDN) is to identify optimum diagnosis and management strategies for women with pelvic floor disorders (PFD) using the highest quality research methods available. The Cleveland Clinic offers a stable academic and research-oriented environment for the conduct of PFDN studies including experienced investigators with complementary clinical and research backgrounds that have a particular interest and a successful history of conducting clinical trials evaluating both surgical and nonsurgical therapies for women with PFD. The specific aims of this application are: 1) to demonstrate that the Cleveland Clinic (CC) Clinical Site has contributed substantially to the academic, administrative, and clinical aspects of the PFDN since joining in its 2nd 5-year cycle; that it possesses the personnel, patient, clinical and administrative resources needed for successful participation; and that continued participation would be advantageous to the successful attainment of the Network's scientific goals and 2) to present a concept proposal for potential conduct by the PFDN. We propose evaluating the comparative effectiveness of sacrospinous hysteropexy (SSH), the most well-studied uterine-sparing pelvic organ prolapse (POP) surgery, relative to total vaginal hysterectomy with sacrospinous ligament fixation (TVH/SSLF), a commonly used hysterectomy-based vaginal uterovaginal prolapse procedure. The specific aims of the concept proposal are: 1) compare the anatomic, functional, sexual and health-related quality of life outcomes of SSH to TVH/SSLF in women undergoing surgery for Stage 2-4 POP uterovaginal prolapse 2 years after surgery; 2) compare surgical recovery and short- and long-term morbidity of SSH and TVH/SSLF in these same women and 3) determine the incremental cost-effectiveness of SSH compared to TVH/SSLF for the treatment of Stage 2-4 POP. Enrolled subjects will be randomized in the operating room on the day of surgery to receive either SSH or TVH/SSLF (1:1) using a random permutated block design. Randomization will be stratified by surgeon to account for the varying experience and expertise. Subjects and study coordinators will be blinded to treatment assignment until completion of the study. RELEVANCE: Nearly one quarter of all women report symptoms of at least one PFD, including prolapse. POP is the most common indication for hysterectomy in postmenopausal women and it is unknown whether the addition of hysterectomy to POP surgery is integral to successful surgical outcome. The results of our concept proposal could justify or eliminate the need for as many as 70,000 hysterectomies in the US each year.

Title: Uterine Leiomyoma Research Center Program
P.I.: Serdar E. Bulun
Institution: Northwestern University at Chicago
Grant No.: HD057877-04
Award: $250,000

Uterine leiomyomata (fibroids) represent the most prevalent benign gynecologic disorder in the US. The cellular and molecular mechanisms regulating the development and growth of leiomyoma are not well understood. Our multidisciplinary team has designed 3

well-integrated projects focusing on Interactions between biologically critical hormonal pathways in uterine leiomyoma involving the transcription factors progesterone receptor (PR) and FOXO, the signaling pathway PI3K/AKT and the pro-fibrotic factor TGF-beta. Project I (Bulun) will be pursued to understand the mechanisms as to how antl-progestins such as RU486 reduce tumor size. We hypothesize that progesterone regulates a number of critical genes, that favors increased proliferation and decreased apoptosis of leiomyoma smooth muscle cells, whereas anti-progestins reverse this effect by enhancing apoptosis and decreasing proliferation. Project II (Kim/Chakravarti) will determine the role of the PI3K/AKT/F0X0 signaling pathway regulating leiomyoma cell growth and survival in response to progesterone. We hypothesize that progesterone Induces proliferation of leiomyoma cells through activation of the PI3K/AKT/F0X0 signaling pathway and that Inhibitors of the AKT pathway should override the proliferative effects of progesterone and promote apoptosis. Project III (Nowak) will define the mechanisms as to how antifibrotic drugs regulate leiomyoma growth. We hypothesize that the Increased proliferation exhibited by leiomyoma smooth muscle cells Is due to a major shift in the extracellular matrix environment caused by increased synthesis of new, monomeric collagen type I by these cells. We will determine whether antifibrotic drugs may be an effective new treatment for leiomyomas. These projects are supported by an Administrative Core (Bulun) and Tissue Procurement and Cell Culture Core (Kurita). Overall, as part of our long range goal, all projects investigate local hormonal signaling regulating apoptosis and proliferation as biologic endpoints and test existing and upcoming pharmaceutical compounds that target these pathways in uterine leiomyomata.

Title: **Wireless Remote Abdominal Pressure System: Developing a More Comprehensive Understanding of Physical Activity and Its Association with Incidence, Progression, and Recurrence of Pelvic Floor Disorders**
P.I.: **Ingrid E. Nygaard**
Institution: **University of Utah**
Grant No.: **HD061787-04**
Award: **$66,667**

Pelvic floor disorders affect one in four American women. Few modifiable risk factors have been identified that might reduce the incidence or progression of pelvic floor disorders. Popular wisdom and scant clinical data suggest that strenuous activity causes or promotes pelvic floor disorders. Given the health benefits of activity, women should be encouraged to be maximally active unless there is scientific evidence to the contrary. Existing physical activity instruments are largely designed to assess cardiovascular exertion and are validated using activity diaries, accelerometers, and step counters. Such measures may not accurately measure activities that increase loading on the pelvic floor (such as lifting). After researching available technologies, we concluded that a tool to understand how physical activities impact abdominal pressure in the real world does not exist. Over the past 18 months, our interdisciplinary team of bioengineers, urogynecologists, electrical engineers, and exercise scientists developed and validated the performance of a prototype for an intravaginal abdominal pressure sensor that accurately

measures pressure in the upper vagina, an easily accessible space that records pressures similar to the true intraabdominal pressure. In this proposal, we plan first to further develop an integrated system (the "WRAPS", Wireless Remote Abdominal Pressure System) to monitor intraabdominal pressure outside of the clinical setting. This system will consist of three key elements: an intravaginal pressure sensor with wireless data transmission capability, a small portable data monitoring and storage unit, and computer based data translation software for downloading and managing the pressure data. In a controlled exercise laboratory setting, we will then use intraabdominal pressure data generated by the WRAPS to determine the reproducibility of intraabdominal pressures measured during specific types of physical activity and will finalize development of a valid questionnaire that categorizes the magnitude of intraabdominal pressures during activities. Finally, in a real-world setting in which participants wear the intravaginal sensor during waking hours for four 1-week periods over the course of a year, we will characterize intraabdominal pressures experienced by women of varying degrees of habitual physical activity and, using WRAPS data as the gold standard, determine whether activity can be appropriately categorized in terms of pelvic loading by means of self-administered questionnaires, the current standard. Obtaining future evidence about the impact of physical stressors on pelvic floor disorders relies on our ability to measure the risk factor in question. This innovative translational collaboration will remove a critical barrier to progress in understanding the etiology of pelvic floor disorders in women.

Title: **Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team**
P.I.: **Pamela A. Moalli**
Institution: **Magee-Womens Research Institute and Foundation**
Grant No.: **HD061811-04**
Award: **$66,666**

Comprehensive Evaluation of Prolapse Meshes by an Interdisciplinary Research Team
Each year roughly 200,000 U.S. women undergo a surgery to repair pelvic organ prolapse (6, 7). Biologic and synthetic meshes are widely used in prolapse repairs to improve anatomical outcomes over native tissue repairs which currently have a failure rate of over 30%. To date, however, there is little scientific data to guide surgeons in the selection of a particular product. As a result, meshes are used based on the recommendations of a local vendor and consequently, are placed in women on a trial and error basis. There is growing evidence, however, that the complications associated with prolapse meshes cause unacceptably high rates of morbidity including infection, mesh shrinkage, mesh erosion, mesh exposure, pelvic, rectal and bladder pain and dyspareunia. Such complications have become significant enough for the FDA to recently release a warning about mesh use, especially when it is placed transvaginally. In this proposal, we therefore, aim to establish an interdisciplinary team of scientists dedicated to the comprehensive testing of previously or newly marketed prolapse meshes and for the development of the next generation of graft materials based on specific scientific criteria. In the first phase of the study, we determine how biochemical and structural changes in

the prolapsed vagina impact passive and active mechanical behavior so as to develop a mesh in which these deficiencies are repaired or compensated for, allowing us to restore the prolapsed vagina to the nonprolapsed condition. In the second phase, we hypothesize that the shortcoming of current prolapse meshes is that they are too stiff. While this results in a repair with increased tensile strength, it occurs at the expense of tissue function with accelerated tissue contraction, decreased elasticity and compliance, and deterioration of smooth muscle function. To test our hypothesis, we implant commonly used synthetic prolapse meshes into the vagina of nonhuman primates with prolapse using the gold standard surgical procedure (the abdominal sacrocolpopexy) and then define the cellular, biochemical and biomechanical impact on the vagina at 6 months post implantation. Eventually, we will implant meshes transvaginally to characterize the distinct host response to this surgical approach. In the third phase, we explore the development of future grafts for prolapse surgery. We hypothesize that because of its bioinductive effects, a combined biologic/synthetic mesh will be superior to a synthetic mesh alone in restoring vaginal structure and function. We propose that a key yet poorly developed component of prolapse repairs is the re-establishment of smooth muscle reactivity and therefore, test the use of a temporary biologically active scaffold in achieving this process. In this way, this grant proposal provides a mechanism to establish the first team of scientists dedicated to the comprehensive unbiased evaluation of prolapse meshes as a means of educating both current and future prolapse surgeons, and the public regarding potential problems associated with certain materials. Indeed, the development of such a group is imperative for protecting the health of women.

Title: **Identification of Genes Predisposing to Pelvic Floor Disorders**
P.I.: **Lisa Cannon Albright**
Institution: **University of Utah**
Grant No.: **HD061821-04**
Award: **$66,667**

The investigators propose a unique and powerful collaboration between basic and clinical scientists in Utah to identify genes affecting predisposition to pelvic organ prolapse (POP). The co-PIs both have significant experience, Dr. Norton in Pelvic Floor Disorder (PFD) genetics and Dr. Cannon-Albright in predisposition gene identification. The investigators will access the Utah Population Database, a computerized genealogy of Utah combined with decades of medical data from the two largest healthcare systems in Utah (serving 90% of the state), to identify and recruit surgically treated cases of POP (1,250 cases in 5 years). All POP cases sampled will be genotyped with the Illumina 610Q SNP marker set. The PIs will apply multiple different genetic analyses to this resource of genotyped POP cases to aid in the identification of predisposition genes. The record linkage of medical procedure codes (identifying surgeries performed on each patient) to individual genealogy data allows us to identify all genetic relationships among the POP cases. We will perform genome-wide association analysis, using software we have developed which allows inclusion of both independent and related cases. We will identify all genetic relationships between the sampled POP cases and perform linkage analysis in informative, high-risk POP pedigrees. We will identify chromosomal regions

shared Identical by Descent (IBD) in very distantly related cases in these pedigrees, and we will identify IBD sharing within the small subset of POP cases (2%) who are inbred. Initial collaborative analysis of data obtained by Dr. Norton's NIH funded study of affected PFD sib-ships has already provided significant evidence for a predisposition gene localization on chromosome arm 9q, and suggestive evidence for at least one other locus on chromosome 1. In summary, we will create a population-based resource of surgically treated POP cases, we will pursue established and new methods to identify and localize predisposition genes affecting POP, and we will begin a detailed search for the chromosome 9 gene we have localized.

Title: **Genetic Determinants of Uterine Fibroids in African-American and Caucasian Women**
P.I.: **Brahim Aissani**
Institution: **University of Alabama at Birmingham**
Grant No.: **HD064398-03**
Award: **$83,333**

Uterine leiomyomas (ULs) are the most common pelvic tumors in women of reproductive age, accounting for over 600,000 hysterectomies annually in the United States. Several lines of evidence support a genetic liability in the pathogenesis of ULs, yet no susceptibility gene is known. Advances in research on the genetics of ULs (fibroids) have so far been limited by the paucity of genetic epidemiologic studies and infrastructure to conduct them. The goal of this epidemiologic study is to evaluate the contribution of a region of Chr.1q43 that predisposes to uterine fibroids but remains inadequately investigated. Genetic predisposition to ULs has been studied primarily in the context of two rare inherited autosomal-dominant conditions, the hereditary leiomyomatosis and renal cell cancer (HLRCC) and the multiple cutaneous and uterine leiomyomatosis (MCUL1) syndromes, where germline mutations were found in the gene on Chr. 1q43 encoding the tricaboxylic acid cycle (Krebs cycle) fumarate hydratase (FH) enzyme. However, a direct role of this important metabolic housekeeping gene in tumorigenesis remains to be proven. Inactivating FH mutations have rarely (< 1-2% of the tumors analyzed) been observed in nonsyndromic (common) ULs; however, loss of FH appears to be a significant event in the pathogenesis of a subset of these tumors. Furthermore, several observations support the existence of an alternative or additional candidate gene on Chr.1q43 acting alone or interacting with FH to increase the risk of ULs in susceptible individuals: 1) the absence of FH genotype-phenotype correlations, 2) the marked genetic heterogeneity in ULs, and 3) the failure to observe ULs or multiple leiomyomatosis in siblings or parents of cases with fumarase deficiency, a severe recessive disorder. Taken together, these observations underscore the importance of exploring an extended FH region in a population-based study of ULs. To this end, we will generate a high-density single nucleotide polymorphism genotyping data across a 2-Mb region spanning FH in subsets of African American (n=582) and Caucasian (n=455) women enrolled in the NIEHS-Uterine Fibroids Study. This is a well designed cross-sectional study of ULs that includes data on most potential confounders. Our study is not intended to shift any paradigm about the origins of ULs; rather it will extensively investigate the role of FH in

nonsyndromic ULs, dissect the intricate genetic correlates of Chr.1q43 markers in the expression of the disease phenotype and evaluate their effects in two populations with a marked difference in disease risk. Recent updates in the genome databases have revealed new potential candidate genes for tumor growth and important structural variations including a large (~ 308 Kb) copy number variation in the vicinity of FH; these new findings further justify a study with the proposed depth and extent of genetic coverage. This study will likely open new avenues for research and may ultimately redirect current preventive and therapeutic approaches or enhance their efficacy.

Title: **Xenograft Study on Growth Control of Human Uterine Leiomyomata**
P.I.: **Takeshi Kurita**
Institution: **Northwestern University at Chicago**
Grant No.: **HD064402-03**
Award: **$83,333**

The ultimate goal of this study is to elucidate the molecular mechanisms of uterine leiomyoma (UL) formation and growth, and identify potential targets for novel therapeutic and preventive treatments of this disease. UL is a benign tumor of the myometrium that affects millions of reproductive-age women. Surgical removal of the entire uterus (hysterectomy) is the primary treatment option, and management of UL puts an enormous burden on the healthcare system. Therefore, finding a new therapeutic treatment replacing surgery is of great interest to the public. Due to the absence of a proper research model system reflecting characteristics of the original tumors, the biological nature and the causes of UL are poorly understood. Although growth dependency of UL on ovarian steroids (172-estradiol and progesterone) is well established, the relative importance and function of 172-estradiol and progesterone are yet to be clarified. In spite of accumulating evidence for the essential role of progesterone in UL growth, no research model has clearly demonstrated a growth-promoting effect of progesterone on UL. To elucidate the function of ovarian steroids in UL, we have established a novel xenograft model in which tissue fragments of human leiomyoma were grafted beneath the renal capsule of immunodeficient mice. The size of the leiomyoma xenografts increased in response to 172-estradiol and progesterone as demonstrated by cell proliferation and accumulation of extra-cellular matrix. In contrast, xenograft growth induced by 172-estradiol and progesterone was blocked by the anti-progestin RU486, indicating the essential role of progesterone and progesterone receptor (PR) in leiomyoma tumor growth. Previously, 172-estradiol has been thought to be the primary stimulus for UL growth. Surprisingly, 172-estradiol by itself neither increased nor maintained tumor size. Likewise, progesterone alone did not affect UL growth in this model. Although not mitogenic, 172-estradiol was required for expression of PR, and was essential for progesterone to act on UL xenografts. Our study clearly demonstrates the pivotal role of progesterone in growth and maintenance of UL. The results of our xenograft model agree with clinical observations, yet radically change the paradigm of steroid hormone-regulated human UL growth by emphasizing the importance of progesterone instead of 172-estradiol. Using the novel xenograft model, we will elucidate

the cellular and molecular mechanisms of human UL tumor growth controlled by 172-estradiol and progesterone.

Title: **Achieving a Critical Mass of Women Biomedical Faculty: Impact of Three U.S. Programs**
P.I.: **Deborah Lynne Helitzer**
Institution: **University of New Mexico**
Grant No.: **HD064655-04**
Award: **$175,144**

Although there are numerous career development programs for women faculty, women continue to leave academic medicine at alarmingly high rates. This study will examine the impact on retention and career success of individual women faculty who participated in three long-standing national programs, each of which targeted a separate career stage, as compared to women and men, at the same career stages, who did not participate in these programs. This research also aims to elucidate the patterns and processes that contribute to the experience of individuals and their institutions as a means to identify the barriers and facilitators—historic and new, individual and institutional—that face women faculty in attaining positions of leadership at academic health centers (AHCs) and transforming institutional culture. Informed by the guidance of an Advisory Board composed of highly respected female and male senior leaders in academic medicine, the goal of the research is to assess the impact of participation in intensive career development training programs on individual women faculty at early and mid-career stages and their institutions, in terms of retention and promotion, while verifying and illuminating the ways in which participation in these programs affect career trajectories. We will attempt to discover how the findings on retention, academic promotion and administrative advancement are influenced by (i) individual dynamics and personal/professional development factors addressed in leadership development programs; (ii) organizational factors in institutions that send their women faculty to such programs; (iii) how these factors may have led to enhancement of leadership development and gender experience for women participating in these programs; and (iv) how the interaction of these factors has or can lead to a change in organizational culture to ensure the ability of institutions to capitalize on the intellectual capital of women science faculty members. Along with this retrospective analysis, we will prospectively identify new emerging challenges that affect women Assistant and Associate Professors attending intensive career development programs, and create an infrastructure for future research on retention and promotion. Additionally, this study will provide a comprehensive set of findings which can serve as the basis for a future design of an innovative women-focused leadership program as well as providing helpful information on the culture change needed to improve recruitment and retention of America's leading scientific minds.

Title: **A Controlled Trial of Gabapentin in Vulvodynia: Biological Correlates of Response**

P.I.: **Candace S. Brown**
Institution: **University of Tennessee Health Science Center**
Grant No.: **HD065740-02**
Award: **$200,000**

Approximately 14 million U.S. women have provoked vestibulodynia (PVD), a type of localized vulvar pain which causes major disruption in the everyday lives of up to 60% of affected women and negatively impacts sexual function in 45%. The financial burden imposed on the health care system is also significant, as these women visit multiple clinicians and specialists, and try numerous, unproven treatments. To date, few randomized controlled trials (RCTs) have been conducted to establish evidence based protocols for PVD management. The first immediate goal is to conduct a multicenter RCT of gabapentin treatment for PVD. Gabapentin was selected because of its efficacy in treating other neuropathic pain conditions and the promising, preliminary data on its use in PVD. This is a significant research project because PVD is a highly prevalent, chronic pain condition that is costly to the health care system and that currently has limited management options available to affected women. The second immediate goal is to define psychophysiologic measures of gabapentin response and to define mechanistically-based PVD subtypes, which may be related to abnormalities in central sensitization, muscle hypertonicity, and autonomic dysregulation. Identifying predictors of treatment response in PVD would have clinical applicability to other chronic pain syndromes, and is consistent with NIH's mission to investigate coexisting pain conditions in order to identify common etiological pathways and develop therapeutic targets. The specific aims are (1): to test the prediction that pain from tampon insertion (primary outcome measure) is lower in PVD patients when treated with gabapentin compared to when treated with placebo. Additional outcome measures include reported intercourse pain and 24-hour pain, and (2) to test the prediction that gabapentin treatment will reduce mechanical allodynia, reduce area and duration of hypersensitivity induced by intradermal capsaicin, reduce vaginal muscle pain to palpation, decrease the number and intensity of somatic tender points, and increase cardiac beat-to-beat variability. This 16-week, randomized, double-blind, placebo-controlled, crossover study will enroll 120 women between 18-50 years of age who report tenderness localized to the vulvar vestibule, pain with tampon insertion, and, when sexually active, insertional dyspareunia. Electronically entered daily diaries will be used to determine if pain is lower in PVD subjects when treated with gabapentin (up to 3600 mg/d) compared to when treated with placebo. The approach is innovative because it focuses on an understudied condition, in a multicenter setting, using a novel outcome measure (the tampon test), and a newly developed web-based recruitment and patient-reporting tool. Data management will include a mechanism-based analysis of drug effectiveness. These study outcomes will ultimately lead to our long-range goal of identifying underlying pathophysiologic mechanisms of PVD in order to create evidence-based differential diagnoses of subtypes of PVD for more effective and cost-effective management options.

Title: **Pittsburgh Pelvic Floor Research Program**
P.I.: **Halina M. Zyczynski**

Institution: Magee-Womens Research Institute and Foundation
Grant No.: HD069006-02
Award: $25,000

The purpose of this proposal is to demonstrate the capabilities of the University of Pittsburgh to participate as a clinical site in the NICHD-sponsored Pelvic Floor Disorders Network (PFDN). Our site has a longstanding track record of successful contribution to multicenter studies of urinary and fecal incontinence, and pelvic organ prolapse. We are particularly well suited to be a clinical site in the PFDN because of our volume, research infrastructure and track record, basic and translational experience and expertise. Access to large numbers of nulliparous women enables us to contribute uniquely to studies of the role of pregnancy and parturition in the etiology and prevention of pelvic floor disorders (PFDs). Magee-Womens Hospital (MWH) is the central resource for gynecologic specialty care for the 19 hospital University of Pittsburgh Health System serving a very large aging population. Our site brings expertise in urogynecology, physical therapy, geriatrics, urology, gastroenterology and mental health. We offer unique technical expertise in genomics, proteomics, tissue regenerative techniques, biochemical and biomechanical impact of meshes on the vagina and central neuronal control of bladder function. We propose to establish a comprehensive, scientifically rigorous clinical and translational research program within the PFDN for prospective comparative studies of mesh materials used in prolapse and incontinence procedures. The program will generate data of immediate clinical relevance as it will present scientifically sound, vendor independent evidence to guide surgeons' selection of specific graft materials and evidence-based practice guidelines for management of mesh complications. The 3 major components of the proposal are: 1) mesh specific infrastructure for implementation in PFDN clinical trials employing mesh inclusive of the development of a Mesh Morbidity Index and establishment of a Biospecimen Repository 2) the first RCT of meshes selected through rigorous analyses of biomechanical and biochemical properties and 3) translational studies on the cellular response to mesh materials and pathophysiology of mesh complications. The RCT will serve to pilot the database, compare clinical outcomes of meshes whilst providing specimens for translational studies.

Title: Pelvic Floor Disorders Network Clinical Sites
P.I.: Lily A. Arya
Institution: University of Pennsylvania
Grant No.: HD069010-02
Award: $25,000

The goal of this application is to competitively identify clinical sites to conduct clinical trials for female pelvic floor disorders. This application from the University of Pennsylvania with Lily Arya MD, MS (Epidemiology) as Principal Investigator demonstrates our research plan for a new treatment for urge urinary incontinence, myofascial physical therapy. This potentially effective and safe method will greatly enhance treatment choice and improve the quality of life of women with urge urinary incontinence. This application outlines our extensive experience with similar large multi-

center clinical trials. We highlight our ability to recruit and maintain subjects in female pelvic floor disorder clinical trials, noting we have been one of the leading recruitment centers in the nation for similar trials. We have often been able to recruit a greater number of subjects than our original estimates. The facilities at the University of Pennsylvania are supportive and outstanding. Our existing research unit and personnel has continuously demonstrated highly successful management of large clinical trials with outstanding organization, attention to detail and compliance with Good Clinical Practice, federal regulations and local Institutional Review Boards. Dr. Arya is an active researcher in the field of health measurement for pelvic floor disorders and she has successfully conducted a number of clinical trials in women's health. Specifically, she and her team of co-investigators and staff have been actively involved in surgical and non-surgical trials for urinary incontinence. She will bring significant expertise regarding study design and health measurement research to the Pelvic Floor Disorders Network. She leads a team of co-investigators who have a track record of collaborative clinical and translational research. We feel that the combination of a high quality personnel, experience in the research area, ability to recruit, and outstanding management and organization will contribute to a high likelihood of successful completion of this and future trials of treatment methods of pelvic floor disorders. RELEVANCE: The University of Pennsylvania has the expertise, infrastructure and experience to be a significant contributor to the Pelvic Floor Disorders Network. The proposed study, to investigate the efficacy of a new treatment for urge urinary incontinance, will improve quality of life of women with urge incontinence and result in considerable savings of health care resources.

Title: **Brown/WIH Pelvic Floor Disorders Network Site**
P.I.: **Deborah Lee Myers**
Institution: **Women and Infants Hospital of Rhode Island**
Grant No.: **HD069013-02**
Award: **$25,000**

The mission of the PFDN is to identify optimal diagnosis and management strategies for women with pelvic floor disorders (PFDs) and this is directly in line with Women and Infants Hospital (WIH)/Brown's mission and commitment. WIH is a women's hospital, focused solely on advancing women's health and research and our extremely high volume, stable patient base, expertise of our multi-disciplinary collaborative and established research infrastructure provide the ideal environment to conduct large-scale, clinical research at the highest level. The aim of this application is for WIH/Brown to become the first PFDN site in New England by demonstrating: 1)our academic productivity and experience in multi-site, collaborative surgical, pharmaceutical and non-surgical clinical trials; 2)highly committed investigators with expertise in research methods and a specialized research team qualified to conduct multiple protocols, manage high quality data, and maintain high recruitment and retention; 3)a long-standing, formal relationship with multi-disciplinary collaborators committed to advancing the care of women with PFDs led by Urogynecology (including Urology, Colorectal surgery, Women's Gastroenterology, Women's Physical Therapy, and Women's Radiology); and

4)our high clinical volume (In 2009, the Division of Urogynecology evaluated 1211 new patients and performed 583 PFD surgical procedures; vaginal, abdominal, laparoscopic and robotic approaches are all represented). We present a concept proposal describing a 3-stage, randomized trial of a combined non-surgical and surgical approach to treatment of mixed urinary incontinence (MUl) in women who have failed conservative therapy and/or elect surgical treatment. Women suffering from MUl are at high risk for failure of segregated treatments and are often excluded from clinical trials focused on either stress or urge urinary incontinence alone. Clinical management of MUl remains a challenge and trials targeting this population are urgently needed. WIH has a long-standing history of supporting network collaboratives and our goal is to participate and become a leader in the PFDN in terms of protocol development and completion, data interpretation and quality, recruitment and retention and high quality dissemination of findings. RELEVANCE: Female pelvic floor disorders including urinary incontinence, pelvic organ prolapse and fecal incontinence are common, disabling conditions and are a significant public health issue. Although a variety of treatment options exist, high quality evidence to guide clinical management and to improve treatment specificity is still needed. Through the PFDN, WIH/Brown is committed to advancing high quality scientific evidence to help improve the care of women and reduce the burden of these disorders.

Title: **RCT of Hypnotherapy vs. Tpolterodine for OAB: Voiding and Brain Activation Changes**
P.I.: **Rebecca Glenn Rogers**
Institution: **University of New Mexico Health Sciences Center**
Grant No.: **HD069025-02**
Award: **$25,000**

The University of New Mexico (UNM) proposes to join the Pelvic Floor Disorders Network (PFDN) to achieve the Network's primary goal of conducting rigorous, multi-center clinical trials to investigate the clinical and health aspects of pelvic floor disorders in women. Our site, in collaboration with other Network sites, aims to reduce the burden of pelvic floor disorders on women and their families. Through the design of innovative trials and participation in ongoing studies, the UNM PFDN site will make significant contributions to the Network. Dr. Rogers, Principal Investigator, and Dr. Komesu, Alternate Principal Investigator, have extensive experience in the design and conduct of multi-center randomized trials and proven leadership and productivity. The UNM PFDN site brings to the Network a busy clinical service with large numbers of under-represented Hispanic and Native American populations, as well as broad institutional support from the Department of Obstetrics and Gynecology and a recently funded Clinical and Translational Research Center. The concept proposal, based on preliminary data generated by our site and the work of others, is an innovative investigation comparing hypnotherapy to long-acting anticholinergic medicine for the treatment of overactive bladder (OAB). In addition to the hypnotherapy comparative-effectiveness trial, the concept proposal focuses investigation into the underlying mechanisms of OAB on the brain, using functional magnetic resonance imaging (fMRI). This translational,

comparative effectiveness clinical trial is an excellent example of cutting edge research that the UNM PFDN site will bring to the Network. Skilled investigators, a busy clinical practice, unique patient populations and broad institutional support make UNM a worthy new clinical site for the PFDN. RELEVANCE: Pelvic floor disorders are common and costly. Performance of rigorously designed, target randomized clinical trials that inform evidence-base health care practices for women with pelvic floor disorders is best done through collaboration with other clinical sites. The University of New Mexico is a highly productive clinical and research site and proposes to join the Pelvic Floor Disorders Network in order to meet the Network's goal of investigating innovative solutions to these common problems.

Title: **Unintended Birth, Fetal, and Infant Loss and Maternal Depressive Symptoms**
P.I.: **Pamela J. Surkan**
Institution: **Johns Hopkins University**
Grant No.: **HD069731-01A1**
Award: **$81,000**

Depression is the most prevalent mental health disorder and globally is two times more likely to occur in women. In rural areas of Bangladesh, women's autonomy in planning pregnancy and the likelihood of successful pregnancy remain uncertain, with stillbirth, perinatal and neonatal death occurring at over five-fold higher rates than in developed countries. These rates are likely to be higher for rural women with little access to medical care. Our aims are to study: 1) the relation of unintended pregnancy to maternal depressive symptoms in the third trimester of pregnancy and at six months postpartum; 2) the relation of unintended pregnancy and fetal and neonatal loss to postpartum maternal depressive symptoms; 3a) whether the relation of unintended pregnancy with postpartum maternal depressive symptoms differs by gender of the offspring; and 3b) whether the relation of fetal or neonatal loss with postpartum maternal depressive symptoms differs by gender of the offspring. Miscarriage, stillbirth, perinatal death, and neonatal death will be examined separately as risk factors. The proposed secondary analysis uses data from a population-based, randomized antenatal micronutrient supplementation trial conducted from 2001 to 2007 in northwestern rural Bangladesh among ~60,000 pregnant women. Women were enrolled in early gestation and followed through 6 months postpartum. Pregnancy outcomes and infant vital status were monitored weekly through 3 months of age. In the third trimester and at 6 months, symptoms of depression were elicited by maternal responses to questions about common depressive symptoms as well as about suicide. Statistical methods will include descriptive analyses and calculation of adjusted risk ratios to examine unintended pregnancy and fetal and neonatal death events as predictors of subsequent depressive symptoms. We will assess the effects of pregnancy intent from each parent as well as discordance between maternal and paternal pregnancy intentions on maternal depressive symptoms. Documentation of unintended pregnancy and loss of a fetus or infant as risk factors for depressive symptoms in a large South Asian population will help to show their extent and guide interventions relevant to a

vulnerable period when maternal mental health is critical for the healthy development of her other children.

Title: **Consortium to Evaluate a Novel Violence Prevention Program on College Campuses**
P.I.: **Corrine M. Williams**
Institution: **University of Kentucky**
Grant No.: **HD069897-01A1**
Award: **$180,193**

Up to 25% of women may be sexually assaulted during college, and one-third of college students have experienced physical aggression from dating partners. While most students neither participate in nor condone violence, many respond passively to a campus culture that may tacitly support violence, as evidenced by violent media images, jokes trivializing violence against women, and sexual harassment. Growing awareness that all members of the campus community can play a significant role in ending dating and sexual violence (DV/SV) has led to an increase in violence prevention interventions for college students. However, very few of these programs have been empirically evaluated. A significant barrier to progress in intervention research is the infrastructure required to implement and evaluate interventions across multiple sites. For this project, the intervention will be Green Dot, an innovative primary prevention intervention to reduce DV/SV among college students, which was developed at the University of Kentucky. The intervention consists of one-hour persuasive speeches, followed by a six to either hour bystander intervention training called Students Educating and Empowering to Develop Safety (SEEDS). In addition, we are creating booster sessions that will be provided to all students who have completed SEEDS training to assist with additional skills-building that may be required. As a developmental project, the proposed research will consist of three phases: 1) pilot work to create survey modules, resulting in a questionnaire that contains measures which are standardized across campuses to evaluate the effectiveness of the intervention and is a manageable length; 2) data collection at UK to streamline data collection procedures when other colleges are brought on; and 3) recruitment of additional implementation and control college sites. The University of Kentucky will operate as the coordinating center for the multi-site evaluation and will continue to serve as the pilot site or data collection and refinement of study methodology. The University of South Carolina has agreed to serve as an implementation site and the University of Cincinnati has agreed to serve as a control site. We will recruit an additional eight colleges (four control and four intervention sites) during the project period. By beginning with this R21 to conduct developmental work and begin problem solving, we can help to ensure the success of subsequent projects. If Green Dot is then determined to be effective across multiple campuses in preventing violence and the associated sequelae of adverse academic, as well as physical and mental health outcomes, experienced by so many college students, then the potential impact of this study is indeed groundbreaking. Additionally, the lessons learned from establishing a multi-site public health intervention trial, with one coordinating center responsible for all data collection via online surveys, has implications for the study of other health issues.

Title: **Mothers and Others: Family-Based Obesity Prevention for Infants and Toddlers**
P.I.: **Margaret E. Bentley**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **HD073237-01**
Award: **$100,000**

Despite increases in obesity among infants and toddlers, few published interventions promoting healthy diet and decreased sedentary behaviors among this age group exist. To fill this gap, we propose a randomized controlled trial among 468 Non-Hispanic black women, their families, and their child caregivers to test the efficacy of a multi-component, tailored intervention versus an attention control (child safety) in promoting healthy weight gain patterns during infancy. The proposed intervention, Mothers and Others: Family-based Obesity Prevention for Infants and Toddlers will be one of the first to meet the unique needs of individual families by delivering anticipatory guidance on infant care, feeding and growth through multiple channels and to multiple caregivers. Primary modes of delivery for the intervention arm will include face-to-face counseling through 9 home visits (1 by a certified Lactation Consultant), 6 tailored health newsletters for mothers and 6 targeted health newsletters for "other" caregivers deemed influential by mothers, as well as ~160 cue-based text messages for mothers and "other" caregivers. The control group will receive messages on child safety delivered through general newsletters and text messages. Our main outcome is infant/toddler growth, captured by mean weight-for-length z-scores (WLZ) at 18 months, mean change in WLZ between 0-18 months, and likelihood of overweight (WLZ e 95th percentile) at 18 months. Differences between groups are expected to be achieved through uptake of targeted health behaviors, including a greater likelihood of breastfeeding initiation, exclusivity and duration; after 6 months, higher dietary intakes of whole fruits and vegetables and lower intakes of energy-dense snack foods; longer durations of infant and toddler sleep and fewer night awakenings; and, lower levels of television and electronic media exposure. We further hypothesize that these targeted health behaviors will be achieved through modifiable risk factors underpinning the intervention, namely more positive breastfeeding attitudes; higher levels of parenting and breastfeeding self-efficacy; higher levels of perceived social support; higher responsive feeding style scores; improved accuracy in perceiving infant/toddler weight status; and, diminished parental perceptions of infant fussiness. We believe Mothers and Others is highly significant and innovative, as it targets a minority population at high risk of early life obesity, it begins during pregnancy, a "teachable moment" for establishing healthy behaviors, it actively engages multiple child caregivers, and it utilizes novel intervention platforms, including tailoring and text messaging. We have assembled a strong, interdisciplinary team of researchers, each with an outstanding record for implementing and publishing research relevant to this intervention. Collectively, we have experience conducting similar interventions in this population; designing, implementing and evaluating the proposed tailoring and novel technology components; recruiting and retaining a similar cohort; and measuring and

analyzing relationships between the proposed modifiable risk factors, targeted health behaviors and outcomes of early life growth.

Title: **A Pharmacokinetic Evaluation of Levonorgestrel Implant and Antiretroviral Therapy**
P.I.: **Kimberly K. Scarsi**
Institution: **Northwestern University at Chicago**
Grant No.: **HD074462-01**
Award: **$150,734**

Family planning services, including hormone contraceptives, are critical for HIV-infected women, in whom prevention of unintended pregnancy not only decreases maternal and child mortality, but also reduces the risk of mother-to-child HIV transmission. Similarly, antiretroviral therapy (ART) is a lifesaving intervention tha improves the health and economic status of HIV-infected women throughout the world. Therefore, it is of significant public health importance to guide the appropriate use these essential medications. To this end, millions of HIV-infected women in low and middle income countries (LMIC) currently use or are gaining access to subdermal progestin-containing implants as a preferred method of long-acting reversible contraception. These implants are often combined with ART despite the lack of critically needed pharmacokinetic (PK) drug-interaction data to inform their safe and effective concomitant use. Highlighting this concern are several case reports of unintended pregnancy that occurred in patients with subdermal progestin-containing implants concurrently receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART, the most commonly used ART in LMICs. While NNRTIs are known to significantly decrease oral pill progestin concentrations, no data are available to inform healthcare providers of the impact of NNRTIs on progestin concentrations following release from subdermal implants. To fill this critical gap in knowledge, the overall aim of this proposal i to conduct a PK study to evaluate the combination of a levonorgestrel (LNG) implant and NNRTI (nevirapine or efavirenz)-based ART in HIV-infected Ugandan women. We hypothesize that lower LNG concentrations will be observed in patients on NNRTI-based ART and although the implant's efficacy may be retained initialy, this negative interaction will jeopardize implant effectiveness near the end of its intended duration of use (4 years). The specific aims of this project are (1) to characterize the PK of LNG released from a subdermal implant over one year in HIV-infected women with and without NNRTI-based ART and (2) to evaluate the potential for a bidirectional drug-interaction resulting from the long-term impact of chronic progestin exposure on antiretroviral concentrations. To achieve these aims, we will enroll 20 HIV-infected women into each of three study groups: a control group not receiving ART and two treatment arms consisting of patients receiving nevirapine- or efavirenz-based ART. Using sparse PK sampling strategies, LNG, nevirapine or efavirenz concentrations will be measured over one-year and compared between and within groups, as appropriate. The LNG data will also be used to develop a PK model that will predict LNG disposition over the following three years of intended use, allowing for identification of the safe duration of LNG implant use in women on NNRTI-based ART. At the conclusion of this project, the first evidence-based medical

knowledge will be available to guide the safe and effective concomitant use of subdermal LNG implants and NRTIs, thereby improving management of reproductive health in millions of HIV-infected women worldwide.

Title: **Effect of Feeding Buddies on Adherence to WHO PMTCT Guidelines in South Africa**
P.I.: **Kiersten Ann Israel-Ballard**
Institution: **Program for Appropriate Technology in Health**
Grant No.: **HD075090-01**
Award: **$300,000**

The 2010 revised WHO recommendations to provide antiretroviral (ARV) prophylaxis or treatment to mothers or infants during the breastfeeding period indicate a paradigm shift in PMTCT care and treatment programming. Yet despite South Africa's adoption of this guidance, myriad challenges currently exist. Confusion in the public health care system related to mixed messaging around safe infant feeding and the provision of-and now withdrawal of-free formula milk have made adherence to exclusive breastfeeding a challenge in South Africa. Cultural, social, and psychological factors influence the ability of women to follow PMTCT guidelines, which include exclusive breastfeeding for six months, adherence to ARV prophylaxis or treatment, and early infant diagnosis. Facility-based interventions alone are often inadequate to effect sustained behavioral changes in the face of multiple contextual factors. Community- and home-based support are needed, yet cost and systems constraints make these infeasible in many PMTCT programs. Our previous data suggest that a feeding buddy strategy could fill this gap and provide a home-based support system for the mother. The feeding buddy, who is selected by an HIV-positive pregnant woman to support her in overcoming sociocultural challenges to adhering to various aspects of PMTCT programs, is not an employed health care worker, but rather an individual known to the mother, making the intervention extremely cost-effective, and requiring minimal resources to implement. PATH is proposing a comprehensive evaluation of the feeding buddy concept in one health district of South Africa. The goal of the proposed study is to evaluate the effect of a feeding buddy to support mothers to adhere to PMTCT recommendations in order to establish feasible models of promoting HIV-free infant survival in resource-limited settings. We hypothesize that mothers who choose a feeding buddy will have increased rates of exclusive breastfeeding and adherence to ARV prophylaxis or treatment, as well as improved rates of early infant diagnosis and stigma reduction. A prospective cohort intervention study, set within a comprehensive ongoing national program addressing maternal and child health will be conducted with the following aims: (1) to determine the effect of a feeding buddy on adherence to exclusive breastfeeding and (2) to determine the effect of a feeding buddy on adherence to ARV prophylaxis or ART regimens. Secondary aims are: (1) to determine the effect of a feeding buddy on adherence to infant HIV testing at 6 weeks and (2) to determine the effect of a feeding buddy on disclosure and stigma. HIV-infected pregnant women (n=600) will be given the opportunity to choose a feeding buddy at an antenatal care visit to support infant feeding and PMTCT recommendations; follow-up will be to six months postpartum. Feeding buddies could be

a simple, low-cost strategy for strengthening existing facility-level efforts to implement the new PMTCT guidelines, and ultimately could contribute toward improving HIV-free survival.

Title: **ORWH/NICHD Leiomyoma Tissue Bank**
P.I.: **James Segars**
Institution: **NICHD Intramural Research Program**
Award: **$50,000**

Uterine fibroids represent a health disparity and affect an average of one-in-four reproductive age women in the U.S. (1). The effect on reproduction is considerable as fibroids are estimated to add $34 billion annually to cost of health care in the U.S. In response to a need identified by the research community, the ORWH-NICHD Fibroid Tissue Bank was established to serve as a repository source of well-characterized fibroid and matched control tissues for NIH-funded investigators pursuing basic research on fibroid growth and pathogenesis. The overarching objective of this collaborative initiative between ORWH and NICHD is to improve understanding of the mechanisms and pathophysiology of fibroid disease. The improved understanding of fibroid-related cellular change is expected to serve as a foundation for development of new and novel treatment approaches. Since the establishment of the tissue bank, we have collected a total of 933 tissue specimens; 851 from fibroids and 82 from control-matched myometrial tissue. The samples are well characterized and preserved in order to permit RNA, DNA, metabolomics, and protein analysis. Patients from minority populations are well represented: 36% of patients were African American, 44% were Caucasian, and 19% had unknown or unreported race or ethnicity. Of note, the bank reflects the unusual diseases unique to the NIH: 57% of patients have rare conditions including HLRCC (14 patients), MEN-I, tuberous sclerosis, and Birt-Hogg-Dubé syndrome. This patient group represents 40% and 50% of the total fibroid and myometrial specimens, respectively, and 41% of the total specimens.

National Institute of Diabetes and Digestive and Kidney Diseases

Title: **Diabetes Prevention Program Outcomes Study**
P.I.: **Sarah E. Fowler**
Institution: **George Washington University**
Grant No.: **DK048489-19**
Award: **$1,050,000**

The George Washington University Biostatistics Center proposes to continue as the Coordinating Center for the Diabetes Prevention Program Outcomes Study (DPPOS). This application is companion to the Clinical Centers' application. The Diabetes Prevention Program (DPP), a multi-center controlled clinical trial in a multiracial population of overweight persons with impaired glucose tolerance, established the efficacy of a life-style intervention aimed at a modest degree of weight loss and increased

moderate-intensity activity, and of metformin in decreasing the development of diabetes by 58 and 31%, respectively. The DPPOS, a 10-year follow-up, was funded in 2002 for a five-year period with the understanding that it would require refunding via competitive renewal. The overarching goal of DPPOS was to study whether the relatively shortterm benefits of delaying diabetes demonstrated in the DPP would translate into a more long-lasting impact that would reduce the public health burden of the diabetes epidemic. Specifically, DPPOS had the following major goals: 1) to determine the effects of DPP interventions on the long-term microvascular and cardiovascular disease (CVD) complications, atherosclerosis and CVD risk factors; 2) to examine the long-term effects and durability of prior DPP interventions on further diabetes development; and 3) to describe the incidence of long-term complications and their risk factors in new onset type 2 diabetes and IGT. To date, after 10 years of DPP/DPPOS, 93% of the DPPOS cohort attends annual follow-up visits. A durable effect of diabetes prevention associated with the life-style and metformin interventions has been demonstrated with 36 and 19% reductions in diabetes incidence, respectively, compared with the placebo group. Interim analyses also reveal significant reductions in CVD risk factors in the intervention groups, with decreased utilization of medications. The development of diabetes is associated with an increased frequency of retinopathy and microalbuminuria. The development of diabetes is associated with an increased frequency of retinopathy and microalbuminuria. This application is designed to support completing the second five-years of DPPOS focusing on complications that require more time to develop. RELEVANCE: The Diabetes Prevention Program (DPP) and first 5 years of the DPP Outcome Study (DPPOS) have demonstrated that a lifestyle intervention program aimed at weight loss, and metformin, prevent diabetes development over a 10 year period. Completion of DPPOS will examine the impact of diabetes prevention on long-term complications affecting the eye, kidney, nerves and heart, and remains critical to public health.

Title: **Molecular Basis of E. Coli Adhesins in Bladder Disorders**
P.I.: **Scott J. Hultgren**
Institution: **Washington University**
Grant No.: **DK051406-15A1**
Award: **$200,000**

Over 15 million women suffer from urinary tract infections (UTI) annually in the U.S., ~85% of which are caused by uropathogenic Escherichia coli (UPEC). 20-40% of patients suffer from multiple and/or chronic recurrences and increasingly are left with few treatment options other than costly long-term antibiotic prophylaxis Indiscriminate use of antibiotics is leading to increased resistance to first-line empiric therapie such as trimethoprim-sulfamethoxazole and the undesirable use of fluoroquinolones for empiric treatment of UTI. Catheter-associated UTI (CAUTI) further exacerbates this problem. Consequently, multi-drug resistance is rising rapidly. Thus, there is a critical need for new therapeutics to better treat and prevent chronic recurrences. There are two bladder associated niches for UPEC during acute UTI: the bladder tissue and the luminal space/urine. FimH, the type 1 pilus adhesin mediates UPEC colonization and invasion of human and murine bladder epithelial cells (BECs). Murine models indicate that after

invasion, UPEC can subvert innate expulsion mechanisms and escape into the cytoplasm where rapid bacterial replication results in the formation of intracellular bacterial communities (IBC) comprised of 104-105 bacteria. IBCs are transient and upon IBC maturation bacteria disperse from the biomass, filament, and spread to neighboring BECs, re-initiating the IBC cycle. This cycle potentiates the establishment of infection allowing the expansion of the bacterial population in a sequestered habitat protected from host immune and antibiotic clearance. Bacterial colonization of BECs, IBC formation, filamentation and biofilm formation on urinary catheters (also seen in mouse models) are all processes seen in human disease. Further, the fimH gene is under positive selection in UPEC clinical isolates consistent with its role in UTI. Murine models and human clinical studies show roles for the same specific cytokines and TLR4 signaling in UTI. In humans, UTI ranges from asymptomatic bacteriuria to acute self-limiting infection to chronic/recurrent UTI. Murine models mimic these disease outcomes and reveal that the nature of host response dictates whether a UTI resolves or develops into long-lasting chronic/recurrent UTI. This grant proposal will use a panel of virulent clinical isolates including a multi-drug resistant strain that has spread globall, to focus on a direct experimental investigation of common but complex clinical problems associated with more severe UTI and/or recurrence. Aim 1 investigates mechanisms by which superinfection of UPEC leads to the development of chronic/recurrent infection. Aim 2 investigates catheterization, which may alter the pathogenesis and may trigger the recurrence of infection in patients with a history of UTI. Aim 3 investigates the efficacy of potent small molecular weight compounds called mannosides, which block FimH function, to treat and prevent UTI in the context of these complicating factors. The proposed experiments will elucidate how sequential infection and catheterization affect the course of UTI and aid in better clinical management and the development of new therapeutics for combating this prevalent infection.

Title: **The Look AHEAD Continuation: Action for Health in Diabetes**
P.I.: **Rena R. Wing**
Institution: **Miriam Hospital**
Grant No.: **DK056992-14**
Award: **$100,000**

Look AHEAD is randomized clinical trial examining the long-term health effects of an intensive weight loss intervention in approximately 5,145 overweight volunteers with type 2 diabetes. Participants are randomized to an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity, or to a control program of diabetes support and education. The primary outcome of Look AHEAD is the aggregate occurrence of severe cardiovascular events (fatal and non-fatal Ml and stroke and cardiovascular deaths) over a planed follow-up of 11.5 years. The original grant application provided funding for the first 7 years of the study (1 year for study design and 6 for execution of the trial). The present grant application is for an additional 7 years of funding to complete the Look AHEAD trial. All aspects of the study have proceeded extremely well—the sample of 5,145 was recruited on time; retention has been excellent and the intervention has been effective in producing

initial weight loss and maintaining it over time. All 16 clinical sites have been successful in recruitment, retention, and delivery of the intervention and the DSMB has been very positive about the execution of the trial. The present application reviews the overall design of Look AHEAD, progress to date, and plans for the future. Specific Aims are to retain the cohort over time, continue to complete annual in-person visits and semi-annual telephone interviews for outcome assessments and continue to administer the lifestyle intervention. These procedures will enable us to analyze the effects of the intervention on serious cardiovascular-related factors and complications, and cost-effectiveness of the intervention.

Title: **Urinary Incontinence Treatment Network: DCC**
P.I.: **Sharon L. Tennstedt**
Institution: **New England Research Institutes, Inc.**
Grant No.: **DK058229-12**
Award: **$100,000**

This proposal is submitted in response to RFA-DK-06-501 for continuation of the Urinary Incontinence Treatment Network (UITN) Data Coordinating Center (DCC) at New England Research Institutes, Inc. The DCC is responsible for the scientific management of the studies, including directing, training, and monitoring the performance of Clinical Centers in enrollment, data collection, and data management as well as for all data analysis, and reports to the DSMB. In Phase I and continuing to Phase II, NERI has provided several unique and innovative tools and capabilities, including a proprietary Web-based data management system, an automated patient randomization system, and an electronic repository for UDS tracings. The DCC is also responsible for network communications and meeting support and provides a secure study website and a public website. DCC scientists play a leadership role in all network activities, including protocol development, standing committees and work groups, manuscript development and presentations. Phase II will focus on conduct of the TOMUS trial as well as continuation of the observational follow-up studies for the SISTEr and BE-DRI studies (i.e., E-SISTEr and E-BE-DRI) of Phase I. Primary Aims of TOMUS are to compare objective and subjective cure rates for stress incontinence at 12 and 24 months between the retropubic and transobturator midurethral sling procedures. Performance of these procedures is increasing rapidly with limited data available on safety and efficacy. Therefore, this study will compare the efficacy and safety of the retropubic and transobturator (inside-out and outside-in) procedures in a 2-arm RCT; 588 women with stress Ul will be enrolled. Primary Aim of E-SISTEr is to compare long-term (60 mos.) effectiveness and durability of the Burch colposuspension and autologous fascial sling for treatment of stress Ul in a randomized cohort of 655 women. Primary Aim of E-BE-DRI is to examine long-term (26 mos.) durability of the addition of behavioral treatment to drug therapy for treatment of urge Ul in a randomized cohort of 307 women. The UITN is a multi-disciplinary, multi-center group of Investigators dedicated to high impact clinical research regarding the prevention, evaluation and management of Ul to improve the quality of life for adults. The UITN is conducting 3 studies of treatments for both stress and urge urinary incontinence.

Title: **Ovarian Hormone Suppression and Regulation of Adipogenesis in Women**
P.I.: **Wendy M. Kohrt**
Institution: **University of Colorado Denver**
Grant No.: **DK092718-02**
Award: **$191,250**

Estradiol (E2) deficiency triggers weight gain, and specifically abdominal fat gain, in women. The shift toward central adiposity after menopause likely contributes to increased risk for the metabolic syndrome and associated chronic diseases (i.e., type 2 diabetes, coronary artery disease, hypertension). The long-term aim is to understand the mechanisms by which E2 deficiency mediates increases in abdominal adiposity. The primary aim (PA1) of the R21 is to determine whether ovarian hormone suppression in premenopausal women, which is known to cause fat gain, triggers an increase in adipogenesis (i.e., increase in cell number) in abdominal adipose tissue. This will be assessed by measuring the changes in cell size distribution and the incorporation of deuterium (2H) into DNA of cells in the non-stromal (i.e., mature adipocyte) fraction. Secondary aims are to determine: SA2) effects of ovarian hormone suppression on mRNA expression of factors involved in adipogenesis (C/EBP1, PPAR3) and markers of macrophage infiltration (CD68, Emr-1) and inflammation (IL-6, TNF-1); and SA3) whether new adipocytes arise from non-resident bone marrow progenitor (BMP) cells using cell surface markers (Notch 4, Platelet-derived Growth Factor Receptor (PDGFR) 2, Integrin 15, CD36) that enable detection by flow cytometry. To achieve these aims, 24 premenopausal women will be studied before and after 30 and 60 days of ovarian hormone suppression via gonadotropin releasing hormone agonist therapy with add-back of placebo (GnRHAG+PL) or estradiol (GnRHAG+E2). Hypotheses are: H1a) GnRHAG+PL for 60 days will result in a larger increase in small adipocytes (< 40 5m) when compared with GnRHAG+E2. Because fat mass increases during GnRHAG+PL, an increase in the number of small adipocytes will be interpreted as an increase in adipogenesis and not as evidence of adipocyte atrophy; H1b) The incorporation of 2H in the non-stromal cell fraction DNA will be increased in response to GnRHAG+PL, as compared with GnRHAG+E2. Because the non-stromal fraction contains mature adipocytes, an increase in 2H-enriched DNA should reflect adipogenesis; H2) Ovarian hormone suppression will increase mRNA expression of factors associated with adipogenesis, macrophage infiltration, and inflammation (C/EBP1, PPAR3, CD68, Emr-1, IL-6, TNF-1) when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-back (GnRHAG+PL vs GnRHAG+E2); and H3) Ovarian hormone suppression will increase BMP-derived adipocytes when compared with baseline (before vs after GnRHAG+PL) and when compared with E2 add-back (GnRHAG+PL vs GnRHAG+E2). To the best of our knowledge, this will be the first in vivo study of the role of E2 as a regulator of adipogenesis in humans. Because it is believed that adipocytes are programmed to achieve a certain volume of fat, an increase in adipocyte number would lead to a gain in fat mass that would be very difficult to

reverse. Thus, identifying strategies that effectively prevent an increase in adipogenesis during ovarian hormone withdrawal would be of high clinical importance.

Title: **Weight Management in Obese Pregnant Underserved African-American Women**
P.I.: **Samuel Klein**
Institution: **Washington University**
Grant No.: **DK094416-02**
Award: **$100,000**

Maternal obesity and inappropriate gestational weight gain (GWG) increase both maternal and neonatal morbidity and mortality. In addition, offspring of obese women are at increased risk for neurodevelopment delay, becoming obese, and developing metabolic diseases. Women who are socio-economically disadvantaged (SED), especially from African American (AA) populations, are particularly susceptible to adverse pregnancy-related outcomes because of their high prevalence rates of obesity. Therefore, successful weight management during pregnancy in SED, AA women has considerable public health implications. We have experience in testing lifestyle interventions among SED non-pregnant women that have been implemented and sustained within community organizations such as Parents As Teachers (PAT), a national home visiting program that provides parent-child education and services free-of-charge to high needs women, prenatally and post-partum, through up to 25 home visits per year until kindergarten. We propose to conduct a 24-month (6-month prenatal and 18-month post-partum) randomized, controlled trial in obese SED AA women to evaluate the ability of an innovative lifestyle intervention program (PAT-i-), delivered by PAT parent educators during prenatal and post-partum home visits, to improve maternal and neonatal/infant weight, metabolic and health outcomes. An extensive programmatic evaluation will determine the applicability of the PAT+ intervention in real world settings by measuring programmatic reach, implementation, acceptability, and sustainability. If effective, PAT+ can be disseminated through this national organization, which currently reaches over 249,000 mothers and 319,000 children participating in 2,173 PAT programs across all 50 states.

Title: **Lifestyle Interventions in Overweight and Obese Pregnant Women**
P.I.: **Xavier Pi-Sunyer**
Institution: **St. Luke's Roosevelt Institute for Health Sciences**
Grant No.: **DK094463-02**
Award: **$100,000**

A randomized controlled trial is proposed to study the effect, in a cohort of racially and ethnically diverse group of overweight and obese pregnant women, of an Intensive Lifestyle Intervention (ILI) compared to Usual Care (UC) on gestational weight gain (GWG), infant fatness, and mothers' post-delivery weight retention. Women in the ILI

arm will receive intensive counseling during pregnancy and group counseling after delivery regarding behavior, nutrition, and physical activity change. Visits to counselors will be weekly and additional telephone and internet contacts will occur. The mothers' will be assessed at 14 and 36 weeks of pregnancy and at 12 weeks and 52 weeks post-delivery. The measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (BodPod). The infants' measurements will be anthropometry, whole body MRI, EchoMRI, and whole body plethysmography (PeaPod) for fatness 12 weeks and 52 weeks. Mothers and children will have cardio-metabolic risk factors measured in plasma. Data will be collected regarding mothers' dietary intake and physical activity (questionnaires and accelerometry) to assist in counseling. Other data to be collected include questionnaires on quality of life, socio-economic status. Careful record will be kept of expenses in providing the ILI, so that cost analysis of the intervention can be calculated. The study is powered on the primary outcome, fatness of the infants at birth. We require 180 participants to attain appropriate power. We will enroll 210 so as to allow for some dropouts along the way. Each mother will be followed during pregnancy and for a year post delivery. Each infant will be followed for a year after birth. We have the ability o continue to follow these participants if further funding is forthcoming, as they are all local to or hospital's catchment area and our own physicians. If aims are achieved, namely that both children and mothers profit from the intervention, there should be a paradigm shift in how overweight pregnant women are treated. At present, there is a dearth of behavioral advice and intervention relating to GWG and physical activity provided to these women. Positive results from our study would provide evidence for ILI preventative intervention.

Title: **Glycated CD59 as a Novel Biomarker of Gestational Diabetes Mellitus**
P.I.: **Jose A. Halperin**
Institution: **Brigham and Women's Hospital**
Grant No.: **DK095429-01A1**
Award: **$200,000**

The goal of this proposal is to assess glycated CD59 in human serum as a pathogenically relevant early bio-marker for screening of gestational diabetes mellitus (GDM). This proposal is highly translational and addresses major Public Health priorities because 1) diabetes affects H 25 million Americans, 2) and GDM is a major source of adverse pregnancy outcomes including macrosomia and pre-eclampsia. The proposed work opens the possibility of using glyCD59 as a biomarker for GDM, an innovative departure from the use of OGTT, a cumbersome, costly and time-consuming test with poor reproducibility and many times unwanted effects including nausea and vomiting. A simpler, easy to use, patient friendly marker that is also involved in the pathogenesis of diabetes and its complications may help fulfill an important clinical need in the widespread screening for GDM and prevention of associated adverse outcomes. The applicants have 1) discovered that human CD59 is inactivated by glycation, 2) provided evidence for a link between the complement system and the pathogenesis of the complications of diabetes, and 3) developed key reagents that allow quantification of

glycated hCD59 in human fluids and tissues. Specifically, we have demonstrated that 1) glycated CD59 is present in target organs of diabetic complications, and 2) glyCD59 can be readily measured in normal urine and serum. Furthermore, our preliminary data show that glyCD59 is a) significantly increased (3-4 fold) in the serum of diabetic and pre-diabetics individuals, and b) seems to respond faster than HbA1c to changes in glycemic load within an individual All necessary tools and expertise to accomplish our aim are available in the laboratory of the applicant and expert collaborators, including monoclonal antibodies specific for glycated CD59 and assay calibrators, access to large and diverse population of pregnant women undergoing pre-natal care at BWH, and diagnostic tools, equipment and expertise to necessary to conduct all studies proposed in the application. Successful accomplishment of our aims would represent a major advancement in screening and early diagnosis of GDM.

Title: **Bedside to Bench—Role of Androgen and Estrogen Receptor Signaling in Pulmonary Arterial Hypertension**
P.I.: **Robert Danner**
Institution: **National Institute of Diabetes and Digestive and Kidney Diseases**
Award: **$80,000**

Idiopathic pulmonary arterial hypertension (IPAH), a subtype of plexogenic pulmonary arteriopathy (PAH), is a rare disorder associated with poor survival. Despite consistent epidemiological evidence demonstrating a 2 to 4 fold female predominance in IPAH, the underlying mechanisms for this imbalance are unclear. Endothelial dysfunction resulting from 1) genetic susceptibility, and 2) a triggering stimulus that initiates pulmonary vascular injury, the so-called two-hit hypothesis, appears to play a central role both in the pathogenesis and progression of PAH. Inflammation may drive this dysfunctional endothelial phenotype, propagating cycles of injury and repair in genetically susceptible patients with IPAH and patients with disease associated PAH (e.g. scleroderma, HIV, and sickle cell disease). Histologic specimens from patients with IPAH reveal the presence of inflammatory cells, including macrophages and T- and B-lymphocytes, within classic plexiform lesions that are the hallmark of PAH. Pulmonary artery endothelial cells (PAECs) in PAH orchestrate the recruitment of inflammatory cells as well as secreting pro-inflammatory and pro-coagulant cytokines into the circulation. Patients with IPAH have higher levels of circulating IL-1β, IL-6, P-selectin and E-selectin in comparison to healthy controls. Therefore, targeting PAEC inflammation may interrupt the cycles of injury/inflammation and repair that contribute to progressive increases in pulmonary vascular resistance in patients with PAH, and thereby delay or prevent right ventricular failure and death. Both estrogen and testosterone promote vasodilatation and affect vascular inflammation through binding to estrogen (ER) and androgen receptors (AR), respectively, members of the nuclear receptor (NR) family of transcription factors. However, the interaction between sex hormone signaling and IPAH-associated vascular injury/inflammation is not understood. Many NRs inhibit inflammation through a trans-repression mechanism that recruits co-repressor proteins to promoter NFκB and AP-1 binding sites in a tissue and target gene specific manner. Using an in silico bioinformatics approach, we found that the androgen receptor (AR) is relatively over-expressed in

primary human endothelial cells compared to phagocytic leukocytes. Initial work in our laboratory using EA.hy926 cells, a human endothelial line, demonstrates that dihydrotestosterone (DHT) can suppress TNFα-induced VCAM1 mRNA expression, while spironolactone, a mixed mineralocorticoid receptor and AR antagonist currently used in PAH for advanced right heart failure, was found to inhibit NFκB signaling. We hypothesize that AR and ER differentially modulate endothelial inflammation in IPAH and this may in part explain the female predominance of this disease. Here, the effects of AR and ER signaling on endothelial dysfunction and inflammation will be investigated in cell culture models. Patients with PAH will be recruited to the NIH to investigate novel MRI-based methods to improve clinical phenotyping and as part of a pilot feasibility study on the effects of early spironolactone on endothelial inflammation in vivo. The Specific Aims include: 1.) Investigate the effects of AR and ER in endothelial cell culture systems that simulate key aspects of PAH pathophysiology using proinflammatory challenges (IL-1β, IL-6, IFNγ), targeted gene knockdown (eNOS, BMPR2) and dominant negative mutant protein expression (Smad proteins); 2.) Characterize the global transcriptomic response of naïve and dysfunctional PAECs (BMPR2 and/or eNOS silencing; Smad dominant negative mutant expression) to plasma from patients with PAH compared to matched controls using oligonucleotide microarrays; and 3.) Patients with PAH will be recruited to the NIH for a pilot study of early treatment with spironolactone to investigate its effects on endothelial dysfunction in vivo. In addition to standard clinical assessment (6-minute walk distance, echocardiography and right heart catheterization), plasma levels of inflammatory cytokines, neurohormonal markers and novel MRI-based techniques for assessing pulmonary artery endothelial function will be used to characterize treatment response. Using 6-minute walk distance as the gold standard measurement of functional status, we will determine the sensitivity and specificity of MRI-based quantification of pulmonary artery endothelial function and MRI derived measurements of right ventricular (RV) structure and function for assessing disease progression.

National Institute on Drug Abuse

Title: **Novel Assessment of Maternal Distress Tolerance Underlying Substance Use Relapse**
P.I.: **Carl W. Lejuez**
Institution: **University of Maryland, College Park**
Grant No.: **DA034176-01**
Award: **$228,000**

Women evidence worse substance use treatment outcomes than men (Greenfield et al., 2007), including higher rates of treatment dropout (Arfken et al., 2001; King & Canada, 2004; Sayre et al., 2002), lower treatment attendance (McCaul et al., 2001) and higher rates of post-treatment substance use relapse (Grella et al., 2006). Yet, substance abuse research often includes little attention to gender-specific factors relevant to particular vulnerabilities of female participants (Brady & Ashley, 2005; Greenfield et al., 2007). One factor especially relevant to risk of relapse for many female drug users is maternal

stress; child care responsibilities and the associated stressors may significantly increase risk of substance use relapse, particularly during high-risk periods for relapse following substance abuse treatment. Further, although maternal factors have been a particular empirical and clinical focus regarding environmental risk factors for drug using women, but the large preponderance of this research is focused on the impact of maternal substance use on child outcomes, with little attention to drug use outcome for these women as an important target in its own right (cf., Pajulo et al., 2006). Accordingly, one promising factor that may help explain the maternal distress and substance use association when reintroduced to one's home environment following discharge from substance abuse treatment is maternal distress tolerance, or the ability to tolerate distress due to parenting issues. Indeed, one's ability to tolerate distress is associated with relapse following substance abuse treatment and length of abstinence attempts. However, despite its relevance to both substance use and parenting responses, little is known about the impact of low distress tolerance on substance using mothers. This may be due, at least in part, to the lack of distress tolerance assessment strategies that target directly the unique experience of maternal distress. To address the lack of research in this area, the following R21 attempts to provide an initial examination of maternal risk factors for substance use relapse, with a focus on the moderating role of distress tolerance. As a secondary aim, we explore a novel and ecologically valid measure of maternal distress tolerance to examine its utility over a standard distress tolerance task. Specifically, we will include 105 predominantly low-income, inner-city African American substance using mothers in their last week of residential drug use treatment that have a child in the critical age of 9 months to 4 years to examine the link between several indices of maternal distress and substance use outcomes with both general and maternal-specific measures of ability to tolerate distress as moderators of this relationship.

National Institute of Environmental Health Sciences

Title: **Dioxin Exposure and the Invasive Pathogenesis of Endometriosis**
P.I.: **Kevin G. Osteen**
Institution: **Vanderbilt University Medical Center**
Grant No.: **ES014942-06**
Award: **$250,000**

Endometriosis, described as the ectopic growth of endometrial tissue, is a debilitating disease of reproductive age women. In North America, at least 5.5 million women are affected by endometriosis at any one time and estimates of the economic cost of treating this disease range from $1-20 billion annually in the United States alone. An emerging view is that a reduced endometrial responsiveness to progesterone (P4), a defect referred to as the "endometriosis phenotype," may play a significant role in development and/or progression of endometriosis. Relative to this question, we have explored whether exposure to TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin or dioxin) promotes development of the P4- resistant, endometrial phenotype. During our past funding period, we utilized adult human endometrial cell and tissue culture models, a chimeric model of experimental endometriosis in immunocompromised mice and a murine model of early

life TCDD exposure to examine the impact of this toxicant. Using human cells, TCDD exposure was found to disrupt the anti-inflammatory action of P4, leading to cellular changes that potentiated the invasive behavior of endometrial tissues in our experimental endometriosis model. Our murine model of early life toxicant exposure revealed that TCDD-mediated defects in uterine P4 sensitivity can indeed arise from a developmental exposure. Perhaps more significant, our murine model also revealed that early life toxicant exposure leads to a heightened sensitivity to inflammation for multiple generations in the absence of additional toxicant exposure. Taken together our studies strongly suggest that disrupting the anti-inflammatory action(s) of P4 during endometrial maturation is the key mechanism by which TCDD-like toxicants alter reproductive function and impact a woman's risk of developing endometriosis. Thus, therapeutic interventions which target inflammatory signaling may have significant efficacy in blocking TCDD-mediated development of the P4 resistant endometrial phenotype associated with endometriosis. To validate this appoach we will utilize in vitro and in vivo studies designed to prevent the development and progression of the endometriosis phenotype as well as prevent the transmission of this phenotype to future generations. We propose three Specific Aims: 1): To evaluate the therapeutic potential(s) of resveratrol (RES) and PGE2 signaling inhibitors to reduce TCDD mediated loss of P4 responsiveness in human endometrial cells.. 2): To evaluate whether the anti-inflammatory effect(s) of RES and PGE2 signaling inhibitors alone or in combination will limit TCDD-mediated growth of experimental endometriosis in our humanized Rag2?(c) mouse model. 3): To evaluate the ability of RES and PGE2 signaling inhibitors to restore uterine progesterone sensitivity and reproductive function in a novel murine model of early life TCDD exposure that exhibits an adult endometriosis-like uterine phenotype.

Title: **Ex Vivo Female Reproductive Tract Integration in a 3D Microphysiologic System**
P.I.: **Teresa K. Woodruff**
Institution: **Northwestern University at Chicago**
Grant No.: **ES022920-01**
Award: **$300,000**

The female reproductive tract is responsible for producing endocrine hormones, developing mature, healthy gametes (oocytes) and providing the site for fertilization and an environment that supports fetal development. There are five main organs in the female reproductive tract-the ovary, fallopian tubes, uterus, cervix and vagina. Each organ is responsible for unique aspects of reproductive function, but act integrally to support overall endocrine health, fertility, and fetal development. The reproductive tract organs are assembled from multiple cell lineages to create individual follicles (that enclose and support oocytes), oviductal/fallopian tubes, uterine myometrium and endometrium, the cervix and the vagina. Traditionally, research of the female reproductive tract has relied on two-dimensional (2D) cultures of isolated primary cells or immortalized cell lines grown on plastic and independent of adjacent cells, tissue architecture, and functional context. Moving to a three-dimensional (3D) culture environment has allowed us to better

understand the function and interaction of cells within individual organs and interrogate interactions between tract tissues in co-cultures (e.g., the follicle and the ovarian surface cells, or the uterine myometrium and endometrium) to measure responses to normal reproductive hormones, pathologic conditions (such as high levels of androgens) or exposure to endocrine disruptors. New biomaterials and 3D culture systems have now presented us with the exciting opportunity to create a complete in vitro reproductive tract whereby each of the cultured organs can be assembled into a linked perfusion culture system. Just as the biological function and responses of 2D monolayer cell cultures differ from those of 3D-cultured organoids, we predict that the biology of the reproductive organs when studied in an integrated series will more closely recapitulate the in vivo environment. In Aims 1 and 2, we propose to develop in vitro cultures of human reproductive tissues that phenocopy in vivo function in terms of hormone production and response to the physiologically relevant reproductive hormones follicle-stimulating hormone (FSH) and estrogen. We will use the 3DKUBE culture platform (KIYATEC), which not only permits control of perfusion to mimic tissue circulation, automated sampling for pharmacokinetic analyses, tissue imaging and in situ bioassays, but also will facilitate integration of the 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.

National Institute of General Medical Sciences

Title: **Pharmacogenetics of Phase II Drug Metabolizing Enzymes**
P.I.: **Richard M. Weinshilboum**
Institution: **Mayo Clinic**
Grant No.: **GM061388-13**
Award: **$237,958**

This proposal represents a request for continued funding of the Mayo Clinic Pharmacogenomics Research Network (PGRN) grant “Pharmacogenetics of Phase II Drug Metabolizing Enzymes”. The Mayo PGRN is an integrated, multidisciplinary, pharmacogenomic research effort based on a decades-long focus at Mayo on the pharmacogenetics of phase II (conjugating) drug metabolizing enzymes. The Mayo PGRN began by applying a “genotype-to-phenotype” research strategy that included, sequentially, gene resequencing, functional genomic, mechanistic and translational studies. During the present funding cycle, the Mayo PGRN has also incorporated the use of genome-wide techniques and pharmacogenomic model systems, with a special emphasis on functional mechanisms responsible for genetic effects on drug response. We

have used that approach to study the pharmacogenomics of the endocrine therapy of breast cancer and selective serotonin reuptake inhibitor (SSRI) therapy of depression—research that grew out of the contribution of phase II enzymes to the biotransformation of the estrogens that play such an important role in breast cancer and biotransformation ofthe neurotransmitters that are central to the pathophysiology and treatment of depression. Recently, we have performed pharmacogenomic genome-wide association (GWA) studies of breast cancer, and we will soon perform similar studies of the SSRI therapy of depression. We propose to continue this genome-wide focus during the next funding cycle, with both clinical and model system GWA studies of the drug therapy of breast cancer and depression, always including replication as well as functional and mechanistic studies. We also propose two "Network Resources", one designed to provide access to "Next Generation" DNA sequencing for all PGRN Centers and the other focused on pharmacogenomic ontology. In summary, the studies in this application build on Mayo PGRN strengths in DNA sequencing and functional genomics—while incorporating genome-wide techniques—to provide insight into the role of inheritance in variation in the efficacy and side effects of drugs used to treat breast cancer and depression. RELEVANCE: Breast cancer is the most frequent cancer of women and depression is the most common major psychiatric illness. Drugs are available to treat both of these serious illnesses, but many patients fail to respond and some suffer serious adverse drug reactions. The Mayo Clinic PGRN will apply modern pharmacogenomic techniques to help make it possible to "individualize" the drug therapy of breast cancer and depression.

National Institute of General Medical Sciences & Indian Health Service

Title: **Oklahoma Native American Research Centers for Health (NARCH VI)**
P.I.: **Gloria Ann Grim**
Institution: **Cherokee Nation**
Grant No.: **GM092238-02**
Award: **$100,000**

The purposes of this project are: to encourage competitive research linked to reducing health disparities; to increase the capacity of the Tribes and University of Oklahoma to work in partnership to reduce distrust by the Native American communities and peoples toward research; and to develop a cadre of Native American scientists and health professionals engaged in biomedical, clinical and behavioral research that is competitive for NIH funding. The sixth Oklahoma Native American Research Center for Health (0NARCH6) continues the productive research and training partnership with the University of Oklahoma Health Sciences Center (OUHSC) by the Tribes, especially the Chickasaw, Creek, Choctaw and Cherokee Nations. Population served consists of 42,749 Chickasaws and 121,680 Cherokees, 49,714 Choctaws and 30,181 Creeks for a total of 244,324 in North East and South Central Oklahoma. The research will include 1) the impact of infections on maternal and child health in Native Americans, 2) research to

develop better diagnostic and prognostic tests for rheumatic disease in Oklahoma tribal members, and to examine the potential roles of environmental triggers for autoimmunity focusing on vitamin D levels, tobacco smoke exposure (through serum cotinine levels) and abnormal immune responses to common viruses, 3) research to prevent excessive gestational weight gain in otherwise healthy but overweight Native American women and consequently decrease the proportion of women who gain in excess of the guidelines has the potential to decrease the risk and costs of obstetric complications associated with excessive weight gain, and 4) to develop methods to understand attitudes, beliefs, and perceived barriers or motivators to organ/tissue donation among American Indians living off-reservation.

Title: **Research To Improve Preconception Health of Adolescent Women (NARCH VI)**
P.I.: **Sara Jumping Eagle**
Institution: **Oglala Lakota Oyate**
Grant No.: **GM087165-03**
Award: **$128,436**

The Oglala Sioux Tribe, in partnership with Stanford Research/University of South Dakota School of Medicine and the Oglala Lakota College, will be addressing priority health issues identified by the tribe and to support and expand the research capacity and infrastructure that will build on the research foundation that has been developed within the tribe over the past decade. Particular attention will be given to undertaking research to improve the preconception health of adolescent girls.

National Institute of Mental Health

Title: **Adjunct Aripiprazole for Symptomatic Hyperprolactinemia in Female Schizophrenia**
P.I.: **Deanna L. Kelly**
Institution: **University of Maryland, Baltimore**
Grant No.: **MH090071-02**
Award: **$189,455**

Risperidone is available generically and one of the most widely used antipsychotic medications; but is associated with elevated prolactin. This elevation is particularly pronounced in women and most recent studies show that the vast majority of women have elevated prolactin levels with approximately 50% also having the corresponding side effects of amenorrhea, oligomenorrhea or galactorrhea. Elevated prolactin may be associated with sexual dysfunction, decreased quality of life, medication nonadherence and decreases in bone mineral density over time. Lowering the dose or switching medications due to this side effect in stabilized patients is not a practical option in most cases. There is little evidence to guide treatment in this important area however dopamine agonists such as bromocriptine or amantadine may exacerbate symptoms, have lacking

efficacy data and are associated with side effects. We have sizeable pilot data to suggest that a low dose of aripiprazole (10 mg/day), a dopamine partial agonist, added to Risperidone can improve symptomatic prolactin side effects. We will complete a double blind randomized 16-week control trial examining adjunct aripiprazole (10 mg/day with increase to 15 mg/day at 8 weeks if no response) vs. placebo in 70 women with symptomatic hyperprolactinemia and hypothesize it will be effective in the resolution of amenorrhea, oligomenorrhea and galactorrhea. We also hypothesize that aripiprazole will significantly improve quality of life, personal well-being and sexual function. And, we will examine improvements in positive, negative and depressive symptoms, sex hormone levels and measures of bone turnover. The significance and innovation of this application is high as this is a significant complaint and concern of women and very little evidence is available to guide treatment in women who are stabilized and doing well on antipsychotic treatments but develop these significant side effects. If funded, this important treatment research study of adjunct aripiprazole treatment will provide invaluable data and treatment options for thousands of women who suffer from schizophrenia and will help move the field towards better tailoring and personalizing antipsychotic treatment, particularly for women who suffer from these problems.

Title: **Treatment of PTSD in Residents of Battered Women's Shelters**
P.I.: **Dawn M. Johnson**
Institution: **University of Akron**
Grant No.: **MH095767-01A1**
Award: **$300,000**

Intimate partner violence (IPV) is a pervasive social problem associated with high rates of posttraumatic stress disorder (PTSD). Moreover, PTSD is associated with considerable morbidity and a higher risk of re-abuse in victims of IPV. Domestic Violence Shelters provide an integral resource for IPV victims in that they provide emergency shelter, support, and access to community resources that can aid in their establishing long-term safety for themselves and their children. However, PTSD symptoms can compromise battered women's ability to access and effectively use these vital personal and social resources, effectively establishing safety for themselves and their children. Despite the fact that annually 300,000 battered women and children access shelter services, and domestic violence shelters provide a prime time to initiate psychological treatment, virtually no research has systematically investigated the treatment of PTSD in residents of battered women's shelters. To address this gap in the literature, we have developed a shelter-based treatment for victims of IPV with PTSD, Helping to Overcome PTSD through Empowerment (HOPE). HOPE is a brief cognitive-behavioral treatment that that adopts an empowerment approach to treatment, emphasizing stabilization and safety, goals consistent with the theoretical and empirical literature on battere women and PTSD. HOPE is a novel treatment in that it adopts an empowerment approach to treating PTSD and emphasizes stabilization and safety; important needs of residents of battered women's shelters with PTSD. In this application we propose to expand upon our pilot work with HOPE and test the efficacy of HOPE relative to supportive therapy (i.e., Present Centered Therapy, PCT) in a sample of 186 female residents of battered women

shelters with IPV-related PTSD. In an effort to facilitate future dissemination of HOPE, sessions will be delivered by community therapists and the study will be conducted in a range of shelter systems. Furthermore, the current proposal, unlike our pilot work, will compare HOPE to an attention matched control condition, have a longer follow-up period in order to determine whether positive findings are sustained over time, will assess the impact of HOPE on child abuse potential, will incorporate objective measures of stress responding (e.g., attentional biases and physiological reactivity to trauma cues), will explore novel mediators and moderators of treatment, and will include a cost-effectiveness analysis. Findings will be used to inform a future dissemination study of HOPE.

Title: **Course and Predictors of Depressive Relapse During IVF**
P.I.: **Lee S. Cohen**
Institution: **Massachusetts General Hospital**
Grant No.: **MH096006-01A1**
Award: **$248,607**

This revised proposal is an R21 application for the ORWH Funding Opportunity Announcement "Advancing Novel Science in Women's Health Research (ANSWHR)" (PAS-10-226). Major depressive disorder (MDD) is prevalent in women of reproductive age, and the course of MDD across infertility treatment and implications for clinical management have not previously received systematic study. At this time, clinicians do not have evidence-based treatment guidelines on which to rely in order to advise women with histories of MDD who plan in vitro fertilization (IVF) or other assisted reproductive procedures. The context of infertility treatment is an intriguing and clinically compelling setting for the stuy of the biological stress response, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and risk for major depression. The aims of the study are: 1) to delineate the clinical predictors of depressive relapse in women with histories of depression across a period of six months while they are undergoing IVF including: antidepressant continuation or discontinuation, previous course of depressive illness, duration of attempt to conceive, and partner support, 2) to describe the trajectory of depressive symptoms over the course of IVF cycles, and 3) to explore biological markers of the stress response, including those pertaining to HPA axis dysregulation and inflammation associated with depressive relapse and stress during IVF treatment. We will conduct a prospective naturalistic investigation in which participants (N=60) will each be followed longitudinally for six months, during which time they will proceed through at least one IVF cycle. Mood symptoms, antidepressant use, psychotherapy, perceived stress, partner support, use of gonadotropins and any hormonal interventions, and all infertility based treatments and interventions across each cycle will be tracked prospectively. The significance of the proposal is derived from: 1) its public health implications in light of the high prevalence rats of both infertility and major depression in women, 2) the lack of systematic data regarding risk of depressive relapse and predictors of relapse in women undergoing IVF, and 3) the need for systematic study of the biological sequelae of stress among women with histories of depression undergoing treatment for infertility.

Title: **Trajectories of Reward Sensitivity and Depression Across Adolescence**
P.I.: **Greg Hajcak**
Institution: **Stony Brook University, The State University of New York**
Grant No.: **MH097767-01**
Award: **$200,000**

There is increasing focus on changes in reward sensitivity that take place across adolescence; in particular, puberty appears to be a time characterized by increased sensitivity to rewards. At the same time, puberty is a time characterized by a significant increase in depressive symptoms, and depression is characterized by reductions in sensitivity to rewards. The current project examines reward sensitivity as a latent trait, capitalizing on a combination of EEG, functional neuroimaging (fMRI), behavioral, and self-report measures. Along the same lines, we consider multiple assessments of depressive symptoms (e.g., parent and child reports) so that depressive symptoms can also be modeled as a latent trait. The current proposal examines both reward sensitivity and depression in a large (N=300) sample of girls, ranging from 9 to 14 years of age; moreover, this sample will be examined two years after the initial visit, so that both cross-sectional and longitudinal relationships can be examined. In our pilot data, we have focused extensively on the feedback-related negativity (FRN), an electrocortical response observed at the scalp as an apparent negativity approximately 300 ms following feedback indicating monetary loss compared to gain. Our work suggests that the neural differentiation between gains and losses is being driven by a reward-related positive potential that is generated in the ventral striatum-part of the basal ganglia that has been implicated in reward-related neural circuits. We have found that the FRN relates to fMRI-based measures of striatal response to rewards, as well as behavioral metrics of reward sensitivity. Moreover, we have found that the FRN is reduced in both adults and adolescents who are more depressed-and have recently found that reduced reward-related brain activity can predict changes in depressive symptoms over the course of two years among adolescents. The current proposal extends this work into a much larger and longitudinal sample, and incorporates multiple measures of reward sensitivity, depressive symptoms, and puberty. We will assess: a) the relationship between multiple measures of reward sensitivity and depressive symptoms in a large sample that spans adolescence at two time points, separated by 2 years (Aim 1); b) normative developmental increases in both reward sensitivity and depressive symptoms, especially as a function of pubertal stage (Aim 2); c) prospective relations between reward sensitivity and depressive symptoms over time, and whether reward sensitivity at the first assessment can predict changes in depression two years later (Aim 3); finally, if pubertal changes predicts a stronger link between reward sensitivity and later depressive symptoms (Aim 3). A number of secondary aims are also evaluated (e.g., specificity to depressive symptoms and not anxious symptoms; utility of salivary testosterone as a marker of pubertal stage; role of stressful life events). The present study will contribute to the literature on the developmental neurobiology of reward, as well as the neurobiological changes related to individual differences in depression and risk for depression across adolescence.

Title: **The Influence of Estrogen on the Fear Extinction Network in Humans**
P.I.: **Mohammed R. Milad**
Institution: **Massachusetts General Hospital**
Grant No.: **MH097880-01**
Award: **$100,000**

The prevalence of anxiety disorders is twice as high in women. The reason for this eleveated prevalence is unclear, partly because most animal research has used only males, and most human research has not considered sex as a variable of interest. This proposal will begin to examine the neurobiological basis for these differences by first studying how natural fluctuations of estrogen in healthy women may influence the resting-state activity and the extinction-induced reactivity of the fear extinction network, including the amygdala, hippocampus, and the ventromedial prefrontal cortex (vmPFC). Additional experiments will involve exogenous manipulations of estrogen in naturally cycling women to see how these manipulations may interact with the functional activation of the fear extinction network. Healthy women will participate in a well-established fear conditioning and extinction protocol at different points of their menstrual cycle. Functional MRI and psychophysiological tools wil be employed to test two overall hypotheses: 1) Naturally elevated estrogen levels during the menstrual cycle will facilitate the resting-state activity and extinction-induced functional reactivity of the fear extinction network, and will be associated with enhanced extinction retention, and 2) Exogenous administration of estrogen to women will enhance extinction retention, which will be associated with enahnced resting-state activity and extinction-induced functional reactivity of this extinction circuitry during extinction recall. Findings from his proposal may help develop sex-specific treatments for anxiety disorders, for example by using hormonal-based pharmacological adjuncts to facilitate the processes of safety learning during therapy.

National Institute on Minority Health and Health Disparities

Title: **Scientific Conference R13**
P.I.: **Balwant Singh Ahluwalia**
Institution: **Howard University**
Grant No.: **MD006773-01S1**
Award: **$1,000**

The focus of this tissue oriented conference is to answer pivotal questions regarding the higher incidence and characteristics of uterine leiomyomas in African American Women (AAW). The conference will feature scientific presentations that address the current state of knowledge and identify emerging issues regarding leiomyomas in the AAW and serve as a catalyst for discussion during the final session on “New Course for Future Research and Directions”. Newer, promising and innovative research that will continue to build

upon and enhance our understanding of the basic pathophysiology of uterine leiomyoma will be discussed. Innovations in treatment modalities with an emphasis on impact to the female reproductive tract, reproductive potential and quality of life will be presented. The target audience includes researchers working in the fields of biomedicine, epidemiology basic, clinical and translational science, therapeutics, academic medicine, government, industry; physicians, nurses, other healthcare workers and the lay community. All participants will be invited to present posters and special area will be assigned for poster presentation. The Conference proceedings will be edited by the editorial committee to prepare for publication in a peer reviewed journal and the entire contents will be posted on the Howard University Web Site. Accreditation Statement: The activity will be planned and implemented with essential areas and policies of the Accreditation Council for Continuing Medical Education through the Howard University College of Medicine Credit Designation Statement. Howard University College of Medicine will designate this educational activity for a maximum of 8 credits AMA Category 1 Credits. Physicians will only claim credit commensurate with the extent of their participation in the activity.

National Institute of Neurological Disorders and Stroke

Title: **NIH Pain Consortium Centers of Excellence in Pain Education (CoEPEs)**
P.I.: **NIDA (coordinating center)**
Institution: **NIH Pain Consortium, funding 12 centers**
Grant No.: **1201100111U**
Award: **$200,000**

The NIH Pain Consortium has established 12 Centers of Excellence in Pain Education (CoEPEs), led by the National Institute on Drug Abuse, to develop and disseminate curriculum resources to improve medical, dental, nursing, and pharmacy education in the assessment, diagnosis, and treatment of pain, while minimizing the abuse of opioid medications, an area that current training under-emphasizes. A wide variety of women's health issues will be addressed, including: Migraine and giant cell arteritis-related headaches; Hormonally-related headaches associated with menstruation, pregnancy, and menopause; Fibromyalgia and/or temporomandibular joint disorders; Stage IV endometriosis experiencing pelvic pain and dysmenhorrhea; Post-operative pain in an infant who underwent a laparotomy to remove an ovarian cyst; Female breast cancer patients and survivors experiencing pain related to or separate from cancer; Pelvic pain of unknown etiology; Musculoskeletal pain in a female who may be a victim of domestic abuse; End-of-life pain management scenario for a female patient with a 30 year history of systemic lupus erythematosus; Irritable bowel syndrome; Neuropathic dental pain, atypical odontalgia (phantom tooth pain), and burning mouth syndrome; and Vulvodynia and chronic fatigue syndrome.

Title: **Neuropathologic Abnormalities Define a Subgroup of Patients with CFS**

P.I.: **Benjamin Natelson**
Institution: **Beth Israel Medical Center**
Grant No.: **NS075653-02**
Award: **$66,509**

Chronic fatigue syndrome (CFS) is a debilitating multi-symptom disorder characterized by unexplained and prolonged fatigue, whose diagnosis is currently based on a relatively broad clinical case definition. Consequently, the pool of CFS patients included in clinical studies of the illness is greatly heterogeneous—a fact that might have impeded research progress to date. A major step forward in understanding the pathophysiology of CFS would involve reducing this heterogeneity by identifying one or more subgroups of patients with different pathophysiological causes of their illness, and then selecting one of these subgroups for inclusion into research studies. Over the past few years, we and others have provided substantial data supporting the existence of a subgroup of patients with a neurobiological cause for their illness, based on stratifying the sample according to the absence or presence of comorbid Axis I psychopathology (CFS-no psych or CFS-NP and CFS-psych or CFS-P, respectively). Compared to CFS-P patients, the CFS-NP patients had more cognitive dysfunction, a higher rate of abnormal cerebrospinal fluid (CSF) findings, lower regional cerebral blood flow (rCBF), and higher ventricular CSF lactate values. A further complication and limitation of these studies is that each had investigated only one brain-related variable, whose utility in separating CFS patients into subgroups was limited. The purpose of the present Exploratory/Developmental Research Grant (R21) proposal is to rigorously assess and confirm whether patients in the CFS-NP group have consistent abnormalities across several different neuropathological variables—an outcome that would be expected if this group, in fact, does have distinct neurobiological underpinnings. Specifically, in the same subjects, we will (a) assess cognitive function using objective neuropsychological testing; (b) conduct biochemical analysis of spinal fluid samples obtained by lumbar puncture; and (c) measure rCBF and ventricular lactate using magnetic resonance imaging and spectroscopy, respectively, in CFS-P and CFS-NP patients. This will allow us to test the hypothesis that CFS-NP patients have more abnormalities in these outcome variables than CFS-P patients. Our second Aim will use the results from the first Aim in a cluster analysis to attempt objective, data-driven classification of the CFS subjects into subtypes, and then compare the resulting subgroups based on membership into CFS-NP or CFS-P groups. This aim will test the hypothesis that the results of the cluster analysis will identify a group with abnormalities across the multiple brain-based variables studied, and this group will be constituted of significantly more CFS-NP patients than in other groups.

Title: **Brainstem Pain-Modulating Systems in Migraine-Related Photophobia**
P.I.: **Mary M. Heinricher**
Institution: **Oregon Health & Science University**
Grant No.: **NS082020-01**
Award: **$300,000**

Migraine is the most common neurological disorder, and affects over 10% of the population in any given year, with over half of these individuals reporting severe impairment. For many patients, a severe, even disabling, component of the migraine attack is photophobia, yet neuroscientists are just starting to investigate the underlying neurobiological mechanisms. The present application tests the overarching hypothesis that brainstem pain-modulating circuits, already implicated in migraine-related pain, also contribute to migraine-related photophobia. This hypothesis is based on the entirely unexpected observation that pain-modulating neurons in the rostral ventromedial medulla, the final output of an important brainstem pain-modulating system, develop photoresponsiveness in animal models of migraine headache, although they do not respond to light under normal conditions. In three Specific Aims using the nitroglycerin migraine model in the rat, we will document light-evoked activity in identified pain-modulating neurons and determine whether this is specific to migraine. We will also determine whether pain-modulating systems contribute to light aversion and light-induced pain enhancement. Finally, we will identify possible pathways through which light gains access to pain-modulating systems. The present proposal brings together electrophysiological and behavioral approaches to show how light engages pain-modulating systems to produce photophobia. These studies will provide insights into the neurobiological mechanisms of migraine-related photophobia, fundamental information critical for developing new migraine treatments.

John F. Fogarty International Center for Advanced Study in the Health Sciences

Title: **Vanderbilt University-CIDRZ AIDS International Training and Research Program**
P.I.: **Sten H. Vermund**
Institution: **Vanderbilt University Medical Center**
Grant No.: **TW001035-14**
Award: **$25,000**

The Vanderbilt University (VU) Center for Infectious Disease Research in Zambia (CIDRZ) AITRP, formerly the VU-University of Alabama at Birmingham AITRP, seeks renewal of its grant, now in its tenth year due to an NIH-initiated one-year extension. We contribute research training to both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care. The VU-CIDRZ training partnership with our international collaborators is designed to train foreign scientists and key research support staff to conduct independent research and training in their home countries, as well as perform at an internationally credible level in collaborations with local and foreign scientists. We now seek to renew our AITRP with a continued focus on Zambia (since 1998), Pakistan (since 1994), India (since 2000), China (since 2000), and our newest partnership in Mozambique (VU training partnership since 2006 and developmental AITRP engagement since 2007). We have completed our older training commitments in Mongolia, Jamaica, and Russia and will complete our training commitments for Bangladesh upon the graduation of a current doctoral training

(anticipated in 2011). We have restricted our AITRP training partnerships to five focus cities in order not to dilute our impact to where we have funded overseas research and strong research training partners. At the same time, we have leveraged support in each of the five venues such that our AITRP resources will go much further than permitted by the grant's funding alone. We will continue to provide a diverse portfolio of long, medium, and short-term training options. To date 58 trainees have received graduate degrees, 97% of whom have returned to work in their home countries, 8 are currently in degree programs and over 2,000 have been trained through our in-country advanced short-courses. We believe VU remains an ideal university partner for this initiative for several significant reasons The migration of the training program to VU offers the opportunity for trainees to receive the absolute highest quality of graduate training and exposure to innovative HIV/AIDS/STD/TB related research, resources, and faculty mentors. The program is uniquely positioned within the infrastructure of the VU Institute for Global Health (VU IGH),directed by Dr. Vermund with its "center-without-walls" philosophy that nurtures noncompetitive partnerships among and within VU and with partner institutions around the globe. We feel that the innovative features of our renewal and our proven track record address the unmet needs in international AIDS training.
RELEVANCE (Seeinstructions): The VU-CIDRZ training partnership with our international collaborators is designed to strengthen both institutional and individual biomedical and behavioral research capacities focused on HIV-related research in both prevention and care in developing countries.

Title: **AIDS International Training and Research Program**
P.I.: **Adaora A. Adimora**
Institution: **University of North Carolina at Chapel Hill**
Grant No.: **TW001039-14**
Award: **$25,000**

This is the second competitive renewal application for the UNC AIDS International Training and Research Program. We propose to continue to provide training in three countries: The Peoples Republic of China, Malawi and Cameroon. Investigators at UNC have worked in China since 1979, Malawi since 1989, and Cameroon since 1998. The UNC AITRP has embraced several guiding principles. First, we use training to build strong ties to key in-country organizations. Trainees with guaranteed "return jobs" in these organizations are preferentially selected. Second, our training opportunities build on funded research projects and bridge many of the strengths of UNC. Wherever possible we combine basic, clinical and epidemiological training and research in order to build critical mass. Third, we have used the Fogarty training to promote international research, working with many collaborators and funding agencies. Fourth, we have developed south-to-south and international collaborations to facilitate training and ongoing research opportunities. For example, University of the Witwatersrand is a training site for Malawi personnel, and we have developed a strong collaboration with the London School of Hygiene and Tropical Medicine for training of physicians from Malawi (a former British protectorate). Fifth, we have looked for opportunities for evolution and innovation. Such efforts have been particularly important in the development of a new Department of

Public Health at the Malawi College of Medicine (which has received dedicated Fogarty support), extensive research ethics and IRB training in China, and rapid technology transfer in all three UNC AITRP countries. Sixth, we are committed to in-country leadership and ongoing mentorship after the trainee has completed our program.

Title: **Emory AIDS International Training and Research Program**
P.I.: **Carlos Del Rio**
Institution: **Emory University**
Grant No.: **TW001042-14**
Award: **$25,000**

Located in Atlanta, the Emory AIDS International Training and Research Program (AITRP) has established itself as an interdisciplinary training environment, that is producing highly qualified HIV/AIDS researchers. The collaborating countries of the Emory AITRP proposed for this application are Mexico, Georgia, Vietnam, Rwanda and Zambia. The specific aims of the research training program include: 1. To build academic capacity in partner countries through the support of in-country education and training. 2. To build HIV/AIDS research human resource capacity through the support of degree-seeking, long-term training. 3. To fill identified gaps in partner country research training capacity through the provision of specialized medium and short-term training. 4. To build in-country capacity to conduct implementation science research that will allow our trainees to become involved in the evaluation of the impact of a variety of interventions that are currently occurring in our collaborating countries such as PEPFAR.

Title: **Haiti AIDS Research Training: Models to Implementation**
P.I.: **Jean William Pape**
Institution: **GHESKIO Center**
Grant No.: **TW006896-09**
Award: **$25,000**

The goal of GHESKIO-Cornell ICOHRTA training program is to increase capacity in integrated clinical, operational, and health services research in support of Haiti's national scale-up of HIV and tuberculosis services. Haiti is the poorest country in the Western Hemisphere and has the highest rates of both HIV infection and tuberculosis. It is estimated that 3% of the adult population is HIV-infected and that the prevalence of tuberculosis is 402/100,000 population (100xUS rates). In response to this epidemic, the Haitian Ministry of Health asked GHESKIO to form a national HIV and TB Network, a collaboration of 32 public and private health care organizations across the country that is charged with "scaling-up" to provide a standardized package of HIV and tuberculosis services to 500,000 persons by 2014. The services include voluntary counseling and HIV testing, management of tuberculosis and sexually transmitted infections, prevention of mother to child HIV transmission, and comprehensive HIV care of children, adolescents, and adults. The Haitian Ministry of Health has asked GHESKIO (Haitian Study Group for the Study of Kaposi's Sarcoma and Opportunistic Infections) to lead this network

through training, supervision, monitoring and evaluation, and through the conduct of operational and health services research. GHESKIO is an international research and training institution that has benefited from 25 years of uninterrupted NIH funding and research capacity building with Cornell University, and support from the Fogarty International Center. GHESKIO is recognized as a center of research excellence, and is a member of the NIH HIV Vaccine Trials Network (VTN), the AIDS Clinical Trials Group (ACTG) and a recipient of support from the United Nations Global Fund for AIDS, TB and Malaria and the President's Emergency Plan for AIDS relief (PEPFAR). In the current proposal, GHESKIO will continue as the primary training institution and extend research capacity to other organizations in Haiti that are participating in the GHESKIO HIV and Tuberculosis Network. The program will continue to emphasize medium- and long-term training in Haiti. Since its inception four years ago the ICOHRTA has provided training to 120 Haitian biomedical personnel, all of whom are working in Haiti, providing HIV/TB services and conducting operational and health services research. GHESKIO, in collaboration with Haitian and International partners, will develop training curricula in clinical, operational, and health services research methodology and in ethics, program management, and scientific writing. A Masters in Public Health Degree program, established with ICOHRTA support, will continue to be offered in Haiti by Quisqueya University, in partnership with GHESKIO and Cornell University.

Title: **Molecular Epidemiology of Drug Resistance and Population Genetic Structure of Plasmodium Falciparum and P. Vivax in Yunnan and Hainan, China**
P.I.: **Fangli Lu**
Institution: **Sun Yat-sen University**
Grant No.: **TW008151-04**
Award: **$50,000**

Malaria remains a serious public health problem in China. In the subtropical Yunnan Province and the tropical Hainan Island of China, malaria has been the most endemic with high transmission of both Plasmodium falciparum and P. vivax. However, most of the attention in terms of research and interventions have been focused in Africa and Southeast Asia, very few studies of malaria in China have been conducted. Because of extensive use, chloroquine (CQ) has now lost its efficacy due to the emergence of resistant strains in most parts of the world. Meanwhile, suspension of the use of CQ has resulted in reappearance of CQ sensitivity. However, there were differences in the evolution of CQ resistance between parasites from Yunnan and Hainan, the exact mechanism needs to be investigated. Sulfadoxine-pyrimethamine (SP) targets the dhfr and dhps genes of P. falciparum, and point mutations that confer resistance have been widely reported worldwide. Documenting the identity and extent of SP resistance is also critical for policy decisions regarding antimalarial drugs. In addition, P. vivax causes a large burden of morbidity in the world including China but traditionally has been understudied. Based on these, our long-term goal of this proposal is 1) to identify single-nucleotide polymorphism (SNP) and characterize the geographic distribution of genetic diversity, population structure, and haplotype variability at drug resistant loci of P.

falciparum from Yunnan and Hainan, China, 2) to examine the geographic population structure, levels of genetic diversity of P. vivax using microsatellite and SNP, and 3) to yield valuable information for making more effective malaria control policies in China. In the past several years we have developed the molecular methods to study the genetics, population diversity, and evolution of malaria parasites, and have done some preliminary studies on malaria field isolates from Yunnan and Hainan using genetic markers, thus enabling us to study the molecular epidemiology of these important malaria parasites in this proposal. The specific aims are to: 1. Determine genetic polymorphisms associated with CQ resistance (CQR) in P. falciparum field isolates from Yunnan and Hainan provinces, China. 2. Determine the point mutation prevalence in the dhfr (pyrimethamine drug resistance) and dhps (sulfadoxine drug resistance) genes associated with SP resistance in P. falciparum field isolates from Yunnan and Hainan provinces, China. 3. Assess the changes of P. vivax genotypes using pvcsp, pvmsp1, pvmsp3-¿ genes, and microsatellite markers and determine the geographic structure and specific epidemiological characteristics of P. vivax transmission in Yunnan and Hainan, China.

Title: **Tobacco Control Network Among Women in Parana, Brazil**
P.I.: **Isabel C. Scarinci**
Institution: **University of Alabama at Birmingham**
Grant No.: **TW009272-01**
Award: **$100,000**

An understanding of women and their tobacco-related issues, as well as the need for the development of gender-relevant tobacco control efforts, have been highlighted as priorities in landmark guiding documents published in the past few years (e.g., WHO Framework Convention on Tobacco Control-WHO FCTC). Brazil is the second largest producer of tobacco in the world, and 95% of the tobacco is produced in the three Southern states (Paraná, Santa Catarina, and Rio Grande do Sul). Although, historically, tobacco use among women in developing countries, particularly Latin America, has been relatively low as compared to men, the smoking epidemic is rapidly spreading to women in developing countries, and these three Southern states have the highest prevalence of women smokers in the country. We have established a Network for Tobacco Control among Women in Paraná, Brazil with the purpose of establishing community and institutional capacity to promote gender-relevant tobacco control efforts among women through Community-Based Participatory Research (CBPR) and training. The goals of the network are to reduce tobacco use and exposure to environmental tobacco smoke (ETS) among women in Paraná, and to develop a cadre of well-trained researchers who will continue to address comprehensive tobacco control strategies at multiple levels. The network conducted an epidemiological survey on the prevalence and factors associated with tobacco use among women across the State of Paraná. Based on the results, the network identified four priorities: (1) to implement policy changes to decrease ETS; (2) to understand the health/social issues of women in tobacco farming; (3) to develop and evaluate a comprehensive, culturally- and gender-relevant, school-based smoking prevention program; and (4) to improve access and delivery of smoking cessation programs through the public health system with a particular focus on “light smokers” as

74.8% of women smokers in our study reported smoking 10 or less cigarettes/day. The network is currently addressing the first three priorities, including support for legislation, which resulted in Paraná having the strongest indoor tobacco ban in the country. The overall goal of this renewal is three-fold: (1) to continue to sustain and strengthen the network; (2) to conduct a group randomized controlled trial to assess the efficacy of a theory-based, culturally- and gender-relevant Community Health Worker intervention for Brazilian women "light smokers" that will augment the smoking cessation programs offered through the public health system; and (3) to expand our current Career Development and Research Training Program to the other two major tobacco growing states in order to develop a cadre of well-trained researchers who will continue to develop and implement gender-relevant comprehensive tobacco control strategies at all levels.

Title: **Vanderbilt-Emory-Cornell-Duke Consortium for Global Health Fellows (VECDor)**
P.I.: **Sten H. Vermund**
Institution: **Vanderbilt University Medical Center**
Grant No.: **TW009337-01**
Award: **$40,000**

The Vanderbilt-Emory-Cornell-Duke Consortium (VECDor) brings the substantial and complementary expertise of experienced institutions to the Fogarty Global Health Fellows Program. The Vanderbilt Institute for Global Health (VIGH) has served as the Fogarty International Clinical Research Scholars and Fellows (FICRS-F) Program Support Center since 2007, working with 87 partner institutions to nurture 419 competitively chosen pre- and postdoctoral trainees from the US and from 27 low- and middle-income countries (LMICs). Topics have included infectious diseases, cancer, heart and lung disease, stroke, diabetes, nutrition, behavioral and mental health issues (including substance abuse), women's and children's health, ophthalmic disease, oral health, neurology, and animal-human health. VECDor's highly experienced global health mentors are already working together in the US and LMIC partner institutions, selected as diverse, well-funded research sites in Africa (Kenya, Zambia, Tanzania, Rwanda), Asia (India, China, Vietnam), Latin America (Brazil, Mexico), and the Caribbean (Haiti). Using a highly efficient support center that maximizes the direction of funds to research training, and leveraging multiple sources of financial and in-kind co-funding, we will link with more than 68 T32 and other NIH-funded training programs and with minority institution partners to select and deploy 80 to 100 US and LMIC trainees with outstanding promise for research careers. VECDor will implement a strategic mentoring and trainee support plan across the consortium, including a substantial preparation phase prior to field deployment and continuing after the research year is completed, to ensure the highest quality research publications and scientific meeting presentations, and maximum trainee success in obtaining research and career development grants. Research themes will address all topic and geographical areas of interest to trainees and NIH Institutes and Centers, emphasizing both communicable and non-communicable diseases. We will document the Program's impact through a long-term monitoring and evaluation (M&E) plan that tracks the career directions and outputs of all Fellows, using FIC's

CareerTrac system, e.g., future employment, K grants, research grants, scientific presentations, and publications. We will further refine our existing web-based tools to share knowledge, foster local and global networking, and strengthen and sustain clinical research skills among global health fellows and alumni. We have brokered substantial institutional and site-based co-funding to leverage NIH resources. VECDor is built on the mutual respect of our US and global partners and our collective track record of research innovation and mentorship. Combining our extensive recent experience in research training program management, robust research funding bases in major diseases of global significance, renowned international research training partners and sites, and enhanced institutional co-funding commitments, VECDor will continue to nurture key members of the global health research workforce of the 21st century, as we have done within the incumbent FICRS-F program.

Title: **Global Health Fellows and Scholars Research Training**
P.I.: **Lee W. Riley**
Institution: **University of California, Berkeley**
Grant No.: **TW009338-01**
Award: **$40,000**

We propose to establish a Support Center (Consortium) involving University of California-Berkeley, Yale University, Stanford University and Florida International University to train postdoctoral fellows, PhD graduate students, and medical students for them to develop a long-term career in global health research. The main objective of the program is to generate a new and young cadre of global health researchers, educators, and professionals who will be prepared to address the new challenges in global health that arise from our constantly changing planet, in particular, those challenges that emerge from the world's burgeoning human settlements known as slums that have developed in urban and rural communities of many low and middle-income countries (LMIC). Slum-specific factors associated with chronic, noncommunicable, as well as infectious diseases, environmental health hazards, risks specific to women and children, intentional and unintentional injuries, and mental disorders are poorly understood, and there are not many researchers dealing with these issues. These diseases comprise a large proportion of the world's health problems. Our training program will emphasize a multidisciplinary, problem-based approach using slum health as a platform to expose trainees to the new concepts, models, and approaches to global health research. The training will be conducted at US government-funded field research sites at 10 locations abroad, including Central and South America, Sub-Saharan Africa, South Asia, East Asia, and Eastern Europe, where the Consortium mentors have been conducting research for more than 3 years. The Consortium includes a large reservoir of postdoctoral fellows and upper division graduate and medical students who will be candidates for the training program. The Consortium has made a special effort to identify potential trainees from under-represented minority groups and it has thus partnered with Florida International University, the largest Hispanic-serving institution in the continental US, which also has a large pool of African-American students. Thus, this research training program will provide an opportunity to draw highly skilled researchers from diverse backgrounds from

a wide spectrum of disciplines, who will use the knowledge gained from this program to develop their own research agenda to improve the lives of people who are exposed to a wide range of interacting health risks that engender new global health challenges.

Title: **Fogarty Global Health Fellows Coordinating Center**
P.I.: **Charles Michael van der Horst**
Institution: **University of North Carolina at Chapel Hill**
Grant Nos.: **TW009340-01, TW009340-01S4**
Award: **$190,000**

The University of North Carolina, Johns Hopkins University, Morehouse School of Medicine, and Tulane University have formed a consortium, based on over 20 years of research and training collaboration, to launch the Fogarty Global Health Fellows Program (FGHF). This consortium brings together 17 primary research training sites in Africa (Ghana, Malawi, South Africa (2), Swaziland, Uganda (2), Zambia), Asia (Bangladesh, China (3), India, Thailand) and South America (Argentina, Brazil, Peru). Our proposal focuses on more advanced trainees, regional partnerships, multilayered mentoring. Each primary training site has a lengthy history of NIH and US government research funding, training of US and international research trainees, and on-the-ground faculty mentors, many of whom were trained through Fogarty International Center programs. Twelve of the proposed training sites are currently part of the Fogarty International Clinical Research Scholars & Fellows program. We will preferentially recruit advanced post-doctoral researchers from more than 50 T32 training grants at the affiliated institutions in all disciplines of health sciences, as well a early-stage post-doctoral researchers, and doctoral and health science students from Schools of Dentistry, Medicine, Nursing, Pharmacy, Public Health and Veterinary Medicine at our 4 universities and around the US. Trainees from the international sites will be "twinned" with US trainees through additional resources including other existing Fogarty training grants and the Gilead Foundation to build research capacity at the sites to which the consortium has long-standing commitment. The areas of research focus include a broad range of topics that are consistent with the NIH Fogarty 2008-2012 Strategic Plan, recognizing the growing importance of non-communicable diseases while continuing the commitment to infectious diseases. Trainee applications will be judged on the quality of the research proposal, their previous track record, and commitment to a global health academic research career. Trainees will be assigned a team of mentors, with at least one senior and one junior mentor, who will closely monitor the progress of the trainee and provide on-site supervision. Drawing on existing linkages between sites and training faculty, we will enhance regional partnerships in order to provide training and guidance for junior mentors. Trainees and their twins will have access to biostatistical and epidemiologic consultation from UNC and Tulane faculty for both data analyses and grant writing purposes as well as supplemental funding for their research from multiple small grant opportunities at UNC. FGHF leverages a unique set of resources, training faculty, and sites in order to directly respond to three of the four Fogarty Strategic 2008-2012 Goals: bridging the training gap, fostering sustainable research, and building strategic partnerships.

Title: **University of California Global Health Institute Program for Fellows and Scholars**
P.I.: **Craig R. Cohen**
Institution: **University of California, San Francisco**
Grant Nos.: **TW009343-01, TW009343-01S1**
Award: **$190,000**

In response to RFA-TW-11-001, the University of California Global Health Institute (UCGHI), including UC San Francisco (UCSF), UC San Diego (UCSD), UC Los Angeles (UCLA) and UC Davis (UCD), along with a network consisting of 21 collaborating international institutions across 14 countries and 5 continents proposes the creation of the UCGHI Program for Fellows and Scholars (UCGHI-PFS). Our specific aims are: 1) To recruit a diverse group of trainees who are diverse in discipline and ethnicity, and who aspire to build successful academic research careers in global health focusing on interdisciplinary research; 2) To provide outstanding, interdisciplinary education and training in global health in collaboration with 230 faculty mentors from the Program, and 21 collaborating well established international institutions; 3) To provide each trainee with a rich and enduring mentored research experience that fosters scientific and career development in global health research; 4) To develop models of interdisciplinary, innovative global health research and training designed to improve health for populations around the world; and 5) To broaden and expand the global health faculty across the four UC campuses, UCGHI and international partner institutions, and strengthen existing global health networks between UCGHI and collaborating international institutions. UCGHI-PFS will recruit candidates from a pipeline of 57 T32 programs, representing 12 of the 15 NIH institutes participating in this RFA. In addition to these programs which annually support 160 predoctoral and 208 postdoctoral fellows, 20% of whom are under-represented minorities, we will recruit international trainees from 8 D43 training grants across al four campuses, affiliated schools and international partner institutions. For each trainee, 4 principal components include: i) an 11-month, hands-on research project on-site with one of our international collaborative partners; ii) a strong, interdisciplinary mentored research experience; iii) instruction in global health and related topics provided through on-site, and on-line courses; and iv) career development to help ensure that trainees attain their short-term career goals and succeed in transitioning to the next career stage. These four components are closely interlinked; a Leadership Group and campus Steering Committees will ensure they form a seamless, integrated program. Innovative aspects include a unified consortium that offers synergy by capitalizing upon the UCGHI's ten campuses, Centers of Expertise and faculty that regularly interact and collaborate; faculty mentors offering training across diverse disciplines (e.g., medicine, nursing, pharmacy, dentistry, public health, veterinary science, oceanography, agriculture, and biological and social sciences); training experiences on a wide range of diseases and problems of global health significance; an ability to leverage common resources across the four participating UC campuses (e.g., UCGHI, CTSAs, CFARs and Research eXchange consortia); and an innovative mentoring initiative.

Title: **Northern/Pacific Universities Global Health Research Training Consortium**
P.I.: **Joseph Raymond Zunt**
Institution: **University of Washington**
Grant No.: **TW009345-01**
Award: **$40,000**

This R25 proposal, the "Northern/Pacific Global Health Research Fellows Training Consortium" includes a consortium of four U.S. universities (the Universities of Hawaii, Michigan, Minnesota and Washington) and partnerships with universities and research institutions in six countries (Kenya, Ghana, Uganda, Peru, China and Thailand). The Consortium will be housed within the Department of Global Health at the University of Washington. The four U.S. universities have each committed matching funds totaling $595,000 to support a second year of fellowship for the most productive fellows and additional fellows. The N/P Consortium will (1) implement an enhanced mentoring program emphasizing a manual of required, specific commitments and guidelines for mentors and mentees; bimonthly Internet-based research-in-progress sessions involving all Global Health Fellows and joint participation of mentors for the presenting trainee(s); (2) help in "globalizing" existing T32 research training programs, and strengthen and broaden the disciplines involved in our Consortium's global health research programs, by actively recruiting senior U.S. fellows from the 161 T32 research training grants of the N/P Consortium, and other trainees (e.g. senior Department of Global Health postdoctoral fellows of the UW Institute for Health Metrics and Evaluation), (3) promote entrepreneurial development of interdisciplinary, cross-institutional, sustainable research partnerships, particularly within neglected areas of global health, engaging comentors from the academic programs that house the T32 grants from which Global Health Research Fellows are recruited; (4) establish a "warranty" for the Global Health Research Fellows, beginning with a tried and proven expedited global research project trajectory during year one, progressing to presentation and then publication of research, a potential second year of fellowship funding for the most promising trainees, to assistance launching independent careers through further opportunities in new research programs as they develop, to ongoing mentoring of alumni in applications for new global health grants, such as Fogarty IRSDA K01 grants, ISGHA K02 grants, other K awards, including CTSA awards and Foundation awards, to creation of an alumni and mentor network involving posting of new publications, funding and job opportunities, and potential participation in cross-consortium Global Health Fellows reunions at global health conferences. This proposal would provide funding for a total of 12-15 trainees each year, depending on the number of second year trainee awards—for a total of 75 trainees. Including the Fulbright/Fogarty Fellows in Public Health (at least one each in Kenya, Ghana and Peru), who will receive the same orientation at NIH and mentoring by participants in this proposal, we anticipate at least 90 trainees over the five-year grant period.

National Center for Complementary and Alternative Medicine

Title: **Brain-Centered Therapy versus Medication for Urgency Urinary Incontinence—A Randomized Clinical Trial**
P.I.: **Loren Howard Ketai**
Institution: **University of New Mexico Health Sciences Center**
Grant No.: **AT007171-01A1**
Award: **$100,000**

Brain-Centered Therapy versus Medication for Urgency Urinary Incontinence RCT Project Summary/Abstract Urinary urgency incontinence, involuntary urine loss associated with a sudden, compelling desire to urinate, is a common and costly public health problem without cure. Urgency incontinence increases with age and its sufferers are primarily women. These women have severely compromised quality of life from the stigma and humiliation of urgency incontinence. They have attendant depression and loss of work productivity, income and independence. They must bear the burden of medication costs, despite medication's limited effectiveness. Due to unprecedented growth of the U.S. population older than 65, urgency incontinence will consume 86.2 billion dollars by 2020. Finding successful, durable treatment for this burgeoning public health problem is an unmet need. This project will evaluate hypnotherapy treatment to meet this need. This proposal will compare efficacy of hypnotherapy to pharmacotherapy in urgency incontinence. Preliminary evidence supports pursuit of hypnotherapy in urgency incontinence treatment. Patients with functional disorders such as urgency incontinence respond differently to physiologic stimulus. This abnormal stress response, "hyper-vigilance," is associated with abnormal brain activation on functional brain imaging. Hypnotherapy offers the hope of modifying this abnormal response in urgency incontinence. A case series and our own pilot data support hypnotherapy's effectiveness in urgency incontinence. Therefore, the long term goal of this proposal is to shift focus of urgency incontinence treatment towards the brain and away from the peripheral nervous system, the target of pharmacotherapy. The objective of this application is to determine whether hypnotherapy can be more effective than current pharmacologic therapy of urgency incontinence. Its central hypothesis is that hypo-therapy modulates interactions between the brain and bladder, providing effective urgency incontinence treatment. This hypothesis will be tested pursuing 2 specific aims: 1) Determine whether a mind/body therapy (hypnotherapy) is a more effective and durable treatment of urgency urinary incontinence than a non-mind/body treatment (pharmacotherapy) 2) Determine whether hypnotherapy treatment of urgency urinary incontinence is associated with greater modification of limbic cortex activation and connectivity on functional MRI than that which occurs following pharmacotherapy. Urge incontinent women (N=152) will be randomized to medications or hypnotherapy and evaluated at months 2, 6 &12. Sixty women will undergo imaging before and after treatment. The rationale for the proposal is based on work which suggests that brain activation is abnormal in subjects with urgency incontinence, that urgency incontinence responds to hypnotherapy, and that the hypnotic state affects sites of abnormal brain activation. This proposal is significant because it seeks to treat urgency incontinence, a growing public health problem, with hypnotherapy, a mind/body intervention. This novel approach uses hypnotherapy to treat urgency

incontinence and offers innovative use of brain imaging to elucidate hypnotherapy's mechanism of action and shifts the treatment paradigm from the bladder to the mind.