FY 2005 ORWH-SUPPORTED RESEARCH INITIATIVES

AGING

TITLE: **Phytoestrogens and Aging: Dose, Time and Tissue** **NIA**
P.I.: **William Helferich, PhD**
INST.: **University of Illinois, Urbana-Champaign**
GRANT NO.: **5 P01 AG024387-02**
KEYWORDS: **aging, dietary supplements, breast cancer, estrogen, nutrition**
STUDY TYPE: **basic**
AWARD: **$100,000**

The overall research objective of this grant is to evaluate the potential beneficial or detrimental effects of dietary phytoestrogens on breast cancer progression, adipose tissue and the brain, using well-established laboratory animal models. Although phytoestrogens are consumed by older Americans for their perceived beneficial effects, these estrogenic compounds have not been adequately evaluated for safety, despite increasing consumption of these chemicals at high levels, especially among older women. The theme of this Program Project is that dosage, timing, and duration of exposure will all be determinants of the biological outcome of phytoestrogen exposure in different target tissues. Since both potential risks and benefits need to be evaluated, these studies cannot be conducted in humans for ethical reasons and can best be conducted in appropriate pre-clinical laboratory animal models. The proposed studies provide a systematic evaluation of the role that various regimens of phytoestrogen exposure may have on target organs that are of special relevance in aging, and these studies will also seek to determine the mechanism of phytoestrogen effects on these different target tissues.

TITLE: **Health, Illness, and Social Life at Older Ages** **NIA**
National Social Life Health and Aging Project
P.I.: **Linda Waite, PhD**
INST.: **University of Chicago**
GRANT NO.: **5 R01 AG021487-02**
KEYWORDS: **sexuality, aging, mental health, prevention, behavioral & social science**
STUDY TYPE: **clinical**
AWARD: **$250,000**

It is well established that social support, particularly marriage, bolsters psychological and physical health as people age. Human sexuality constitutes one essential, but poorly understood parameter of both healthy aging and social life at older ages. Physicians and public health policy makers lack a scientific base of information for advising older people or designing programs that might promote sexual health, support prolonged independence, relieve anxiety, prevent dysfunction or disease, or address current issues influencing intimate social and sexual relationships among older Americans. The Interactive Biopsychosocial Model (IBM) developed for this research is an extension of Engel's biopsychosocial model. Health is conceptualized as a function of biophysical and psychocognitive dynamics between individuals over time and incorporates social embeddedness in shaping that process. A nationally-representative probability sample of 3,000 community-residing women and men ages 57-84 will be followed longitudinally in two waves over five years. We will oversample African American and Hispanic adults. Face-to-face interviews and biomarker collection will take place in respondents' homes. Data collection will elicit: 1) demographics; 2) social networks; 3) social and cultural activity; 4) physical and mental health including cognition; 5) well-being; 6) illness; 7) medications and alternative therapies; 8) history of sexual and intimate partnerships; 9) patient-physician communication regarding sexuality; sexual identity, functionality, desire, opportunity, and attitudes about sexuality and intimacy. Biomarker collection will include: height, weight, blood pressure, serum (glucose metabolism, HIV, hepatitis, syphilis), urine (gonorrhea, chlamydia, trichomonas), saliva (endocrine evaluation), and sensory testing (vision, hearing, touch, taste, smell). Three specific aims will be addressed: 1) describe health and health transitions of older community-residing Americans; 2) evaluate the relationship between health and older adult sexuality; and 3) examine sexuality within social networks and their sociocultural context.

TITLE: **California Native American Research Center for Health (NARCH)** **IHS**
P.I.: **Deven R. Parlikar, MBA, Indian Health Council**
Dr. Mario Garrett, PhD, San Diego State University
GRANT NO.: **1 S06 GM074084-01**
KEYWORDS: **Native American, care-giving, elderly**
STUDY TYPE: **clinical**
AWARD: **$25,000**

The California Native American Research Center for Health (CA-NARCH) is a partnership of tribal and university organizations committed to working together to reduce health disparities in Native American populations and to increase the number of Native American (NA) scientists and health professionals. The Southern California Tribal community, which ranges from the California-Mexico border to Riverside County with 17 reservations, is the service area of the CA-NARCH project. The Indian Health Council, located in North San Diego County, is the lead agency, and houses the core administrative/research center. The university partners are San Diego State University and the University of California, San Diego. The goals of the CA-NARCH are to (1) develop a cadre of NA scientists and health professionals engaged in biomedical, clinical, behavioral, and health services research who will be competitive in securing NIH and AHRQ funding; (2) increase the capacity of both research institutions and NA organizations to work in partnership to reduce distrust by NA communities toward investigators in research; and (3) encourage competitive research linked to the health priorities of the native organizations and to reduce health disparities. Goal 1 will be accomplished by further implementing student and faculty development programs. The core administrative/research center will continue to focus on Goal 2. The CA-NARCH has begun the process of developing new research Initiatives to address Goal 3. In addition, this application includes two specific research projects and a pilot project proposed by one of our Native American faculty members: 1) examination of the association of Type II diabetes with active and passive tobacco exposure in Southern California Native Americans; (2) examination of perceived burden and resilience among caregivers of frail Native American elders in San Diego County; and (3) examination of alcohol consumption patterns and knowledge of fetal alcohol syndrome among Native American women of childbearing age.

TITLE: **Caregivers' Strengths-Skills: Managing Older CA Patients** **NCI**
P.I.: **Victoria H. Raveis, PhD**
INST.: **Columbia University Health Sciences, New York**
GRANT NO.: **1 R01 CA115315-01**
KEYWORDS: **symptom management, palliative care, behavioral intervention, low income, caregiving, quality of life, depression**
STUDY TYPE: **clinical**
AWARD: **$50,000**

We propose to implement and evaluate the efficacy of a short-term problem-solving skills training program for familial caregivers to lower income older (60+) post-treatment cancer patients. The goal of the intervention is to equip family caregivers with problem-solving skills and knowledge that will provide them with a more adaptive means of attending to any symptoms their elderly relative may be experience during the cancer survivorship period. By focusing attention on families' potential role in palliative care efforts during the post-treatment period, we propose that we will be able to impact patients' health related quality of life, by fostering enhanced symptom recognition, improved symptom control, advocacy with health professionals, and adherence to symptom management options. Familial caregivers to older cancer patients who have completed active treatment will be accrued from Community/Migrant Health Centers (C/MHCs). Caregivers and patients will be followed for ten months. The specific aims are to:

(1) Deliver a brief problem-solving training program with regard to symptom management ("Problem-solving") to enhance caregiver skills (i.e., perceived self-efficacy, social problem-solving and communication) of familial caregivers to older post-treatment cancer patients.

(2) Evaluate the efficacy of problem-solving in enhancing caregiver skills, relative to participating in a caregiver support group ("Support"): (a) Assess short- and long-term change in caregiver skills reported by caregivers assigned to either the Problem-solving condition or the Support condition; and, (b) Compare change reported by caregivers in the Problem-solving condition, relative to reports by those in the Support condition;

(3) Assess the impact of change in caregiver skills on: (a) Change in patients' symptomology and physical functioning, depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with care ("patient outcomes"); (b) Change in caregivers' depressive symptomology, anxiety, quality of life, perceptions of and satisfaction with patient care ("caregiver outcomes").
(4) Disseminate information that informs family training in palliation and symptom control to participating C/MHCs and other C/MHCs serving these populations, contingent on demonstrating beneficial program outcomes.

ALCOHOL AND OTHER SUBSTANCE ABUSE

TITLE: **Sex Differences in Opioid Analgesia** **NIDA**
P.I.: **Anne Z. Murphy, PhD**
INST.: **University of Maryland, Baltimore**
GRANT NO.: **5 R01 DA16272-04**
KEYWORDS: **opioids, gender, pain, analgesia**
STUDY TYPE: **clinical**
AWARD: **$50,000**

Chronic pain afflicts millions of people each year. Opioid based narcotics are the most prevalent therapeutic treatment for chronic pain management, with morphine being the most commonly prescribed. There are now well-established sex differences in the ability of morphine to alleviate pain; in animals models of acute pain, the effective dose of morphine is approximately *5-lOx* greater for females in comparison to males. Similar results have been reported in humans. To date, the underlying mechanisms mediating sex differences in opiate sensitivity are not known. The midbrain periaqueductal gray (PAG) and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. Our major hypothesis is that the opiate-sensitive intrinsic and extrinsic circuitry of the FAG is sexually dimorphic and is the major determinant of sex-based differences in opioid analgesia. Previous studies examining the dimorphic effect of opioid administration utilized acute assays of nociception. Studies proposed in Aim 1 will characterize the sexually dimorphic effect of central morphine administration using a model of chronic inflammatory pain. Our preliminary data indicate that the PAG-NRM pathway is sexually dimorphic. Studies proposed in Aim 2 will use neural tract tracing techniques to delineate the anatomical organization of the PAG-NRM-spinal cord circuit in males and females. Aim 3 will examine the functional organization of this circuit in a model of prolonged inflammatory pain. The PAG is enriched in opioid receptors. Studies proposed in Aim 4 will characterize both the distribution and expression pattern of the opioid receptors. The influence of chronic inflammatory pain and gonadal steroid manipulations will also be examined. In summary, these studies will establish that the intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and provide the neural substrate for sex based differences in opioid analgesia.

TITLE: **Reducing Alcohol and Risks Among Young Females** **NIAAA**
P.I.: **Lydia N. O'Donnell, PhD**
INST.: **Education Development Center, Newton, MA**
GRANT NO.: **5 R01 AA014515-03**
KEYWORDS: **alcohol, African American, Latina adolescent females, HIV/ AIDS, alcoholism, basic & social science, infectious diseases, minority health**
STUDY TYPE: **clinical**
AWARD: **$150,000**

An intervention study will be undertaken to characterize and address the combined effect of early alcohol use and risky behavior within a population of urban African American and Latina adolescent females who are at high risk for HIV, AIDS, and other infections. Past research by the investigative team has documented that nearly 10% of females in our target population are at risk in 7^{th} grade and more than half by spring of 10^{th} grade. Although alcohol use is more comparable with national figures, the combination of early alcohol and risky behavior is troubling, yet under-addressed by existing interventions. This

randomized experiment will test a theoretically-derived and empirically-grounded "selective" intervention that specifically targets high-risk young adolescent females. The intervention builds upon a promising strategy for influencing adolescents: parent education. Three parenting mechanisms (PM) shown to influence adolescent risk behavior will be targeted: parental monitoring (P-PM), household rule setting (HR-PM), and communication (C-PM).

TITLE: **Substance Use & Girls: Stress, Hormones, & Puberty** **NIDA**
P.I.: **Judy A. Andrews, PhD**
INST.: **Oregon Research Institute, Eugene**
GRANT NO.: **1 R21 DA018414-01A1**
KEYWORDS: **hormones, puberty, substance abuse, stress, girls**
STUDY TYPE: **clinical**
AWARD: **$171,563**

While girls' use of cigarettes, alcohol and marijuana is less than that of boys in the early elementary years, the prevalence of girls' substance use quickly catches up to and surpasses that of boys by 8th grade. The proposed study is a pilot for a primary study investigating the processes related to the initiation and escalation of substance use among girls in early adolescence focusing on three domains, stressful events, pubertal maturation and timing, and hormonal influences. In the general model guiding the primary study, these domains are related to early substance use among girls through daily affect, aggression, depression, and affiliation with substance using peers. The specific aims of this study are: (1) To examine the feasibility of an intensive multi-method assessment conducted with 5th and 8th grade girls and their mothers assessing girls' life stress, emotional responses, pubertal maturation and hormones across the menstrual cycle. (2) To examine the variability, reliability and validity of daily and weekly measures of emotional responses, as measured by daily affect ratings, association with substance-using peers, and affiliative coping, for 5th and 8th grade girls and to examine the amount and timing of daily and weekly data required to obtain adequate samples of these variables and hormonal levels. The investigators will also assess the psychometric properties of some of our questionnaire-based measures, with a particular focus on the 5th grade sample. (3) To obtain estimates of effect sizes for: (a) between participant bivariate relations among chronic and episodic stressful events, hormonal levels, and precursors to substance use as a function of grade (5 vs. 8th) and pubertal timing (early vs. on-time/late); and between these variables and early substance use for 8th graders; and (b) within participant bivariate relations between hormonal levels, emotional responses, affiliative coping, and affiliation with substance-using peers, as a function of grade and pubertal timing. To address these aims, the investigators will assess 80 girls, 40 in both the 5th and 8th grade, with 20 early maturers in each grade using multiple methods, including questionnaires completed by both mothers and girls, a Life Stress Interview to assess chronic and episodic stress, and an assessment of the girls' physical maturation by a female nurse. For a minimum of four weeks, they will obtain weekly measures of estradiol, testosterone, progesterone and cortisol, as well as momentary and end of day assessments using an Electronic Personal Data Assistant (PDA). All assessments will be timed to menstruating girls' menstrual cycle, with timing of non-menstruating girls yoked to that of menstruating girls.

TITLE: **Impulsivity Related to Cocaine Dependence and Trauma** **NIDA**
P.I.: **Angela E. Waldrop, PhD**
INST.: **Medical College of South Carolina, Charleston**
GRANT NO.: **1 K23 DA018718-01A1**
KEYWORDS: **Post-Traumatic Stress Disorder (PTSD), Substance Use Disorder (SUD), HIV risk behaviors, impulsivity, sexual abuse, minorities, African-American, Hispanic**
STUDY TYPE: **clinical**
AWARD: **$87,440**

Training and research plans outlined in this proposal are meant to prepare the candidate to begin an independent research career in which she will design and conduct research on substance use, PTSD, and risky behaviors, with an emphasis on their relationship to impulsivity. The major training goals of the candidate are (a) develop expertise in SUD's: assessment, treatment, and research, (b) develop expertise in comorbidity of SUD's and PTSD, (c) develop expertise in human laboratory research and behavioral

measurement of impulsivity, (d) gain expertise in behavioral HIV risk research, (e) enhance skills in grantwriting and management, and (f) increase expertise in advanced statistical analyses. The specific aims of the research plan are to (a) investigate impulsivity among women with and without cocaine dependence and with and without at least subthreshold PTSD related to sexual trauma, and (b) to examine the relationships among HIV risk behaviors and the laboratory and self-report measures of impulsivity. The findings of the proposed study will then be used to inform future research in the area of impulsivity among women with comorbid substance use disorders and PTSD, perhaps leading eventually to the development of an intervention to address the harmful consequences of a variety of impulsive behaviors. The candidate has chosen three outstanding co-sponsors and one consultant to assist her in the development of the skills necessary to achieve the training goals and complete the proposed research plan. Dr. Kathleen Brady, the primary mentor, has a substantial record of research on substance use disorders and PTSD. Dr. Heidi Resnick has significant expertise in trauma-related research, particularly in sexual assault populations. Dr. Warren Bickel has published extensively in the area of impulsivity research with substance using populations. All three mentors are highly regarded for their work in their respective fields of research. Each has an extensive record of federal funding and mentoring junior colleagues. The research environment in Clinical Neuroscience at MUSC is an ideal environment for the candidate to meet her goals with a long history of successful grant funding, participant recruitment, and advanced research training.

TITLE: **Tobacco Cessation Treatment for Pregnant Alaska Natives** **NIDA**
P.I.: **Christi Patten, PhD**
INST.: **Mayo Clinic, Rochester, MN**
GRANT NO.: **1 R21 DA019948-01**
KEYWORDS: **tobacco use, tobacco cessation, treatment development, women, pregnant, culturally-relevant, minorities, Alaska Natives**
STUDY TYPE: **clinical**
AWARD: **$146,700**

Tobacco use is the single largest cause of premature and preventable death in the U.S. The prevalence of tobacco use among adults is currently highest among Alaska Natives. Over 50% of Alaska Native women residing in the Yukon-Kuskokwim (Y-K) Delta of western Alaska use smokeless tobacco or smoke cigarettes during pregnancy. Alaska Natives of this region are of Yup'ik or Cup'ik Eskimo, or Athabascan Indian ethnicity. No prior work has evaluated tobacco use interventions for pregnant Alaska Native women. This proposal builds on our successful partnership and track record of collaboration with Y-K Delta Alaska Natives. The objective of this proposal is to develop and pilot test a novel, culturally-tailored behavioral approach to tobacco cessation for pregnant Alaska Native women. As a result of this project, the investigators expect they will have developed a replicable, feasible, and acceptable counseling intervention, the efficacy of which can be tested in future larger-scale randomized clinical trials. Social cognitive (learning) theory is the conceptual basis for the proposed intervention. This project will take place in two phases. In Phase 1, a multi-component, culturally-tailored, tobacco use intervention with and for Alaska Native pregnant women, including a videotape and brief telephone counseling will be developed. This work will include development of a counselor manual and development of the intervention with focus groups. During this phase, 10 pregnant women will complete the protocol, which will be modified and refined based on feedback from participants and counselors. Phase 2, consisting of a pilot clinical trial, will apply a randomized, two group design with assessments at the first prenatal visit (baseline) and at the last prenatal visit approximately 36 weeks gestation. Pregnant women will be recruited and randomized to either a standard (N=30) or enhanced (N=30) tobacco use intervention. The overall health related objective of this line of research is to develop effective treatment programs with and for Alaska Native pregnant women that will ultimately reduce the risk of tobacco-related disease.

TITLE: **Gender Responsive Treatment for Women in Prison** **NIDA**
P.I.: **Nena Messina, PhD**
INST.: **University of California, Los Angeles**
GRANT NO.: **R21 DA018699-01A1**
KEYWORDS: **treatment, drug abuse, recidivism, women prisoners, sex/gender, HIV risk behavior, health disparities, minority women, multidisciplinary**
STUDY TYPE: **clinical, multidisciplinary**
AWARD: **$139,940**

This 2-year pilot study will determine the relative effectiveness of a women-focused (WF) treatment program based on relational theory ("Helping Women Recover": Covington, 1999; 2003) compared to a standard prison therapeutic community (TC) treatment program to promote positive behaviors among women inmates. Covington contends that relational theory provides a useful conceptual basis for planning and implementing appropriate drug abuse treatment services for women offenders, as this model focuses services on women's specific needs and incorporates services that are implemented in a manner that promotes women's psychological growth and helps them to discontinue the cycle of substance abuse and criminal behavior. This curriculum, however, has not been empirically tested. Specifically, 100 women at Valley State Prison for Women in California will be randomly assigned to the WF or TC treatment prison programs. The specific aims of this study are: 1. To pilot test the efficacy of a theoretically based, multi-faceted, WF curriculum to promote positive behaviors among women offenders (i.e., increased self-efficacy and psychological well-being, aftercare participation, and reductions in drug use and recidivism) compared to the impact of a standard prison TC program. 2. To qualitatively assess treatment staff and client perceptions' of the elements of the WF program which are intrinsic to the theoretical basis of the curriculum to refine and improve the WF model of treatment for women in prison. Findings from the proposed pilot study will be used as a platform for the development of a later, larger, and more rigorous study on WF treatment within a prison setting.

TITLE: **Molecular Basis for Sex-Selective Effects of Ethanol** **NIAAA**
P.I.: **Leslie L. Devaud, PhD**
INST.: **Idaho State University, Pocatello, ID**
GRANT NO.: **2 R01 AA011877-06A1**
KEYWORDS: **alcohol, gender differences, sex hormones, neurosteroids, neurotransmission, alcohol withdrawal, neuronal pathways, neuropharmacology, hippocampus, frontal cortex**
STUDY TYPE: **basic**
AWARD: **$233,539**

This proposal continues investigations into the neurobiological basis for sex differences in ethanol dependence and withdrawal. To date, the investigators have identified important differences between male and female rats in adaptations of GABA-A and NMDA receptors during ethanol dependence and early withdrawal across several brain sites. Recently they found significant and robust behavioral sex differences in the timing for recovery from ethanol withdrawal. Whereas both males and females showed significant withdrawal signs at 24 hr, females, but not males, appeared to have recovered by 3 days. Therefore, the overall goal of this project is to elucidate the mechanistic underpinnings for behavioral expressions of ethanol withdrawal at 24 hr and 3 days. The investigators hypothesize that differences in recovery from ethanol withdrawal involve sex-selective changes in GABAergic and glutamatergic neurotransmission that occur as a result of the differing hormonal milieu between males and females. To test this hypothesis we will compare and contrast findings in young adult male, cycling diestrus female and ovariectomized female rats. The proposed studies will allow us to delineate the importance of hormonal modulation in conferring sex differences in recovery from ethanol withdrawal. This project will test the hypothesis by these aims: 1. assessment of several ethanol withdrawal behaviors, including responses to drug treatments, at early (24 hr) and later (3 days) withdrawal, 2. identification of concomitant sex differences in brain activation with analysis of modulation of GABA-A and NMDA receptors at these same times of withdrawal, and 3. analysis of ethanol withdrawal-induced changes in GABA, glutamate and steroid levels. The investigators expect to find that the differing hormonal milieu between males and cycling females regulates adaptations of GABAergic and glutamatergic neurotransmission that confers recovery from ethanol withdrawal.

Molecular Basis for Sex-Selective Effects of Ethanol Cont'd. **NIAAA**

Findings resulting from these proposed studies should show that inherent, neurobiological regulation due to hormonal status is an important factor influencing actions of ethanol, with adaptations being different for recovery than development of dependence. Increasing the understanding of sex-selective mechanism underlying withdrawal should help guide the investigator towards improving treatments for alcohol withdrawal in both women and men.

CANCER

TITLE: **Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines** **NCI**
P.I.: **Allan Hildesheim, PhD; Douglas R. Lowy, M.D.**
INST.: **National Cancer Institute, Bethesda, MD**
GRANT NO.: **Z01 CP10177**
KEYWORDS: **human papillomavirus, cervical cancer, vaccine development, STDs**
STUDY TYPE: **clinical**
AWARD: **$600,000**

Worldwide, Cervical cancer annually accounts for over 400,000 incident cases, resulting in approximately 200,000 deaths. The impact of this disease is particularly devastating in developing countries where women are medically underserved and access to Pap smear screening is not readily available. To address this major issue in women's health, NCI and the Office for Research on Women's Health, is launching a large, double blinded, randomized clinical trial to evaluate whether vaccination with the bivalent HPV16/18 VLP-based vaccine developed at NCI and manufactured by GlaxoSmithKline will protect against the development of histopathologically confirmed, incident CIN2+ (cervical intraepithelial lesion grades 2/3), adenocarcinoma in situ, and invasive cervical cancer. This pivotal efficacy trial will be conducted in Costa Rica, an area with high rates of cervical cancer. Approximately 20,000 young women will be invited to join the trial, with 12,000-15,000 women expected to participate. Eligible women who agree to participate will be administered 3 doses of either a control vaccine or the HPV 16/18 VLP vaccine over a six month period and will be followed for four years. The trial is expected to extend through 2009. It is hoped that results from this effort will support licensure of a prophylactic HPV16/18 vaccine that protects against the development of HPV16/18 induced cervical cancer and its precursors.

TITLE: **Tumorigenic Subversion of Mural Cells in Breast Cancer** **NCI**
P.I.: **Linda Joyce Metheny-Barlow, PhD**
INST.: **Georgetown University Cancer Center, Washington, DC**
GRANT NO.: **R21 CA115829-01**
KEYWORDS: **breast cancer, tumor-promoting, cell-directed therapies**
STUDY TYPE: **basic**
AWARD: **$129,000**

The induction of tumor vasculature, known as the 'angiogenic switch', is a rate-limiting step in tumor progression. Most functional studies have focused on the responses of endothelial cells to pro-angiogenic stimuli; however, there is mounting evidence that the supporting mural cells (smooth muscle cells and pericytes) play a key regulatory role in maintaining a mature, quiescent vasculature. In tumors, mural cell association with the endothelium is decreased and abnormal. Previous work has shown that restoration of functional inhibitory maturation to vasculature by Angiopoietin-1 inhibits tumor growth, suggesting that stabilization of tumor vessels may be a desirable therapeutic goal in the treatment of cancer. The hypothesis underlying this work is that breast cancer cells functionally alter mural cell and endothelial cell contacts and subvert the mural cell from its normal anti-angiogenic role to a vessel-promoting role as part of the angiogenic switch. Paracrine interactions between endothelial cells, mural cells, and breast cancer cells will be studied using in vitro membrane and spheriod models that mimic the organization of the blood vessel wall, as well xenograft models with modified mural cells, in order to address three specific aims. Aim 1 will identify critical alterations in mural cell function in response to breast cancer cells that may contribute to the maturation defect exhibited by the tumor vasculature. Aim 2 will investigate the ability of tumor cells to activate matrix metalloproteases specifically in mural cells as part of the acquisition of a pro-angiogenic

functional state. Aim 3 will address whether the differentiation utilization of specific sphingosine-1-phosphate receptors plays a role in the tumor-induced maturation defect and activation of mural cells. Together, these studies will i) provide proof-of-principle that tumors can subvert the function of normally inhibitory mural cells to a tumor-promoting state, and ii) identify pivotal molecular players involved in these activities to serve as targets for future mural cell-directed therapies to restore quiescence to the vasculature.

TITLE: **Pharmacogenetics of the Endocrine Treatment of Breast Cancer** **NIGMS**
P.I.: **David A. Flockhart, M.D., PhD**
INST.: **Indiana University-Purdue University at Indianapolis, Indianapolis, IN**
GRANT NO.: **2 U01 GM061373-06**
KEYWORDS: **pharmacogenetics, breast cancer, translational research, tamoxifen (TAM)**
STUDY TYPE: **basic, translational**
AWARD: **$250,000**

Drugs that interfere with the actions of estrogen represent a cornerstone in the treatment of breast cancer, and are important tools with which to study the actions of estrogen in women. These drugs are increasingly effective in breast cancer, but which drug is best for each woman remains unclear. Our work in the first cycle of the Pharmacogenetics Research Network identified, through a series of laboratory and clinical studies, new genetic patterns that predict effects of the estrogen receptor modulator tamoxifen. We now propose to build on these data to examine the influence of an extended series of candidate genes on the effects of the aromatase inhibitor class of drugs and to refine the genetic signatures that predict tamoxifen effects. Our work will involve the following broad specific aims: 1) To identify common genetic variants of the human estrogen receptors and important nuclear coactivators and repressers of these receptors using a combined bioinformatic and direct sequencing approach; 2) To test the hypothesis that these variants alter gene expression or function using in vitro assays; 3) To test the contribution of variants identified during specific aim 1 and 2 to tamoxifen response in the clinical trial of tamoxifen pharmacogenetics already conducted. 4) To characterize the involvement of genetically polymorphic drug metabolizing enzymes in the human metabolism of the available aromatase inhibitors: letrozole, exemestane and anastrozole in vitro. 5) To test the hypothesis that variants in candidate genes identified in aims 1-4 are associated with well curated phenotypic outcomes, including estrogen metabolite concentrations, pharmacokinetics, hot flashes, breast density, bone metabolism and serum lipid subfractions in breast cancer patients receiving anastrozole, exemestane and letrozole. The results of this proposal will generate new information that, linked with our novel tamoxifen pharmacogenetics findings, will generate a series of genetic tools key to optimizing drug selection for women with breast cancer and to our understanding of the mechanisms of estrogen action.

TITLE: **Patient-Centered Communication During Chemotherapy** **NCI**
P.I.: **Douglas M. Post, PhD**
INST.: **Ohio State University, Dept of Family Medicine**
GRANT NO.: **1 R21 CA115388-01**
KEYWORDS: **symptom management, palliative care, pain, depression, fatigue, breast cancer, behavioral intervention**
STUDY TYPE: **clinical**
AWARD: **$50,000**

Pain, depression, and fatigue are among the most common disease and treatment-related symptoms experienced by cancer patients. Studies have indicated that communication problems between cancer patients and clinicians are a major barrier to the effective management of these symptoms. This project is designed to address this important problem through the development and evaluation of a PDA-based patient communication intervention for breast cancer patients undergoing chemotherapy treatment. The intervention will be comprised of two integrated components: symptom monitoring and tailored patient communication training. Patients will be asked to complete fatigue, depression, and pain inventories on a PDA at the beginning of chemotherapy and once per week through the completion of treatment. On the day prior to an appointment for chemotherapy treatment, a summary of fatigue, depression, and pain scores will be integrated with a tailored patient communication skills training program and displayed on the PDA

for patient viewing. Patients will be taught, through role modeling, how to effectively communicate the types of symptoms they have experienced between treatments. They will also be encouraged to bring the PDA with their symptom summaries to each chemotherapy visit and to share this information with their health care provider. Year one of the project will primarily be devoted to the development and usability testing of the intervention. A feasibility trial will be conducted during the second year. Fifty patients with breast cancer will be recruited into the trial at the start of their chemotherapy treatment. A repeated measures design will be used to assess the effects of the intervention on symptoms of fatigue, depression, and pain over the course of treatment. At the end of treatment, focus groups will be conducted with study participants to assess their responses to the intervention and their perceptions of the system's value to both themselves and future cancer patients. In addition, the feasibility of the project, defined as the proportion of patients recruited into the study and the proportion of patient adherence to instructed use of the system, will be analyzed. Specific aims of the project include: 1) Develop the patient-centered communication intervention; 2) Conduct usability testing to ensure the successful completion of the intervention; 3) Examine study feasibility and patient reactions to the intervention; and 4) Evaluate intervention effects on pain, depression, and fatigue symptoms over time.

CARDIOVASCULAR DISEASE

TITLE: **Genetics of Early-Onset Stroke** **NINDS**
P.I.: **Steven J. Kittner, M.D.**
INST.: **University of Maryland, School of Medicine, Baltimore**
GRANT NO.: **5 R01 NS045012-03**
KEYWORDS: **ischemic stroke, thrombomodulin, protein C, fibrinolysis systems, endothelial protein C receptor, plasminogen activator inhibitor-1, endothelial protein C receptor polymorphisms, African-American, Caucasian, brain disorders, cardiovascular, genetics, prevention**
STUDY TYPE: **clinical**
AWARD: **$300,000**

The long-term objective of this application is to characterize the genetic basis for ischemic stroke susceptibility in order to develop more effective prevention and treatment strategies. Current evidence suggests that the genes encoding the thrombomodulin-protein C and fibrinolysis systems are promising candidate stroke susceptibility genes because of their pivotal importance in thrombosis regulation and response to inflammation. The researchers postulate, that: 1) novel genetic variants in the thrombomodulin, endothelial protein C receptor, and plasminogen activator inhibitor-1 genes predispose to the development of stroke, particularly infection-associated stroke and 2) endothelial protein C receptor polymorphisms are associated with large vessel stroke, while thrombomodulin polymorphisms are associated with lacunar (small vessel) stroke. To obtain a sample size adequate to test these hypotheses, we propose a population-based case-control study of ischemic stroke (1,033 cases and 1,064 controls) among young African-American and Caucasian men and women. To complement an existing sample of female cases and controls, male cases (n=600) will be recruited using a network of 59 hospitals in the Baltimore-Washington area. Age, gender, and race matched controls (n=600) will be recruited by random digit dialing. A neurologist panel will perform stroke phenotyping. Historical risk factor data and blood samples for genetic studies will be obtained at a face-to-face interview. A comprehensive molecular analysis of the coding, promotor, and intronic regions of the three candidate genes will be performed to determine if sequence variation in these loci is associated with stroke. In addition to analyses of individual polymorphisms, intragenic haplotypes will be constructed and common haplotypes tested for association with stroke. Population substructure analysis will be used to identify and account for population stratification bias in the analyses. The proposed study will complement other associated studies of older stroke patients and will be a continuing resource for understanding the genetic basis of stroke risk.

TITLE: **Sex Differences in Purkinje Cell Sensitivity to Ischemia** **NINDS**
P.I.: **Paco Herson, PhD**
INST.: **Oregon Health Sciences University, Portland**
GRANT NO.: **1 R21 NS052591-01A1**
KEYWORDS: **stroke, neuroprotection, progesterone, ischemia, neurons, sex hormones**
STUDY TYPE: **basic**
AWARD: **$228,750**

Stroke or Brain Attack is a sexually dimorphic disease. Women enjoy protection from stroke relative to men, in part due to endogenous levels of sex steroids, the estrogens and progesterone. While estrogen has been well studied, little is known about progesterone's neuroprotective properties. The steroid is an important but controversial component of hormone therapy in women. Progesterone reduces ischemic brain injury in vivo, however the mechanism is not known. The investigators hypothesize that one important mechanism of neuroprotection is via progesterone's enhancement of GABA-A receptor activity, counteracting the high levels of excitatory input to neurons during and immediately following ischemia. This R21 application tests this overarching hypothesis, using whole cell voltage-clamp experiments and single cell PCR in cerebellar Purkinje cell (PC) culture, as a novel and initial step in understanding progesterone's neurophysiological actions in complex animal ischemia models. They focus on PCs because of important early observations that PCs, like the well-studied hippocampal CA1 neuron, are uniquely hyper-vulnerable to ischemia. While data from these GABA sensitive cells and cerebral ischemia are few, our recent studies emphasize that non-ischemic female PCs are selectively sensitive to enhancement of GABA-A receptor activity by progesterone metabolites. Furthermore, their preliminary data indicate that female mice require continued exposure of sex steroids to maintain enhanced sensitivity to progesterone metabolites relative to male mice. Therefore, they will test three specific hypotheses 1) Acute progesterone protects PCs from ischemia through activation of the GABA-A receptor. 2) Chronic progesterone enhances female cells to acute progesterone neuroprotection and 3) that chronic progesterone decreases the expression of the gamma-subumt of the GABA-A receptor resulting in increased sensitivity to acute progesterone. Their findings will begin to elucidate the cellular mechanisms of progesterone neuroprotection and sex differences in Purkinje cell response to ischemia.

TITLE: **Altered Glucose and Lipid Metabolism in Obesity and CVD** **NHLBI**
P.I.: **Maureen J. Charron, PhD**
INST.: **Albert Einstein College of Medicine, Bronx, NY**
GRANT NO.: **5 R01 HL073163-03**
KEYWORDS: **metabolic disturbances, cardiovascular disease, insulin-stimulated GLUT4 transporter, diabetes, genetics, obesity, prevention**
STUDY TYPE: **basic**
AWARD: **$200,000**

This application proposes studies in mice to examine metabolic disturbances and cardiovascular disease in animals that express only one functional copy of the insulin-stimulated GLUT4 transporter (a mouse model of type 2 diabetes), and hypothesizes that metabolic and cardiovascular changes may be mediated by altered expression of adipocyte-specific Acrp30 (adiponectin). The specific objectives of this proposal are 1) to understand the molecular mechanisms underlying the metabolic changes that specifically affect male, but not female GLUT4+/- mice or GLUT4+/- mice that over-express GLUT4 in muscle; 2) to test genetically whether correction of Acrp30 downregulation in male GLUT4+/- will prevent or delay the onset of insulin resistance, visceral obesity and/or cardiovascular disease (CVD). Additionally, they will test whether complete lack of circulating Acrp30 in Acrp30-/-mice will provoke metabolic disturbance in female GLUT4+/- and exacerbate disease in male GLUT4+/- mice; 3) to assess the effects of high fat diet-induced changes in disease progression in GLUT4+/- compared to C57BL/6J mice; and 4) to determine transcripitional and translational changes in white adipose tissue (WAT) associated with visceral obesity and alterations following treatment with thiazolidinedione insulin sensitizers in hope of identifying novel therapeutic targets. Combined, this approach will provide a comprehensive systematic characterization of a mouse model of obesity associated CVD derived from early impairment of insulin mediated glucose flux into WAT, and directly address for the first time whether alterations in Acrp30 influence disease progression.

TITLE: **Inflammation and Insulin Resistance in Peripheral Arterial Disease** **NHLBI**
P.I.: **Mark A. Creager, M.D.**
INST.: **Brigham and Women's Hospital, Boston**
GRANT NO.: **3 R01 HL075771-03**
KEYWORDS: **PAD, CVD, sex differences, inflammatory**
STUDY TYPE: **epidemiologic (case-control)**
AWARD: **$10,000**

Patients with peripheral arterial disease (PAD) frequently have functional limitations and symptoms of claudication that impact adversely on their quality of life. Many progress to critical limb ischemia requiring revascularization. Vascular inflammation and insulin resistance are two important and interdependent conditions that are associated with atherosclerosis. Moreover, both inflammation and insulin resistance cause abnormalities in vascular function and insulin resistance interferes with skeletal muscle metabolism. As such, inflammation and insulin resistance provide attractive targets for therapy that could potentially ameliorate the development of symptomatic PAD or improve the function and clinical outcomes of patients with PAD. Accordingly, the applicants propose three specific aims to determine whether inflammation and insulin resistance contribute to the functional and clinical consequences of PAD. First, a prospective, nested, case-control evaluation will be performed to test the hypothesis that baseline plasma levels of inflammatory cytokines (e.g. interleukin (IL)-4, IL-6, IL-18, macrophage inhibiting cytokine-1, CD 40 ligand) among healthy men are associated with the development of future symptomatic PAD. Second, to test the hypothesis that inflammation and insulin resistance contribute to reduced walking distance in patients with intermittent claudication by impairing vascular reactivity and skeletal muscle metabolic function, plasma markers of inflammation and insulin resistance, endothelium-dependent and independent vasodilation (by vascular ultrasonography) and skeletal muscle glucose utilization (by [18F] FDG positron emission tomography) will be measured before and after 12 weeks of treatment with rosiglitazone, atorvastatin or placebo in a 2x2 factorial design protocol. Third, to test the hypothesis that inflammation and insulin resistance are associated with the incidence and progression of vein graft disease in patients undergoing lower extremity vein bypass, functional and morphologic changes in vein grafts (measured by ultrasound and magnetic resonance imaging) will be assessed and related to inflammation and insulin resistance and to a composite clinical outcome of graft occlusion, re-intervention or major amputation. It is anticipated that the findings from this investigation will uncover novel pathophysiologic mechanisms and foster a new paradigm for the treatment of PAD.

TITLE: **Phytoestrogens and Progression of Atherosclerosis** **NCCAM**
P.I.: **Howard Hodis, M.D.**
INST.: **University of Southern California**
GRANT NO.: **3 U01 AT001653-02S4A1**
KEYWORDS: **complimentary and alternative medicine, bone mineral density, post-menopause, and heart disease**
STUDY TYPE: **clinical, randomized double-blind clinical trial**
AWARD: **$36,544**

This application is a supplement to a recently funded randomized controlled trial, Phytoestrogens in Progression of Atherosclerosis (U01-AT001653). This supplement is focused on the effect of isoflavone-rich soy protein (ISP) supplementation on bone mineral density, bone metabolism and bone turnover in postmenopausal women. Fear and discontent with traditional hormone therapy has resulted in an escalating use of soy products as a postmenopausal therapeutic alternative. However, current information derived from clinical trials of the efficacy of soy on bone health has been limited since studies have been of short duration (mostly 3-12 months) and conducted in small sample sizes. Data concerning the effects of soy on bone health from long-term trials conducted in a large cohort of postmenopausal women are missing. As such, the design, duration and size of the parent trial make it an ideal platform upon which to adequately assess the effects of ISP supplementation on bone health. Since the central portion of the clinical trial has been funded, a very robust database will be obtained at considerable savings. The objective of this supplement is to investigate the effect of ISP supplementation on bone mineral density, metabolism and turnover in 300 healthy postmenopausal women in a 2.5 year, randomized, double-blind, placebo-controlled trial. The 4 Specific Aims are: 1) To determine the effect of ISP supplementation on bone

mineral density; 2) To assess the effect of ISP on markers of osteoblast activity by measuring serum bone-specific alkaline phosphatase; 3) To assess the effect of ISP on markers of osteoclast activity by measuring urinary excretion of N-telopeptide; and, 4) To assess the effect of ISP supplementation on regulation of bone turnover by measuring serum RANKL and osteoprotegerin. We hypothesize that ISP supplementation will attenuate bone loss associated with aging and/or postmenopausal estrogen loss. Providing direct evidence for the efficacy of ISP in reducing osteoporosis with a clinical trial using well-validated measurements of bone mineral density, bone metabolism and bone turnover has immense public health implications for women's health.

CRANIOFACIAL

TITLE: **Brief Focused Treatment for TMD: Mechanisms of Action** **NIDCR**
P.I.: **Mark D. Litt, PhD**
INST.: **University of Connecticut, School of Medicine, Farmington, CT**
GRANT NO.: **5 R01 DE014607-03**
KEYWORDS: **temporomandibular disorders (TMD), pain, coping, mood, cortisol, cytokines, behavioral & social science, dental/oral disease, chronic pain conditions**
STUDY TYPE: **clinical**
AWARD: **$100,000**

TMD is a widespread chronic pain condition. Successful psychosocial treatments for TMD have been developed, but the mechanisms by which these treatments achieve their effects are not well known. The goal of this project is to evaluate the possible mechanisms responsible for treatment gains in TMD treatment. Men and women with complaints of chronic facial pain for at least 3 months' duration will be recruited from the University Dental Clinics and from the community via advertisements and randomly assigned to either a Standard Conservative Treatment (STD) employing an intraoral splint plus anti-inflammatory agents, or to a Standard Treatment + Cognitive-Behavioral Treatment Program (STD+CBT), that will include standard treatment but also focus on changing self-efficacy and decreasing catastrophization. Both treatments will entail 6 clinic visits. Dispositional and situational variables derived from a comprehensive model of pain coping will be measured before and after treatment. The situational variables, including coping responses, mood states, situational appraisals and self-efficacy, will be measured in an experience sampling paradigm four times daily using a hand-held computer. This will be done to minimize retrospective biases that may have hampered earlier studies of treatment process. Dependent variables will be self-report measures of distress, pain, and interference with activities, as well as blood plasma levels of cortisol and selected cytokines, measured at the end of the 6-week treatment period, and at follow-up points thereafter up to a 12-month follow-up. It is expected that the STD+CBT treatment will result in measurable changes in constructs such as self-efficacy and catastrophization, and that these changes will be related to improved outcomes compared to the STD controls. It is also expected that outcome differences between groups will be associated with changes in inflammatory mediators (cytokine levels). Finally, it is suggested that changes in situational treatment process variables will be associated with changes in cytokine levels. The results may indicate the true active mechanisms of successful TMD treatment. If these mechanisms can be successfully identified it would have important implications for the development of more effective treatment programs.

TITLE: **Genotype and TMJD Vulnerability Types** **NIDCR**
P.I.: **Christian S. Stohler, DMD**
INST.: **University of Maryland Professional School, Baltimore**
GRANT NO.: **5 R01 DE015396-03**
KEYWORDS: **temporomandibular, pathogenesis, candidate gene, estrogen, dental/oral disease, genetics, chronic pain conditions**
STUDY TYPE: **basic and clinical**
AWARD: **$100,000**

Temporomandibular joint disorders represent a major health problem and persistent TMJD pain is difficult to manage successfully. The majority of cases involve muscle. Laboratory evaluations proposed in this

application permit new and critically important insight into the pathogenesis of persistent TMJD pain. The use of approaches from several different scientific disciplines, such as genetics, endocrinology, neurobiology of pain and imaging of peripheral tissue are proposed to probe and understand the system response of human subjects with respect to disease characteristics of TMJD and for which measurement opportunities in animals are limited. Based on supporting data, this research aims to provide new knowledge regarding the significance of a candidate gene that appears to exert a strong effect on critical hallmark features of persistent TMJD muscle pain. Because sensitivity to pain and inhibition of pain are traits of considerable variability, the effect of this gene on subject's response characteristics to experimentally induced jaw muscle pain will be studied. Furthermore, because women in their reproductive age make up the majority of patients treated with TMJD, the proposed research also focuses on whether estrogen significantly alters the system's response in subjects of a particular genotype.

TITLE: **Neuronal Plasticity Related to TMJ and Fibromyalgia** **NIDCR**
P.I.: **Dean A. Dessem, PhD**
INST.: **University of Maryland Dental School, Baltimore**
GRANT NO.: **5 R01 DE015386-03**
KEYWORDS: **temporomandibular, fibromyalgia, neurons, musculoskeletal, gender, dental/oral disease, chronic pain conditions**
STUDY TYPE: **basic**
AWARD: **$100,000**

The long-term objective of this project is to elucidate the role of craniofacial primary afferent neurons in musculoskeletal disorders such as temporomandibular disorders and fibromyalgia (FM) using animal models. Two hypotheses are proposed: Hypothesis 1) Masticatory muscle inflammation increases the number of trigeminal ganglion (TG) muscle afferent neurons that express: substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin-1 receptor (NK-lr) and CGRP receptor (CGRPr). This increase involves a phenotypic switch in which muscle primary afferent neurons that do not normally express neuropeptides express SP, CGRP, NK-lr, CGRPr following inflammation. It is proposed that this change contributes to muscle allodynia and hyperalgesia and can be modulated by pharmacologic manipulations thus providing insight into therapeutics for deep tissue pain. This hypothesis will be tested by quantifying the distribution of TG muscle afferent somata and peripheral axons containing SP, CGRP, NK-lr, CGRPr in three groups: i) control, ii) inflamed muscle, iii) inflamed muscle with intervention (anti-nerve growth factor, NK-lr and CGRPr antagonists). This hypothesis will also be tested by determining the levels of CGRP, SP and gene expression for CGRP, SP within the TG using radioimmunoassay and reverse transcriptase polymerase chain reaction. Hypothesis 2) SP and CGRP alter the functional properties of TG muscle afferent neurons in part by evoking spontaneous activity and increasing their excitability. It is predicted that substantially more group II, III and IV TG muscle afferent neurons will be modulated by SP and CGRP following inflammation and that these functional alterations can be modulated pharmacologically. This hypothesis will be tested by characterizing the a) spontaneous and evoked activity and b) active and passive membrane properties of TG muscle afferent neurons prior to muscle inflammation, following muscle inflammation, and following muscle inflammation combined with pharmacological intervention. This will be achieved using intracellular electrophysiological recordings from masseter muscle afferent neurons in a trigeminal ganglion-masseter nerve in vitro preparation. Determination of soma size, axon diameter, and SP, CGRP immunoreactivity for physiologically characterized TG muscle afferent neurons will also test Hypothesis 1. Because a gender difference is reported for TMD and FM, both hypotheses will be tested in males, estrous females and diestrous females.

TITLE: **Estrogen Regulation of Inflammation Related to TMJ** **NIDCR**
P.I.: **Phillip R. Kramer, PhD**
INST.: **Texas A&M University Health Science Center, Dallas**
GRANT NO.: **5 R01 DE015372-03**
KEYWORDS: **gene, macrophage, rheumatoid factor, dental/oral disease, estrogen, TMJ disorders**
STUDY TYPE: **basic**
AWARD: **$100,000**

The long-range goal of this research is to identify and characterize genes through which steroidal hormones affect the onset and/or severity of human disease. The objective is to determine a gene in macrophages affected by estrogen withdrawal, as seen post-partum and at menopause, that functions in immune processes. The central hypothesis is that changes in estrogen concentrations directly regulate IgG Fc gamma receptor III-A (CD16a) expression resulting in a modulation of pro-inflammatory cytokine production and/or release from macrophages upon receptor binding. This hypothesis is based on recent findings in vitro that 1) the level of Fc gamma RIIIA transcript increased in macrophage-like THP-1 cells and in primary, peripheral blood macrophages after estrogen removal and 2) that the observed increase was dependent on transcription. The hypothesis also includes data from another lab that binding of Fc gamma RIIIA by anti-Fc gamma RIll monoclonal antibodies stimulates macrophage TNF-alpha and IL-1 alpha release. Fc gamma RIIIA is a receptor that selectively binds IgG molecules, an important rheumatoid factor (RF) in auto-immune disease. Collectively, these data suggest that RF binding of this receptor stimulates cytokine release in rheumatoid arthritis and associated temporomandibular joint disorders (TMJD). To test the central hypothesis, aim one will characterize macrophage cytokine production and release from stimulated macrophages after modulating Fc gamma RIIIA expression. TNF-alpha and IL-1 alpha will be measured after changing Fc gamma RIIIA expression levels using various estrogen and Fc gamma RIIIA antisense treatments. Aim two will focus on the mechanism inducing cytokine production and/or release upon Fc gamma RIIIA crosslinking. Signal transduction pathways and activated transcription factors will be identified as well as regulatory TNF-alpha and IL-1 alpha promoter sequences. Aim three will address the mechanism by which estrogen regulates Fc gamma RIIIA gene transcription in macrophages. The function of estrogen receptors ER alpha and/or ER beta will be directly addressed pharmacologically (e.g., antiestrogen) and through mutation studies of the Fc gamma RIIIA promoter.

TITLE: **International Research Registry Network for Sjögren's Syndrome** **NIDCR**
P.I.: **John S. Greenspan, PhD and Troy Daniels, DDS, MS**
INST.: **University of California, San Francisco, CA**
GRANT NO.: **N01 DE32636**
KEYWORDS: **research registry, Sjogren's syndrome, international, dental/oral disease**
STUDY TYPE: **clinical**
AWARD: **$200,000**

This contract will support the creation of an International Research Registry Network for Sjögren's syndrome. As part of this registry, key elements will include: 1. to establish a set of standardized diagnostic criteria for the recruitment of Sjögren's syndrome patients; and 2. to collect, process, store, ship and analyze clinical information and biological specimens from patients and families with Sjögren's syndrome; and 3. to disseminate to researchers clinical information and biological specimens from patients with Sjögren's syndrome.

TITLE: **Mast Cell Role in Masseter Muscle Repair** **NIDCR**
P.I.: **Joyce A. Morris-Wiman, PhD**
INST.: **University of Florida, Gainesville**
GRANT NO.: **5 R21 DE016317-02**
KEYWORDS: **TMJ, pain, inflammation, dental/oral disease**
STUDY TYPE: **basic**
AWARD: **$100,000**

Temporomandibular disorders (TMD) affect approximately 12% of the US population, predominately women in their childbearing years and of those affected by TMD, greater than 60% have masticatory muscle pain as their main complaint. Mast cells have been demonstrated to be not only associated with a decrease in muscle viability after damage, but also may be responsible for pain associated with muscle

inflammation. This proposal will examine events in masseter and in limb muscle repair in response to a freeze injury, to detect differences that might explain the impaired repair capacity of the masseter and to examine how mast cell response may contribute to this decreased regenerative potential. Standardized injury models that duplicate naturally occurring muscle damage in masseter during bruxism are essential to our understanding of the processes that contribute to muscle inflammation and pain in TMD. We plan to test the hypothesis that the primary defect in masseter muscle repair resides in its inflammatory response to damage, manifested as increased numbers of mast cells and recurrent necrosis and resultant fibrotic repair. Further, we plan to examine events in masseter muscle repair in response to damage from concentric and eccentric contraction. This will allow us to experimentally test the hypothesis that concentric or eccentric contractions such as those experienced during jaw clenching or bruxism result in muscle fiber damage in the masseter that prompts a prolonged inflammatory response and delay in repair.

TITLE: **Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants (TMJ Device Registry)** **NIDCR**
P.I.: **James R. Fricton, DDS, MS**
INST.: **University of Minnesota**
GRANT NO.: **N01 DE22635**
KEYWORDS: **TMJ, medical devices, chronic pain conditions, dental/oral disease**
STUDY TYPE: **registry**
AWARD: **$100,000**

The development of the National Institute of Dental and Craniofacial Research's TMJ Implant Registry and Repository (NIDCR's TIRR) at the University of Minnesota will allow collection of clinical information and biological specimens on patients with TMJ implants throughout the United States. This will stimulate both basic and clinical studies and improve our understanding of the pathobiology of TMJ diseases and disorders. In addition, the availability of retrieved implant materials will help in the design and development of a new generation of implantable materials and advance our understanding and success of treatment of patients with TMJ implants.

DIABETES

TITLE: **Diabetes Prevention Program Outcomes Study (DPPOS)** **NIDDK**
P.I.: **Sarah Fowler, PhD**
INST.: **George Washington University, Washington, DC**
GRANT NO.: **5 U01 DK048489-12**
KEYWORDS: **diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, prevention, cardiovascular disease**
STUDY TYPE: **clinical**
AWARD: **$300,000**

The Diabetes Prevention Program (DPP) addressed its primary objective, establishing the efficacy of lifestyle modification and metformin in decreasing the incidence of diabetes in an ethnically diverse population at high risk for an average of 2.8 years; however, many important issues remain unanswered. Specifically, whether the decrease in the development of diabetes can be sustained is unknown. Moreover, determining whether the delay or prevention of diabetes will translate into a decrease in retinopathy, nephropathy, neuropathy, and cardiovascular disease, all of which require more years to develop than the DPP period of study, is critical to establish the true impact of the DPP on public health. The long-term follow-up study of the DPP, entitled the Diabetes Prevention Program Outcomes Study or DPPOS, is designed to evaluate the long-term effects of active DPP interventions on the development of a) diabetes during a further 5-11 years of follow-up and b) composite diabetes-related microangiopathic and cardiovascular disease outcomes. The hypotheses being tested are that both the continued lifestyle intervention and metformin will provide continued separation in the rates of diabetes development, compared with the former placebo group, and that the prevention or delay of diabetes during the DPP and DPPOS will translate into reduced rates of composite outcomes and improved health status. The secondary objectives of the DPPOS are to evaluate the long-term effects of DPP interventions on selected individual health outcomes, the established and putative risk factors for those outcomes, and the costs and cost-utility associated with delay or prevention of diabetes.

TITLE: **Gestational Diabetes and Preeclampsia Cytokine Profiles** **NIDDK**
P.I.: **Ravi Thadhani, M.D.**
INST.: **Massachusetts General Hospital, Boston**
GRANT NO.: **1 R01 DK67397-01A1**
KEYWORDS: **Gestational diabetes, preeclampsia, cytokine, proteomics**
STUDY TYPE: **clinical**
AWARD: **$100,000**

Gestational diabetes mellitus (GDM) and preeclampsia (PE) are associated with significant morbidity and mortality during pregnancy and risk for diabetes and cardiovascular disease after pregnancy. Biological mechanisms suggest alterations in specific cytokines (cytokines and growth factors) linked to inflammation, insulin resistance, and angiogenesis lead to GDM and PE. These cytokines may also serve as early markers or disease during pregnancy, and if present postpartum, critical markers for future disease. Currently, no single biochemical measure reliably identifies women at risk for these complex disorders during pregnancy, and those at risk for future disease. Likely, alterations in a specific combination of cytokines ('cytokine signatures') characterize GDM and PE. Limitations in technology and lack of prospective studies have prevented efficient and accurate quantification of cytokine combinations. Careful application of novel, multiplexed profiling techniques to quantify biologically important cytokines in women followed prospectively during pregnancy overcomes these limitations. The investigators will test 3 hypotheses (in serum and urine): 1) Cytokine (TNF-alpha, IL-1beta, IL-6, MCP-1, IL-8) alterations identified early in pregnancy distinguish women who develop GDM or PE, and after pregnancy, characterize these same women; 2) Angiogenesis-related placental growth factors (PIGF, FGF-2) and an inhibitor (sFlt-1) are altered early in pregnancy among women who develop GDM and PE; 3) Disease-specific microarrays quantifying a set of pre-specified highly informative (aims 1, 2) cytokines can be developed, and this prospectively identifies incident GDM and PE. Their ongoing prospective pregnancy cohort permits excellent power and efficiency to test each aim. A multidisciplinary team with expertise in the epidemiology of diabetes and hypertension in pregnancy, placental biology, microarray technology, and bioinformatics will perform an innovative and cost-efficient study to understand the biology of GDM and PE, identify early markers for the conditions and suggest potential for interventions.

ENDOCRINOLOGY

TITLE: **Estradiol and Hippocampal Development** **NINDS**
P.I.: **Margaret M. McCarthy, PhD**
INST.: **University of Maryland, Baltimore**
GRANT NO.: **1 R01 NS50525-01A1**
KEYWORDS: **hippocampus, brain, learning, memory, hypothalamic-pituitary-adrenal (HPA) stress axis, sex differences, cognitive functioning**
STUDY TYPE: **basic**
AWARD: **$333,155**

The hippocampus is a brain region regulating two divergent but related life functions; learning and memory and regulation of the hypothalamic-pituitary-adrenal stress axis. The rodent provides a powerful model for investigating the importance of the hippocampus in both these responses. In the adult, the hippocampus is a sensitive target organ for both gonadal and adrenal steroids. Estradiol modulates synaptic plasticity in the CA1 region and improves cognitive functioning on spatial learning tasks. The effects of estradiol on hippocampal development have been less intensively studied and largely framed in the context of sexual differentiation of the brain. In this scenario, neonatal androgens of testicular origin are locally aromatized to estradiol by neurons and thereby exert a masculinizing effect on the neuroarchitechture. However, the investigators recently discovered that contrary to expectation, the developing female hippocampus possesses high levels of estradiol. This lead them to speculate that the developing female hippocampus synthesizes estradiol de novo from cholesterol and this results in levels similar to that of males produced from testicular androgens, thereby reducing sex differences in cognitive functioning in adults. This tenet can be deconstructed into three testable hypotheses: 1) The developing female hippocampus makes estradiol de novo from cholesterol. 2) The developing male hippocampus does not make estradiol de novo from cholesterol but instead derives estradiol from testicular androgen. 3) Developmental estradiol

synthesis in females reduces sex differences in cognitive function. The investigators will test each of these hypotheses via three specific aims that involve characterizing the source of estradiol, determining the functional significance of estradiol action to hippocampal development and identification of cellular endpoints modulated by estradiol. These results will be informative to normal hippocampal development and may serve as an entry point into understanding adult sex differences in learning and memory and stress responding.

GASTROENTEROLOGY

TITLE: **Improving IBS Outcomes** **NINR**
P.I.: **Margaret M. Heitkemper, PhD**
INST.: **University of Washington, Seattle, WA**
GRANT NO.: **5 R01 NR04142-08**
KEYWORDS: **irritable bowel syndrome (IBS), polymorphisms, gender, serotonin, behavioral & social science, digestive disease, chronic pain conditions**
STUDY TYPE: **translational**
AWARD: **$100,000**

In the United States, it is estimated that 10-20% of the population experience symptoms compatible with a diagnosis of irritable bowel syndrome (IBS). IBS is a functional condition characterized by change in bowel patterns, (e.g. constipation, diarrhea), interfering with functional activities and increasing health care utilization. Current recommended therapies include diet manipulation, self-management, psychotherapy, and motility and pain modulation via pharmacological therapy. The primary aim of this research is to compare the distribution of SERT polymorphisms across predominate bowel pattern subgroups and gender in people with IBS. It is hypothesized that the distribution of SERT polymorphisms (5'-flanking promoter region [5-HTTLPR] and in exon2 [VNTR] will differ across predominate bowel pattern subgroups and the distribution of SERT polymorphisms will differ by gender. Exploratory aims of this study include: 1) Evaluate the relationships of SERT polymorphisms to symptom experiences and psychological profile; 2) Test whether the degree of improvement in response to the CSM therapy differs by SERT polymorphism; and 3) Evaluate the relationship of platelet rich plasma 5-HT levels to SERT polymorphisms, predominate bowel pattern. This study will provide information on the potential role of serotonin processing in IBS as well as potential gender and bowel symptom predominance. Such results may ultimately be used to tailor therapies for this common health problem.

GENITOURINARY

TITLE: **Epidemiology of Interstitial Cystitis/Painful Bladder Syndrome** **NIDDK**
P.I.: **Sandra Berry, PhD**
INST.: **RAND Corporation, Santa Monica, California**
GRANT NO.: **5 U01 DK 070234-02**
KEYWORDS: **urinary frequency, bladder pain, patient screening, survey research, quality of life, endometriosis, interstitial cystitis, chronic pain conditions, urologic disease**
STUDY TYPE: **epidemiological**
AWARD: **$200,000**

Interstitial cystitis (IC) is characterized by chronic and debilitating bladder pain, usually accompanied by urinary frequency and urgency. Because research has been hampered by the lack of a clear and well-accepted case definition, little is known about the prevalence of IC in the population, the full burden of disease for IC patients, the kinds of care they seek, and the kinds of treatment they receive. At present, there is no standardized questionnaire for patient screening or epidemiological studies. The lack of information about IC makes if difficult to meet patients' needs for medical and non-medical care. Therefore, this project will establish (1) a case definition of IC in women for patient screening or epidemiological studies using a Delphi panel of experts in IC and diseases with similar symptoms; (2) develop and validate a symptom questionnaire that can be used to identify female IC patients and

distinguish them from those with similar conditions (e.g., overactive bladder, urinary tract infection, and endometriosis); (3) develop an IC-specific measure of self-reported functional status, including physical, mental, social, sexual/relationship, role functioning and other factors identified by IC patients as important; (4) survey more than 300,000 women for urinary symptoms and, using the validated symptom questionnaire, screen more than 23, 000 to estimate prevalence of IC in the United States and provide a sample of 354 women over age 18 who fit the case definition for IC and 300 who have IC-like symptoms; (5) describe the impact of IC on patient's lives, including IC-specific functional status and the impact of IC on quality of life, mental and physical health, stress and coping, social support, sexual functioning, social functioning, labor force participation and income, as well as utilization of traditional and alternative care and compare these results with existing data on disease burden for other chronic diseases.

TITLE: **A New Tool to Diagnose Female Urinary Incontinence** **NICHD**
P.I.: **Catherine Bradley, M.D., M.S.C.E.**
INST.: **University of Iowa Hospitals, Iowa City, IA**
GRANT NO.: **1 K23 HD047654-01A1**
KEYWORDS: **career development and training, patient-oriented research, clinicaltrials, urologic disorders, and urinary incontinence**
STUDY TYPE: **basic**
AWARD: **$100,000**

Catherine Bradley, M.D., M.S.C.E. is a full-time faculty member in the Department of Obstetrics and Gynecology at the University of Iowa. Her long-term goal is to become a successful, independent investigator focusing on patient-oriented research in female urinary incontinence (UI). She has recently completed a Master's program in Clinical Epidemiology, and she intends to pursue further formal research training, specifically in areas of questionnaire development, psychometric analyses and the use of survey data in epidemiologic studies. This award would allow her to pursue a research career development plan that includes additional advanced courses and instruction in biostatistical and epidemiologic methodology, the closely mentored completion of this research protocol, and participation in a broad range of research activities by interacting with established research groups and their ongoing projects. Dr. Bradley's immediate goals for the award period include: 1) complete coursework targeted in areas of research methodology and analysis important to this protocol, 2) further develop her critical thinking skills in clinical and epidemiologic study design and statistical analyses through the mentorship described in this application and by attending seminars and meetings, 3) become involved in multiple types of clinical and epidemiologic research, such as clinical trials and cohort studies, by working closely with her mentors at the University of Iowa and elsewhere, 4) conduct, analyze and interpret results from the proposed questionnaire development research project, 5) present research findings to the scientific community via presentations and publications and 6) develop an area of research expertise that will lead to future study opportunities. As her main research effort, Dr. Bradley proposes to develop and test a Questionnaire for female Urinary Incontinence Diagnosis (QUID). Her hypothesis is that a self-administered symptom-based questionnaire can accurately predict if a woman has stress and/or urge UI. The specific aims are to measure the validity, reliability and responsiveness of the QUID. To fulfill these aims, she will complete a prospective, split-sample longitudinal study of outpatients with UI symptoms. Criterion validity of the QUID will be tested by comparing the QUID'S diagnoses to formalized clinical diagnoses as the gold standard. Precise measurements of the QUID'S sensitivity and specificity in the diagnosis of stress and urge UI will be performed. Reliability, reproducibility and responsiveness of the QUID will be measured. This study will produce a rigorously developed and tested questionnaire, which will be a useful diagnostic tool for clinicians and researchers who wish to accurately predict the underlying diagnoses behind female UI symptoms. The combination of clinical and research resources available at the University of Iowa provides an ideal environment for Dr. Bradley's research career development. Dr. Bradley has the enthusiastic support of the Colleges of Medicine and Public Health, the Department of Obstetrics and Gynecology and her mentors and collaborators.

TITLE: **Mechanisms of Female Urinary Incontinence in Diabetes** **NIDDK**
P.I.: **Margot S. Damaser, PhD**
INST.: **Loyola University Chicago**
GRANT NO.: **1 R21 DK070905-01**
KEYWORDS: **Diabetes, pregnancy, incontinence, vaginal delivery**
STUDY TYPE: **basic**
AWARD: **$187,555**

Diabetes mellitus (DM) causes debilitating and devastating complications, including these of the lower urinary tract (LUT), such as urinary incontinence. Women with DM have a higher prevalence of LUT complications, contributing to the high prevalence of urinary incontinence (30-60%) among adult women in the US. In addition, women are at increased risk of later development of stress urinary incontinence due to pelvic floor injuries sustained during vaginal delivery of children. Vaginal delivery causes ischemic injury to tissues of the pelvic floor, including muscle, fascia, and nerves. The pudendal nerve, which innervates the external urethral sphincter and contributes to urinary continence, is particularly vulnerable to ischemia, crush, and stretch during delivery. Type I DM affects women at or before their childbearing years and increases their risk of incontinence after vaginal delivery. However, the mechanistic relationship between DM and urinary incontinence is poorly understood. In pursuit of their common interests, the Principal Investigator, Dr. Damaser, and the co-Investigator, Dr. Daneshgari, have jointly developed a theory that the accumulation of advanced glycosylation end products (AGEs) from prolonged hyperglycemia induces intracellular oxidative stress, limiting the ability of LUT muscles and associated nerves to recover from the injuries sustained during vaginal delivery, particularly pudendal nerve injury. This could provide the mechanism for the relationship between DM and urinary incontinence. This research grant proposes to develop a unique animal model and obtain feasibility and preliminary data for a future R01 application. It proposes development of an animal model addressing both bladder complications of diabetes and gender differences in development of incontinence, a LUT disorder. In addition, it would promote a productive research collaboration for the study of the LUT between a clinician (Dr. Daneshgari) and a basic scientist (Dr. Damaser). The Hypothesis of this project is that the response of diabetics to pudendal nerve injury involves 1) a decreased neuroregenerative response and 2) increased duration and severity of incontinence symptoms, both of which are temporally associated with an accumulation of advanced glycated endproducts. Investigators will test this hypothesis with 2 specific aims: (I) Determine if pudendal nerve crush in diabetic animals results in: a. decreased pudendal nerve regeneration and b. increased duration and severity of urinary incontinence symptoms; and (II) Determine if these altered responses in diabetic animals are temporally associated with increased accumulation of AGEs. Techniques to be utilized include cystometry, leak point pressure testing, morphometry, light and electron microscopy, and in situ hybridization of β_{II} tubulin mRNA, mass spectrometry, immunohistochemistry and ELISA. The data from this R21 exploratory research grant will be used to propose a R01 research grant to explore the mechanism of the observed effects. The long term goals for this project include using this novel animal model to study the mechanism of urinary incontinence in women with DM, to develop & test novel mechanism-based pharmacologic agents, and to develop & test techniques and strategies which could be used to prevent and/or treat incontinence in women with DM.

HIV/ AIDS

TITLE: **Impact of Delivery Models in HIV Health Care** **FIC**
P.I.: **Ximena L. Burbano, M.D.**
INST.: **Fundacion Santa, Bogota**
GRANT NO.: **5 R01 TW006218-03**
KEYWORDS: **HIV/AIDS, health services research, prevention, infectious diseases**
STUDY TYPE: **clinical**
AWARD: **$20,000**

Colombia, which ranks fourth in the total number of HIV reported cases in Latin America, has designed different Delivery Health Care Models to provide coverage for HIV infected patients. The proposed health research initiative, by a new foreign investigator, will evaluate for the first time, the utilization and cost implications of different representative delivery health care models in Bogota, Colombia. Assessment of cost-effectiveness is vital not only in the area of treatment but also in regard to the use of diagnostics,

provision of care, support services, and prevention strategies and programs. A multi-step evaluation of three main Delivery Health Care Models (Open Pre-Paid, EPS, Social Security) available in Bogota, will be undertaken. First, information will be obtained to determine the type of specific services available for each delivery model. Second, data obtained from 450 HIV-infected individuals (150/model) will be systematically collected and prepared for statistical analysis. In the third phase, models will be compared in terms of health services utilization, costs, cost-effectiveness and which health care model best accomplishes delivery and sustains adherence to HAART. Evaluation of service utilization will consider the impact on disease progression, as indicated by CD4 cell count and viral burden. Outcomes will be aggregated to determine the level of total services required for adequate care for each delivery model. Findings from this project should provide necessary information to help determine the optimal use of HIV delivery services and help develop public health strategies to achieve equity in health services, for HIV infected people in Colombia, and possibly other countries in Latin America.

TITLE: **Interventions to Reduce HIV1 Incidence after Delivery** **FIC**
P.I.: **James N. Kiarie, M.D.**
INST.: **University of Nairobi, Kenya**
GRANT NO.: **5 R01 TW006640-03**
KEYWORDS: **HIV/AIDS, postpartum, counseling, prevention, topical microbicides**
STUDY TYPE: **clinical**
AWARD: **$20,000**

Women in sub-Saharan Africa face a high risk of HIV-1 acquisition during the first year postpartum which can be reduced by antenatal voluntary counseling and testing (VCT) and using female controlled HIV-1 prevention methods. In preventing heterosexual HIV-1transmission, the success of female controlled methods such as female condoms, the vaginal diaphragm, and vaginal microbicides depends on their use by women at a high risk of HIV-1 infection. In studies of prevention of mother-to-child transmission little attention has been paid to women identified as HIV-1 negative and their risk of becoming infected after delivery. An understanding of the factors that influence HIV-1 incidence among uninfected mothers, and which female controlled prevention methods are most acceptable to them, is crucial for preventing HIV-1 acquisition in these women, and hence, preventing additional mother-to-child transmission of HIV-1 in future pregnancies. This study proposes to determine the potential effectiveness of female controlled HIV-1 prevention methods, and the impact of participation in perinatal HIV-1 prevention programs on HIV-1 incidence in the first year after delivery (assessed using a detuned ELISA at 9 to 12 months postpartum) in three sites in Kenya. The specific aims of the study are to: 1. Determine the correlates of incident HIV-1 infection among Kenyan women in the first year postpartum; 2. Compare the incidence of HIV-1 infection among women who have participated in perinatal HIV-1 prevention programs to the incidence among those who have not participated in these programs; 3. Determine women's knowledge, attitudes, and willingness to use vaginal microbicides, the female diaphragm, and female condoms; 4. Estimate the effectiveness of the various HIV-1 prevention methods based on theoretical efficacy, the number and HIV-1 infection risk of women willing to utilize these methods. This study will provide important information on how to increase the effectiveness of female controlled HIV-1 prevention methods by targeting women at a high risk of acquiring HIV-1 infection. The study will also identify ways to increase the impact of antenatal VCT in reducing HIV-1 incidence.

TITLE: **AIDS International Training and Research Program (AITRP)** **FIC**
P.I.: **Arthur L. Reingold, M.D.**
INST.: **University of California, School of Public Health, Berkeley, CA**
GRANT NO.: **3 D43 TW000003-06**
KEYWORDS: **training, virology, HIV/AIDS, infectious diseases**
STUDY TYPE: **clinical**
AWARD: **$50,000**

The University of California, San Francisco-Gladstone Institute of Virology & Immunology Center for AIDS Research (UCSF-G1VI CFAR) will collaborate with the University of California, Berkeley's (UCB) Fogarty International AIDS Training Program (AITRP) providing support for competitive training grants. Training grants will be led by CFAR members in collaboration with in-country collaborations in five

resource-limited settings selected for the scale and stability of on-going international HIV research. Training will focus on scientists from countries and projects integral to the UCB/UCSF AITRP. Training will be provided in country or in San Francisco and will take advantage of CFAR member expertise and CFAR Scientific Core capabilities. Training projects will be selected in a competitive mentored process after a publicly announced request for training proposals. Letters of intent responsive to the UCSF-GIVI focus on enhancing cross disciplinary translational research will be invited to submit full but brief proposal linking training needs in country with ongoing research projects. Proposals will be reviewed by an expert peer panel with final funding decisions made by the UCSF-G1VI CFAR Co-Directors. Effectiveness of training will be monitored and assessed by written progress reports and evidence of subsequent research grant funding and publications. To accomplish this goal, the following aims will be addressed: 1.) Evaluate the training needs at each of the five CFAR international sites; 2.) Support investigators from one or more priority sites in training at the UCSF-GIVI CFAR, and /or; 3.) Support UCSF-GIVI investigators to provide training at one or more priority sites(s); 4) Provide access to UCSF-GIVI CFAR' core laboratories and other resources for UCB/UCSF AITRP priority site investigators in pilot research projects; 5.) Monitor and evaluate the success of research training support at priority sites as evidenced by important research grants, publications, and/or findings.

TITLE: **Scale-up of Community-based HIV Prevention and Care** **FIC**
P.I.: **Warren D. Johnson, M.D.**
INST.: **Well Medical College of Cornell University, Dept. of Medicine, New York, NY**
GRANT NO.: **3 D43 TW000018-18**
KEYWORDS: **infectious diseases, epidemiology, biosocial, HIV/AIDS, treatment and prevention, rural health**
STUDY TYPE: **clinical**
AWARD: **$50,000**

This proposal requests support for the Harvard University Program in Infectious Disease and Social Change/ Partners in Health/ Zanmi Lasante to continue training Haitian scientists in the performance of biomedical, epidemiological and biosocial research in the programmatic implementation of HIV prevention and treatment and the care of individual patients with HIV in rural Haiti. The program is based at Clinique Bon Saveur in Change, Haiti, with responsibility for the provision of healthcare services for the population of the Central Plateau. The principal investigator is Paul Farmer, M.D., PhD, who is based at Harvard Medical School in the Program in Infectious Disease and Social Change. The training team has many years of experience in HIV prevention and treatment in rural Haiti, including the prevention of mother-to-child transmission, diagnosis and treatment of TB and sexually transmitted disease, the prevention of opportunistic infections and the use of highly active antiretroviral therapy. The principal investigator of the AITRP grant, Dr. Warren Johnson, is a long-standing supporter of the work done in Change and the Central Plateau, and this collaborative training program has been highly successful. The program will continue to emphasize long-term training and advanced research training in Haiti. Because HIV does not exist as a separate entity, the approach at PIH/ZL is to integrate the prevention and treatment of HIV with the most vulnerable and high prevalence groups that are seen at Clinique Bon Saveur. HIV-related services include: 1.) HIV prevention and treatment, including expansion of access to voluntary counseling and testing (VCT); 2) the screening and treatment of STIs; 3) the prevention of mother-to-child transmission; and 4) TB case detection, treatment and VCT (approximately 50% of HIV patients in the central plateau present with TB). These four activities are referred to by PIH/ZL as the "four pillars" of HIV control. The overall program goal of this grant is to provide training that will increase local capacity to perform research on service integration, diagnosis and treatment of HIV in central Haiti within these four pillars of HIV control. Long-term benefits will include the increases in research capacity for future HIV related research activities in Haiti.

TITLE: **Aids International Training and Research Program (AITRP)** **FIC**
P.I.: **King K. Holmes, M.D., PhD**
INST.: **University of Washington, College of Medicine, Seattle, WA**
GRANT NO.: **5 D43 TW000007-18**
KEYWORDS: **HIV/AIDS, international, prevention, treatment, immunology, infectious diseases, vaccine development**
STUDY TYPE: **clinical**
AWARD: **$50,000**

This program proposes to develop a fifth International AIDS Research and Training Program (IARTP) site in New Delhi at the All India Institute of Medical Sciences (AIIMS) to address the growing HIV epidemic in India. Other target countries have been Kenya, Peru, Mozambique and Thailand. The University of Washington (UW) IARTP selected AIIMS as the site for program expansion for several reasons. First, AIIMS is a premier institution for biomedical research and training in India, and successful collaborative research is already being performed between scientists at the UW (Uma Malhotra and Julie McElrath) and AIIMS (Pradeep Seth and Madhu Vajpayee) within the framework of an existing longitudinal cohort of HIV-1 infected subjects at AIIMS. Second, UW International Training and Research in Emerging Infectious Diseases (ITREID) has a site in New Delhi and the two programs will collaborate in their research and training efforts in the region. The IARTP program direction and the core/resource faculty will be identical to that described for the parent program. The overall goal of this proposal is to develop a center for excellence in HIV-1 research in India with independent and sustainable research capacities in the prevention and control of HIV. A number of training needs and research priorities have been identified and include: a) Strengthening of the infrastructure for field research through training and capacity building in the area, b) Development of the site for international research trials to assess prevention and treatment regiments through training in clinical research, c) Strengthening the immunology research program through training of laboratory scientists in state-of-the-art-immunology assays. The site will emphasize training in the Epidemiology Track and the Laboratory Track and will focus on long-term and medium-term training. Recruitment of scientists into the Laboratory Track will occur in the Department of Microbiology. Recruitment efforts for trainees interested in the Epidemiology Track will take place in the Department of Community Medicine in collaboration with the Head of the AIDS Education and Training Program in New Delhi. Collaborative research and training during the first year will emphasize: a) Seroprevalence and correlates of HIV-1 seropositivity in patients attending the Sexually Transmitted Infection Clinic, b) Clinical profile of HIV-1 clade C infection in India, c) Cellular immunity to HIV-1clade C viruses and diversity consideration in vaccine development, and d) HIV-1 shedding and mucosal immunity. The existing longitudinal patient cohort will provide a foundation for new cohorts and continued collaborative research. Through these endeavors in multidisciplinary research and training, it is anticipated that the program will facilitate the establishment of critical expertise in biomedical and prevention research at the AIIMS to combat the growing HIV-1 epidemic in the region.

TITLE: **Brown/Tufts AIDS International Training & Research Program (AITRP)** **FIC**
P.I.: **Kenneth H. Mayer, M.D.**
INST.: **Miriam Hospital, Brown University, Providence, RI**
GRANT NO.: **2 D43 TW000237-12**
KEYWORDS: **HIV/AIDS, training, international, Asian, Pacific Islanders, prevention, women's health, nutrition, metabolic, molecular virology**
STUDY TYPE: **clinical**
AWARD: **$100,000**

The Brown/Tufts University Fogarty AIDS International Research Training Program is applying for continued support of its educational activities for the next 5 years, 2005-2009. The AIRTP has trained 48 clinical, laboratory, behavioral, and public health researchers from India, the Philippines, Cambodia, Indonesia, Bangladesh, and Thailand in the previous 5 years in multiple aspects of AIDS research. Trainees have been extremely productive, with almost 70 peer-reviewed publications, more than 100 presentations at all major international AIDS research conferences, participation in many international advisory capacities and organizations, ranging from the WHO to the Gates Foundation. Several trainees have been successful in developing their own independent research programs with R-O1 funding, as well as participation in HPTN, ACTG, and TREAT ASIA networks. In this new cycle the Brown/Tufts ARTP proposes to focus on longer term training, budgeting to provide tuition for at least 5 long-term trainees per year at either Brown

or Tufts. Trainees may elect to participate in MPH, Masters Programs in Epidemiology, Biostatistics, or Clinical Decision Analysis, as well as PhD programs. In addition, they have developed 6-month intensive training courses in a variety of clinical research disciplines, including Molecular Virology, Clinical Trial Research Design, HIV Prevention Research, Women's Health, Nutrition and Metabolic Studies, as well as Pharmacology. In order to identify the highest calibre trainees, the AIRTP has developed a formal advisory process, which includes the Directors of several national AIDS programs, Public Health Research Institutes, and Research Universities each of the affiliated countries. In addition, a formal mentoring program has been developed which will ensure that each international trainee is in frequent contact with a designated Brown or Tufts faculty mentor whose research interests are congruent with those of the relevant trainee. Prospective candidates will be proposed by international advisors and their selection with be conducted during the monthly meetings of the Brown-Tufts Fogarty AIRTP Executive Committee, which includes accomplished faculty from all affiliated institutions with diverse academic training and a commitment to international public health training. The Committee will continue to meet monthly to evaluate the progress of each trainee, to consider applications for new trainees into our program.

IMMUNITY/AUTOIMMUNITY

TITLE: **Mechanism Regulating Neutrophil Activation in Pregnancy** **NIAID**
P.I.: **Howard R. Petty, PhD**
INST.: **Wayne State University, Detroit**
GRANT NO.: **5 R01 AI51789-05**
KEYWORDS: **Autoimmunity, rheumatoid arthritis, pregnancy**
STUDY TYPE: **translational**
AWARD: **$50,000**

This grant will identify and characterize differences in the innate and adaptive immune response between genders, with a specific call for interdisciplinary clinical and basic research studies that may be important in the understanding and treatment of autoimmune diseases. Neutrophils are key cells in the development of homeostatic as well as pathologic inflammatory responses. These cells play a central role in the generation of tissue damage in autoimmune diseases (i.e., rheumatoid arthritis) as well as in infectious diseases, including sepsis. The studies outlined in this application are designed to study the differences in neutrophil function in non-pregnant women, pregnant women, and men. The study offers a unique opportunity for the identification of endogenous mechanisms affecting women's health. Studying neutrophil biology during pregnancy will result in a mechanistic understanding of factors responsible for clinical improvement in certain autoimmune diseases during pregnancy and will also lead to the development of novel therapeutic approaches to control inflammation and autoimmunity.

TITLE: **Sex-Based Differences in the Immune Response** **NIAID**
P.I.: **Betty Diamond, M.D.**
INST.: **Albert Einstein College of Medicine, New York**
GRANT NO.: **5 R01 AI51767-04**
KEYWORDS: **autoimmunity, hormones, animal models, estrogen**
STUDY TYPE: **basic**
AWARD: **$50,000**

The grant will undertake studies to investigate the effects of estradiol on the negative selection of naive autoreactive B cells in BALB/c and C57B1/6 mice. The goal of the study is to understand what genes and pathways are involved in estrogen-mediated B cell survival and B cell activation, and to understand what underlies an estrogen mediated breakdown in humoral self-tolerance. The 3 Specific Aims are: Aim 1, investigates the estradiol-induced alterations in marginal zone (MZ) B cell phenotype, function, and gene expression, and finally addresses B cell repertoire selection. Aim 2, addresses the role of estradiol in the generation of MZ B cells and the role of intracellular tyrosine kinase, Pyk-2, in the phenotype formation of these cells, and focuses on how estradiol rescues MZ B cells, and some potentially autoreactive B cells, in

Pyk-2 deficient mice. Aim 3 will characterize estradiol-induced signaling pathways that may alter B cell repertoire selection in BALB/c versus C 57B1/6 mice, and will identify the cell type responsible for differential responsiveness to estradiol. The work should provide informative data about the survival of cells that may initiate an autoimmune response, and the role of sexual dimorphism in this phenomenon.

TITLE: **Predictors of Pregnancy Outcome in SLE and APS** **NIAMS**
P.I.: **Jane E. Salmon, M.D.**
INST.: **Hospital for Special Surgery, New York, NY**
GRANT NO.: **5 R01 AR049772-03**
KEYWORDS: **thrombosis, pregnancy loss, systemic lupus erythematosus, antiphospholipid antibodies, genetic polymorphisms, recurrent fetal loss, poor fetal outcome, placentas, autoimmune diseases, genetics, prevention**
STUDY TYPE: **clinical**
AWARD: **$400,000**

Thrombosis and pregnancy loss are common features of systemic lupus erythematosus (SLE), particularly in the presence of antiphospholipid (aPL) antibodies. The in vivo mechanisms by which aPL antibodies lead to vascular events and, specifically, to recurrent fetal loss are largely unknown. Our studies in a murine model of antiphospholipid antibody syndrome (APS) indicate that in vivo complement activation is necessary for fetal loss caused by aPL antibodies. This proposal represents a first time effort to translate novel research observations on the potential role of complement activation in the pathogenesis of aPL antibody-mediated pregnancy loss to a clinically relevant human study. No study has investigated whether complement is activated in patients with aPL-associated poor pregnancy outcomes (with or without SLE), and whether particular patterns of complement activation characterize and thus can distinguish these patients from SLE patients without aPL antibodies or fetal loss, and from patients with normal pregnancy. Preliminary data in murine APS, the availability of more accurate tests of complement activation, and the recent development of effective and specific complement inhibitors argue persuasively that the role of complement in aPL associated pregnancy complications should now be examined. Accordingly, the specific aim of the study is: To determine whether elevations of split products generated by activation of the alternative or classical complement pathways predict poor fetal outcome in patients with antiphospholipid antibodies and/or SLE. The investigators propose a prospective observational study of over 400 pregnant patients, enrolled at 6 major clinical centers, and grouped and analyzed according to the presence or absence of aPL and preexisting SLE. A core group of investigators with recognized expertise in SLE and aPL pregnancy, high-risk obstetrics, the basic biology of complement, and statistical methods in SLE studies have been assembled. Detailed medical and obstetrical information during the course of pregnancy and serial blood specimens for complement and cytokine assays will be obtained, and analyzed to identify predictors of poor fetal outcome. Placentas will be studied to characterize tissue pathology and mediators of injury. RNA, DNA, serum, and urine will be stored for studies to elucidate temporal changes in gene expression during the course of complicated and uncomplicated pregnancies and to investigate genetic polymorphisms. The investigators hypothesize that this study will provide insights into the mechanisms of complement-mediated inflammatory disorders and suggest means to prevent, arrest, or modify these conditions. Characterization of clinically applicable surrogate markers that predict poor pregnancy outcome will enable the investigators to initiate an interventional trial of complement inhibition in patients at risk for aPL antibody-associated fetal loss. The identification of such surrogate markers in aPL and SLE patients may also prove generally applicable to anticipate complications during pregnancy in disease-free women.

TITLE: **Brain Connections** **NIAMS**
P.I.: **Michelle A. Petri, M.D.**
INST.: **Johns Hopkins University, Baltimore, MD**
GRANT NO.: **5 R01 AR49125-04**
KEYWORDS: **Systemic Lupus Erythematosus, cognitive dysfunction, basic behavioral, behavioral & social science, brain disorders, depression, fibromyalgia, mental health**
STUDY TYPE: **clinical**
AWARD: **$100,000**

Neuropsychiatric manifestations of Systemic Lupus Erythematosus (NPSLE) are both common and an important source of morbidity. Of the case definitions for NPSLE syndromes that have recently been developed, cognitive dysfunction appears to be the most prevalent. Little is known about the influence of co-morbidities or ethnicity/race on disease outcomes or the underlying biological basis for this important NPSLE syndrome. Perhaps most importantly, no rational therapeutic approach for the treatment of SLE-related cognitive dysfunction currently exists and is unlikely to be developed without a better understanding of disease mechanisms. One hundred newly diagnosed patients with SLE from 10 sites will be studied for the development of cognitive dysfunction, determined using both repeatable computerized and traditional neuropsychological tests. We will evaluate the relationship of structural and functional brain imaging (using anatomic magnetic resonance imaging and resting FDG-PET), several relevant biomarkers (antiphospholipid antibodies, cytokines and adhesion molecules) and co-morbidities (race/ethnicity, depression, fibromyalgia and corticosteroid use) to cognitive dysfunction, and the impact of cognitive dysfunction on quality of life. Factors distinguishing transient or reversible versus irreversible cognitive dysfunction will be determined using a repeated measures analysis approach. The ability to study the relationship between changes in cognitive functioning and these other variables in a group of newly diagnosed SLE patients is crucial to the successful discovery of early pathologic changes that could be potentially amenable to disease-reversing therapies.

TITLE: **Antibodies to NR2 in SLE** **NIAMS**
P.I.: **Betty Diamond, M.D.**
INST.: **Yeshiva University, New York**
GRANT NO.: **5 R01 AR49126-04**
KEYWORDS: **NMDA receptor, antibody, cognition disorder, systemic lupus erythematosus, glutamate receptor, inhibitor/antagonist, human tissue, brain disorders**
STUDY TYPE: **clinical**
AWARD: **$80,000**

Cognitive impairment occurs in a large percent of lupus patients. We have recently demonstrated that a subset of anti-DNA antibodies in patients with Systemic Lupus Erythematosus (SLE) binds to a defined linear epitope on the NR2 NMDA receptor. These antibodies can be found in the cerebrospinal fluid (CSF) as well as in serum. This project will explore further the antigenicity of the NR2 receptor in SLE and the functional consequences of anti-receptor antibodies. The serum from lupus patients will be studied to determine whether there are antibodies to other epitopes that function as a receptor agonists or antagonists and whether there is T cell recognition of NR2 epitopes. Also rodent models will be studied to determine whether serum antibody can penetrate an intact blood-brain-barrier, what concentrations of antibody that must be present in the CSF to cause disease, and whether there are selectively vulnerable populations of neurons. The overall goal of this collaborative interactive program is to develop the scientific foundation for prevention therapies for cognitive decline in SLE.

TITLE: **Virginia Mason/UCHSC Autoimmune Center** **NIAID**
P.I.: **George S. Eisenbarth, M.D.**
INST.: **University of Colorado, Denver, CO**
GRANT NO.: **5 U19 AI50864-05**
KEYWORDS: **autoimmunity, diabetes, Rheumatoid Arthritis, genetics, prevention**
STUDY TYPE: **translational**
AWARD: **$200,000**

This grant consists of 3 research projects. The overall objective of this application is to derive markers of autoimmune disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in genetic, immunologic and environmental

determinants that lead to disease. Project 1 will use tetramers to analyze the peripheral antigen-specific T cell profile in IDDM. Project 2 will identify three cohorts of individuals at increased risk for RA and attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. The third project will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

TITLE: **How Does Blockage of CD40/CD40L Prevent Autoimmunity?** **NIAID**
P.I.: **Matthias Von Herrath, M.D.**
INST.: **Scripps Research Institute, La Jolla, CA**
GRANT NO.: **5 U19 AI51973-05**
KEYWORDS: **autoimmunity, diabetes, autoimmune disease CD antigen, CD40 molecule, antibody inhibitor, antigen antibody reaction, autoimmune disorder, cooperative study, disease /disorder prevention /control, immunotherapy**
STUDY TYPE: **basic - animal models**
AWARD: **$100,000**

All three projects of the consortium application are targeted at better understanding induction of long-term tolerance by costimulation blockade of CD40/CD40L interactions with aCD40L antibody. The investigators believe that this immune-based intervention is one of the most promising and attractive approaches currently in clinical trials for several autoimmune disorders. Many of these ongoing interventions (psoriasis, transplantation etc.) show much promise and only one trial had to be stopped due to deleterious side effects (enhanced blood clotting), which was likely caused by the antibody preparation or too high dosages, since it did not occur in other clinical studies. Although it is known that CD40-CD40L interactions are required for dendritic cell maturation and activation, as well as generation of effector lymphocytes, many mechanistic issues remain unresolved. The most crucial of these will be addressed by the three projects united in the present U-19. Effects on lymphocyte differentiation and effector functions (Sarvetnick), T cell proliferation, differentiation and APC-trafficking (Miller) and induction of regulatory APCs or lymphocytes able to down-modulate aggressive autoimmune responses antigen specifically (von Herrath) will be studied by the single components. In addition to analyzing differential effector mechanisms, three distinct models for autoimmune diseases will be utilized (Sarvetnick, NOD; Miller, EAE; von Herrath, RIP-LCMV). This multi-focal approach will result in a more rapid and thorough understanding of a CD40L induced immune modulation and/or suppression. Furthermore, paradigms or discoveries applicable to a human situation should ideally be validated and tested in various animal models. Therefore, the direct comparison of three autoimmune models will enable us to define, which in vivo consequences of costimulation blockade occur more commonly and which are restricted to a given experimental situation.

TITLE: **Fine Specificity of Scleroderma Autoantibodies** **NIAMS**
P.I.: **Judith James, M.D.**
INST.: **Oklahoma Medical Research Foundation, Oklahoma City, OK**
GRANT NO.: **5 R01 AR48045-05**
KEYWORDS: **Scleroderma, immune response, autoimmunity, autoimmune disease, Raynaud's disease, autoantibody, scleroderma, ribonucleoprotein, immunodiffusion, western blotting**
STUDY TYPE: **translational**
AWARD: **$200,000**

Systemic sclerosis (scleroderma) is a disfiguring, multi-system disease of unknown etiology, which is characterized by a broad spectrum of disease manifestations with varying organ involvement. Raynaud's phenomenon, the dysregulated vascular contraction of the terminal arteries of the circulatory system, is present in almost every case. Vascular insufficiency in these patients is associated with a vasculopathy causing tissue ischemia, which is directly linked to progressive fibrosis of specific target organs, such as the skin, lung, heart, gastrointestinal tract, and kidney. Although the underlying pathophysiology of this disorder remains an enigma, the presence of anti-nuclear antibodies in scleroderma patients is nearly universal. Targets of these autoantibodies include topoisomerase 1 (Scl-70), nuclear ribonucleoproteins (nRNP), centromere, PM-Scl, and Ku. Anti-topoisomerase-1 (topo-1) autoantibodies are quite specific for

scleroderma, and are present in precipitating levels in 20-40% of patients. Anti-topo 1 is associated with diffuse skin thickening, lung involvement, and the development of lung, colon, and brain cancer. Scleroderma patients with anti-nRNP autoantibodies may have a more cutaneous form of the disease and universally suffer from Raynaud's phenomenon. Over the past decade the immunochemistry of lupus autoantigens have been extensively characterized. These previous studies provide the technical background for this proposal. Epitope mapping experiments of the lupus spliceosomal autoantigens have led to a peptide induced model of lupus autoimmunity. These studies have identified a potential etiological trigger and pathogenic mechanisms. These well-honed techniques will be applied, as well as a similar scientific strategy, to analyze the humoral fine specificity of the anti-nRNP and anti-topoisomerase autoantibodies found in scleroderma. Preliminary data suggest a dramatic difference in the anti-nRNP response of SLE patients and scleroderma patients with nRNP autoantibodies. This project seeks to identify the common humoral epitopes of nRNP and topoisomerase-1 in scleroderma and primary Raynaud's, to describe the development of these humoral autoimmune responses over time (and with therapy), to establish potential etiological triggers of these rheumatic diseases, and to understand the role of these specific autoantibodies in scleroderma, disease pathogenesis.

TITLE: **Studies of Collagen Gene Regulation in Two Murine Models** **NIAMS**
P.I.: **Stephen H. Clark, PhD**
INST.: **University of Connecticut, Farmington, CT**
GRANT NO.: **5 R01 AR48082-05**
KEYWORDS: **Scleroderma, fibroblasts, microarrays, autoimmunity, collagen, gene expression, genetic regulatory element, molecular pathology, pathologic process, protein biosynthesis, scleroderma, fibrosis, gene mutation, genetic regulation, genetic transcription, reporter gene**
STUDY TYPE: **basic - animal models**
AWARD: **$200,000**

This proposal will utilize two mouse mutations that are models for scleroderma, tight skin (Tsk) and tight skin 2 (Tsk2). Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark feature of the human disease. The long range of objective of the proposed research is to utilize these two mutations combined with several lines of transgenic mice as experimental tools to dissect molecular mechanisms of disease pathogenesis. Specific experiments are proposed for the identification of genes involved in the regulation of extracellular matrix synthesis in dermal fibroblasts. Two experimental strategies are planned and are encompassed in three specific aims. Specific aim 1 focuses on identifying cis-acting elements in the type I collagen gene required for the increased production of Collal mRNA in mutant dermal fibroblasts. Defining "fibrotic" specific elements will provide a basis for the identification of the transacting factors that interact with these DNA segments to increase Collagen gene expression. These elements will be defined by studying the expression of Collal CAT reporter transgenes bearing various segments of the 5' promoter region as well as specific deletions of the first intron. The expression of each transgene will be evaluated in skin samples isolated from Tsk, Tsk2 and normal mice. Also, transgene expression will be measured in dermal fibroblasts cultured from skin explants isolated from these mice. To generate experimental mice, Tsk and Tsk2 mutant mice will be crossed with transgenic mice bearing the various collagen transgene constructs. A potential role of the Collal first intron in the upregulation of transcription of the Collal gene has been shown with the Tsk and Tsk2 mutations (our preliminary data) as well as in scleroderma dermal fibroblasts. In specific aim 2 the role of the Collal first intron in regulating transcription of the Collal gene and the development of the Tsk and Tsk2 fibrotic skin phenotype will be determined. For these experiments a targeted deletion in the Collal first intron will be employed. This experimental model has a unique feature permitting the determination of the levels of Co11a1 mRNA produced by the deleted and normal allele in the same RNA preparation. Further this genetic system allows the monitoring of gene expression in the context of the endogenous gene. A second experimental direction involves identifying genes in dermal fibroblasts that are associated with elevated levels of collagen production employing microarray analysis. The experimental plan outlined in specific aim 3 includes the development of reagents to isolate specific populations of dermal fibroblasts cultured from both mutant and normal animals based on their collagen gene expression. This will be accomplished by employing a collagen promoter GFP reporter transgene that has been documented to

display elevated expression in dermal fibroblasts isolated from both Tsk and Tsk2 mutant mice. Flow cytometric analysis of dermal fibroblasts expressing this transgene will permit the isolation of cell populations based on their level of collagen expression. RNA's will be extracted from high collagen and low collagen producing cell populations. These RNA's will be utilized in a microarray analysis to identify genes differentially expressed in high collagen producing cells compared to low collagen producing cells and visa versa. It is anticipated that genes identified in this experimental paradigm will permit the dissection of molecular pathways that are involved with the onset of scleroderma and potentially lead to therapies to control extracellular matrix metabolism.

TITLE: **EBNA-1 in Lupus** **NIAID**
P.I.: **John B. Harley, M.D.**
INST.: **Oklahoma Medical Research Foundation, Oklahoma City**
GRANT NO.: **5 R01 AI31584-12**
KEYWORDS: **Systemic Lupus Erythematosus, Epstein-Barr virus, Epstein Barr virus, systemic lupus erythematosus, B lymphocyte, autoimmune disorder, cytomegalovirus**
STUDY TYPE: **basic**
AWARD: **$200,000**

The environmental factors associated with systemic lupus erythematosus (SLE) include Epstein-Barr virus (EBV). Once infected, EBV is well known to persist in all human hosts for life. The investigators believe that novel approaches to the detection of this pathogen and to the assessment of the host response to this pathogen are warranted. Among the most interesting viral products is Epstein-Barr virus Nuclear Antigen-l (EBNAl), which contains a peptide sequence that inhibits antigen presentation and class I HLA-dependent cytotoxic T cell responses. Preliminary data show that EBNA-l also contains sequences that appear to be differentially bound by SLE as opposed to normal sera. We propose to study SLE from the perspectives of the anti-EBNA-l humoral immune response, of EBNA-l expression in B cells, and of EBNA-l sequence variants. We plan to use the Early-lmmediate antigen-l (El-l) of cytomegalovirus (CMV) as a control antigen. This project is a research for AI 31584 for year 09. Work in the current funding period is focused upon serology before diagnosis of SLE, made possible by over 20,000,000 sera in the Army Navy Serum Bank. The results to date from the first 130 SLE patients and 520 controls have established that autoimmune serological changes are present years before clinical manifestations and that autoantibody specificities vary greatly with regard to their temporal relationship to illness. Because of the high EBV infection rate among women and African-American men, the temporal relationship between EBV infection and SLE could not be tested. The final aim of this competitive renewal is to continue accruing the appropriate military cases and controls to provide sufficient power to test the hypotheses that EBV infection precedes clinical onset of SLE and that anti-EBNA-l precedes the onset of lupus autoantibodies. Establishing the role of ubiquitous agents, such as EBV, in chronic disease is especially difficult. In this situation, specific associations of SLE with immune response variations, with viral gene product expression, and with viral variants will be sought in an effort to explore particular mechanisms of pathogenesis as a strategy to more convincingly implicate EBV in the etiology of SLE.

TITLE: **UCSF Autoimmunity Center of Excellence (ACE)** **NIAID**
P.I.: **David Wofsy, M.D.**
INST.: **University of California, San Francisco, CA**
GRANT NO.: **5 U19 AI056388-03**
KEYWORDS: **immunology, molecular biology, autoimmune diseases, clinical trials, immunotherapies, murine lupus, lupus nephritis, diabetes, multiple sclerosis, prevention, urologic disease**
STUDY TYPE: **clinical**
AWARD: **$60,000**

The broad aim of this application is to translate advances in immunology and molecular biology into practical, safe, and effective therapies for people with autoimmune diseases. Toward this end, the investigators will participate in collaborative clinical trials of novel immunotherapies, and we will conduct basic research into the mechanisms that lead to autoimmunity as well as the mechanisms that can be harnessed to prevent autoimmunity. This proposal to become an Autoimmunity Center of Excellence

consists of a Clinical Center, two basic research projects, and an Immune Function Monitoring Core as described below: Clinical Center. Investigators involved in this application have extensive experience in the conduct of clinical trials in diverse autoimmune diseases. This application focuses primarily on systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type I diabetes mellitus (IDDM). Two clinical protocols are proposed, both based on basic research conducted at UCSF by participants in this proposal. Protocol 1 is based on the observation that blockade of T cell costimulation by CTLA4Ig, in combination with conventional therapy with cyclophosphamide, produces long-lasting benefit in murine lupus. It tests the hypothesis that this approach to therapy will be effective in people with lupus nephritis. Protocol 2 is based on the observation that HMG-CoA inhibitors ('statins') retard murine models for MS. It tests the hypothesis that atorvastatin will prevent progression to MS in patients at high risk.

TITLE: **Treatment of Autoimmune Disease by Costimulatory Signal (ACE)** **NIAID**
P.I.: **Samia J. Khoury, M.D.**
INST.: **Brigham and Women's Hospital, Boston**
GRANT NO.: **5 U19 AI046130-07**
KEYWORDS: **autoimmune disease, prevention, autoimmune disorder, immunotherapy, clinical research**
STUDY TYPE: **clinical**
AWARD: **$60,000**

There have been tremendous advances in the field of autoimmunity in the last 20 years, and our understanding of the mechanisms underlying autoimmune disease has grown exponentially. True tolerance is likely to arise not from improved immunosuppression, but from improved understanding of the normal mechanisms that generate and maintain self-tolerance, and the ability to manipulate these mechanisms for the prevention and treatment of autoimmune diseases. The mechanisms of autoimmunity that underlie many diseases are similar, and an integrated multi-specialty approach for evaluating new and emerging therapies would provide the opportunity to integrate knowledge from the various specialties. The investigators will study the therapy of autoimmune disease by blocking co-stimulatory signals with CTLA4Ig and by blocking T cell activation with rapamycin. This strategy has two advantages. First, these are antigen non-specific steps in T cell activation and immune responses. This means that tolerance can be achieved without needing to know the identity of the antigen. Second, restricted delivery of signal two and alteration in cytokine production and profiles are probably involved in normal mechanisms of self-tolerance. Third, by inhibiting T cell activation with rapamycin in addition to costimulatory signal blockade, they may be able to induce long term tolerance by allowing the occurrence of activation induced cell death. The human diseases that our program will focus on are multiple sclerosis (MS), autoimmune diabetes (IDDM), and psoriasis. All are organ specific diseases where T cells appear to be essential in initiating the immune response and lead to the particular disease pathology. Project #1 is the clinical trials project, in which we propose a clinical trial of CTLA4Ig in diabetes, a clinical trial of CTLA4Ig + rapamycin in early MS and describe the available patients and facilities for a potential psoriasis trial. The goals of project #2 are to investigate the role of NK T cells in human diabetes. Project #3 will take a direct approach by cloning T cells and NK T cells from the pancreas and pancreatic lymph nodes of patients with diabetes. The approach of treating autoimmune diseases by preventing T cell activation is timely and has a high likelihood of success. There is a body of evidence including clinical trials supporting the use of CTLA4Ig in autoimmune disease, and also evidence for the synergistic role of rapamycin. The data obtained from the clinical trials and the critical information from the basic science projects will be valuable in getting us closer to our goal of tolerance induction for autoimmune disease.

TITLE: **Suppression and Exacerbation of B and T Cell Responses (ACE)** **NIAID**
P.I.: **Ignacio Sanz, M.D.**
INST.: **University of Rochester, NY**
GRANT NO.: **5 U19 AI056390-03**
KEYWORDS: **Diabetes Mellitus, Multiple Sclerosis, Systemic Lupus Erythematosus, autoimmune diseases, pathogenesis, disease-specific autoantibodies**
STUDY TYPE: **clinical**
AWARD: **$60,000**

The overarching goal of this proposal is to establish an Autoimmunity Center of Excellence at the University of Rochester. This goal is based upon our belief that the understanding of human autoimmunity requires the concerted effort of basic and clinical scientists working together in an intellectual framework that provides constant feedback between bench studies and therapeutic interventions. Our Center will concentrate on studies relevant to the pathogenesis and treatment of Type 1 Diabetes Mellitus (T1DM), Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE). Both types of studies are based on the unifying idea that abnormalities of B- and T-cell function are at the core of these autoimmune diseases. Basic Project 1 will investigate the role of regulatory T-cells (Treg) in the pathogenesis of T1DM and will generate new reagents that will allow investigators to more specifically identify human Treg cells. Basic Project 2 will elucidate the role of IL- 12p40 monokines in MS and determine whether defects in Treg function exist in patients with this disease. Basic Project 3 will study B-cell homeostasis and the cellular origin of disease-specific autoantibodies in SLE. In addition, this project will investigate whether abnormal Treg function contributes to the activation of autoimmune B-cells and T-cells in SLE. These pathogenic mechanisms will serve as the theoretical basis for our clinical trials. Clinical Project 1 will study the clinical and immunological consequences of B-cell depletion in SLE using the anti-CD20 monoclonal antibody Rituximab. Clinical Project 2 will test the clinical and immunological effects of anti-IL-12 in patients with MS. We expect that the studies proposed will result in information that will not only improve our understanding of the disease in question but will also suggest new avenues of research for the other autoimmune diseases targeted by our Center.

TITLE: **Modulation of B Cell Responses in Autoimmunity (ACE)** **NIAID**
P.I.: **Eugene W. St. Clair, M.D.**
INST.: **Duke University, Durham, NC**
GRANT NO.: **5 U19 AI056363-03**
KEYWORDS: **B cell responses, immunotherapy, autoimmune diseases, lupus, arthritis**
STUDY TYPE: **clinical**
AWARD: **$60,000**

The proposed Center will focus on the modulation of B cell responses in autoimmunity. In autoimmunity, B cells not only serve as the source of pathogenic autoantibodies, but they also may function as antigen presenting cells (APCs) and stimulate pathologic inflammation through a variety of mechanisms. B cell function is regulated via the B cell receptor complex as well as other B cell-specific cell surface ZAI1 CL-I (M2) 3 1 U19 AI056363-01 ST CLAIR, E antigens, including CD20 and CD22. Growing evidence, including our results, indicates CD20 and CD22 are attractive targets for immunotherapy of autoimmune diseases. In addition, the investigators have shown inflammatory stimuli, such as tumor necrosis factor α (TNFα), can promote the emigration of B cells from the bone marrow, transferring large numbers of developing B lymphocytes to the periphery. We hypothesize aberrantly activated B cells are pivotal to the clinical expression of autoimmunity, and the resulting inflammatory state affords an environment for abnormal development of autoreactive B cells and further dysregulation of the immunological response. Two interrelated basic research projects are proposed to investigate this hypothesis. Dr. Thomas Tedder, Professor and Chair of Immunology, will direct a project examining the roles of CD20 and CD22 in the regulation of B cell function in mouse, taking advantage of a unique panel of CD20 and CD22-directed monoclonal antibodies developed in his laboratory. The other project will be headed by Dr. Garnett Kelsoe, Professor of Immunology, and will investigate to what extent inflammatory stimuli, such as TNFα influence the trafficking of immature B cells and selection of the autoreactive B cell repertoire. A clinical component led by Dr. St. Clair and other experienced physician-scientists will complement the basic research projects. This group has expertise in rheumatoid arthritis (RA), systemic lupus erythematosus, pemphigus vulgaris (PV), and other autoimmune diseases as well as access to many different patient

populations for clinical studies. One of the proposed trials will evaluate the safety and clinical efficacy of anti-CD22 monoclonal antibody therapy for RA, while the other will investigate infliximab (anti-TNFα) therapy for PV. Each of the trials includes mechanistic studies that are integrated with the goals of the basic research projects, providing synergy within the Center. An Administrative Core will oversee the management of these projects. Overall, the Proposed Center will efficiently bridge basic and clinical investigations and should produce new insights into the immunotherapy of autoimmune disease.

TITLE: **UAB Autoimmunity Center for Excellence (ACE)** **NIAID**
P.I.: **Robert H. Carter, M.D.**
INST.: **University of Alabama at Birmingham**
GRANT NO.: **5 U19 AI056542-03**
KEYWORDS: **translational therapies, immunology, autoimmune diseases, autoimmune disorder, autoimmunity, cooperative study, clinical research**
STUDY TYPE: **clinical**
AWARD: **$60,000**

The University of Alabama at Birmingham (UAB) has an outstanding record in basic immunology and in testing of novel, translational therapies for autoimmune diseases. The UAB Autoimmunity Center of Excellence (ACE) is a multidisciplinary, collaborative program to unite these strengths to accelerate the development and testing of translational therapies for autoimmune disease. To accomplish this, the UAB ACE will promote basic and translational research and sponsor clinical trials of novel immunomodulatory agents. As part of this mission, the UAB ACE will foster communication between basic and clinical investigators and between those focused on different immune-mediated diseases at UAB and nationally. Four projects are proposed. The Clinical Component (Project 1) includes highly experienced investigators from six clinical areas. Two potential clinical trials are proposed, targeting Death Receptor 5 in Lupus, an approach developed at UAB, and IL-1 in psoriatic arthritis, using a high affinity blocker brought to UAB investigators by the pharmaceutical industry. Three basic projects center on the unifying theme of analysis of the interaction of T cells and cytokines and/or TNF-family factors in maintenance or restoration of tolerance, including: Project 2) function of Death Receptor 5 on activated T cells in autoimmunity, Project 3) the role of cytokines and TNF-family proteins in reconstitution of T cell tolerance after immunosuppression, and Project 4) the function of IL10-expressing T cells in tolerance in mucosal immunity. The interactive nature of these projects is illustrated by the fact that each basic project involves assays or models derived from at least one of the others. The Administrative Core will coordinate ACE activities, facilitate interactions and collaborations, promote scientific development, set the strategic agenda, and perform continuous evaluation of ongoing projects. The Immunomodulatory Studies Core will promote analysis of changes in cells or cytokines in human tissues in disease and in mechanistic studies of participants receiving biologic therapies. Both cores will serve all proposed projects. Thus, the ACE will unite UAB investigators to bring the strength of immunological research and the breath of experience in clinical trials in a range of immune-mediated diseases to jointly develop new therapies for autoimmunity.

TITLE: **An Animal Model for Graves' Disease/Ophthalmology** **NEI**
P.I.: **Juan C. Jaume, M.D.**
INST.: **UCSF/ VAMC, Dept. of Medicine, San Francisco**
GRANT NO.: **5 R03 EY014962-03**
KEYWORDS: **Graves' Disease, hyperthyroidism, autoantibodies, ophthalmopathy, animal model, autoimmune disease exophthalmic goiter, eye disorder, hormone receptor, hormone regulation /control mechanism, hyperthyroidism, thyrotropin**
STUDY TYPE: **basic**
AWARD: **$151,500**

The ophthalmopathy of Graves' disease is a disfiguring, sight threatening condition of unclear pathogenesis and no specific or definitive therapy. Graves' disease primarily manifests with hyperthyroidism that results from the stimulation of the TSHR by specific autoantibodies that mimic the effect of TSH. Often the ophthalmopathy accompanies the hyperthyroidism. Rather than being considered two separate entities, hyperthyroidism and ophthalmopathy are different manifestations of the same underlying autoimmune process. No spontaneous animal model of Graves' disease exists. Recently, an animal model has been

developed in which a proportion of individuals manifest immunological and endocrinological features of Graves' disease. We have generated and extended such mouse model. The overall goal of this proposal is to use this Graves'-Iike animal model to investigate critical issues of Graves' disease as is Graves' ophthalmopathy as follows: 1. Graves' ophthalmopathy in the Graves'-Iike mouse model. New observations suggest the immunizing cells used in the model behave as APC that constitutively express B7-1 molecules and bias the immune response to a Th1 type. These APC also have the capacity of presenting non-specific antigens present in culture medium. With this information we have modified our immunization protocol to improve specific (TSHR) antigen presentation and deviate the immune response to a Th2 type characteristic of human Graves'. We propose to: a. Study the development of Graves' disease/ophthalmopathy in both, Th1 and Th2 settings. b. Examine the role of CD40 for orbital fibroblast-B/T cell cross talk. c. Study the regulation of TSHR in orbital fibroblasts/preadipocytes. 2. Characterize TSHR antibodies in their relationship to Graves' ophthalmopathy.

INFECTIOUS DISEASES

TITLE: **Seroprevalience/Incidence of Genital Herpes** **FIC**
P.I.: **Edith Nakku-Joloba, PhD**
INST.: **New Mulago Hospital, Kampala, Uganda**
GRANT NO.: **5 R01 TW006672-03**
KEYWORDS: **herpes, epidemiology, infectious diseases, prevention, rural health, vaccine related**
STUDY TYPE: **Public health, clinical**
AWARD: **$20,000**

Prevalence of herpes simplex type 1 and 2 virus (HSV-1 and 2) infection is high worldwide and is highest in developing countries like Uganda. International and local health organizations have called for studies to characterize genital herpes epidemiology in sub-Saharan Africa. Population estimates are needed for policy, for planning interventions, for valid measures of the effect of interventions and for research on new therapies and potential vaccines. The overall goal of this study is to determine the burden of infection and assess the modifiable risk factors associated with Herpes simplex types 1 and 2 infection in Kampala, Uganda with an aim of prevention of spread and relief of those who suffer with genital herpes. The proposed study will aim i) To estimate the age and sex specific prevalence of Herpes simplex type 1 and 2. ii). To estimate the incidence of Herpes simplex type 1 and 2 in an inception cohort of HSV-2 negative persons in an urban population in Uganda and iii) to identify modifiable risk factors associated with Herpes simplex types 1 and 2 prevalence and incidence in this population. The proposed study will be a two-stage stratified random population sample survey of female and male participants 15 to 65 years old in Kawempe division of Kampala District. To estimate prevalence of HSV-1 and 2, a cross-sectional serological survey at baseline will be done using type specific ELISA tests for herpes simplex type 1 and 2. Incidence will be assessed in an inception cohort of HSV-2 negative persons by 6 monthly testing for HSV-2. Risk factors for genital herpes will be assessed using a standardized questionnaire to collect information on age, sociodemographic characteristics, sexual behavior, sexual partner characteristics such as age differentials, and HIV infection status. Incidence densities and relative risks will be calculated from new HSV-2 infection and risk factors that predispose to HSV-2 incidence such as age, sex, (gender), sexual behavior, and HIV infection analyzed in a Cox proportional hazards model. By conducting a population study in an urban area in a country where rural studies show high prevalence we will describe the epidemiology genital herpes, gaining new knowledge about genital herpes in urban Uganda and highlighting the modifiable risk factors which can be targeted for effective interventions.

TITLE: **Natural Antimicrobials Against Bacterial Vaginosis** **NCCAM**
P.I.: **Mikhail Tchikindas, PhD**
INST.: **Rutgers University, New Brunswick, NJ**
GRANT NO.: **1 R21 AT002897-01**
KEYWORDS: **lifespan, vaginosis, CAM, interdisciplinary research**
STUDY TYPE: **Basic**
AWARD: **$187,678**

Bacterial vaginosis (BV) is a complex multi-microbial infection associated with the depletion of lactobacilli, the major flora of a healthy vagina and the overgrowth of Gardnerella vaginalis, Peptostreptococcus spp. and Prevotella bivia. BV may lead to premature labor. Endotoxins produced by the BV-associated bacteria cause serious brain/CNS damage in developing fetuses. Healthy vaginal Lactobacillus rhamnosus strain 160 produces an antimicrobial peptide, bacteriocin, designated as lactocin 160, which is active against BV associated microorganisms. He will examine their major hypothesis that this novel ribosomally-synthesized peptide is a potent antimicrobial agent for the prophylaxis and treatment of BV through the following three specific aims. He will determine lactocin 160's stability, safety, and spectrum of antimicrobial activity against BV associated vaginal pathogens. He expects lactocin 160 to be stable (alone and in combination with the selected natural antimicrobials), to have a broad range of antimicrobial activity against vaginal pathogens, and to be safe for human use (Specific Aim 1). Investigation of the mechanism of action by which lactocin 160 inhibits BV-associated microorganisms will lead to the understanding of the interaction between the cellular membrane and the peptide. He will determine whether one or both components of the Proton Motif Force are inhibited by lactocin 160 and if its activity is voltage-dependant, in other words, influenced by the growth phase of the pathogens. The investigator will find out if ATP in the bacteriocin-treated cells will be hydrolyzed intracellularly, or will leak off the cell (Specific Aim 2). Finally, he will prove that lactocin 160 has increased bactericidal activity against vaginal pathogens at low pH established specifically by lactic acid and when combined with synergistically acting natural and safe antimicrobials such as Zn lactate, saponin, and Polylysine, all of which have a mechanism of antimicrobial action different from lactocin 160 (Specific Aim 3). Our research will lead to a new approach for BV prophylaxis and treatment.

MENOPAUSE

TITLE: **The Study of Women's Health Across the Nation (SWAN III)** **NIA**
P.I.: **Kim Sutton-Tyrrell, PhD**
INST.: **University of Pittsburgh**
GRANT NO.: **5 U01 AG012553-11**
KEYWORDS: **aging, hormones, menopause, minorities, reproductive aging, risk factors, CAM, diabetes, hypertension, kidney-incontinence, behavioral & social science, cardiovascular**
STUDY TYPE: **Clinical**
AWARD: **$250,000**

The Study of Women's Health Across the Nation (SWAN) is a multicenter, multiethnic, community based longitudinal study designed to characterize the biological, symptomatic and psychosocial changes that occur during the menopausal transition and the effects of these changes on women's health during and after the transition. Current and prior funding (SWAN I and II) has supported a baseline and six annual follow-up examinations during which 895 (48%) women will have transitioned to postmenopause. This application requests funding to complete four additional follow-up visits (SWAN III) to allow an adequate evaluation of the late perimenopause and early postmenopause, a period that has not been well studied, particularly among non-white women. We will continue our current tracking of changes in reproductive hormones, bleeding patterns, symptoms, bone loss, cardiovascular (CV) risk factors blood pressure, body size, and other related characteristics and will undertake new scientific endeavors in targeted areas. These include measurement of vascular stiffness to assess early CV disease, assessment of vertebral morphometry at four sites using DEXA technology, and the addition of one cognitive function test. In addition, we will focus on linking the midlife experience to age-related outcomes (e.g. cognitive function, urinary incontinence) and chronic diseases (e.g. fractures, diabetes and hypertension). Specimens from the additional follow-up visits will continue to contribute to the SWAN biological specimen repository (annual blood and urine samples as

well as DNA and immortalized cells). This is a separately funded component that broadens the opportunities to address future hypotheses about health and disease in aging women. As women reach the end of early postmenopause (two years following the final menstrual period), we will shift from an annual to a bi-annual follow-up examination schedule with mail and telephone contact in the alternating years. This will permit cost-effective and less intensive follow-up. SWAN's organization and operations have been modified to enhance productivity and we are poised to publish important biological, symptom and behavioral results pertaining to the menopause transition. With SWAN III, many of the original goals of SWAN will be brought to fruition. We will build upon the rich foundation developed during SWAN I and II and link these data to important menopause-related and health outcomes in SWAN III.

TITLE: **Phytoestrogens and Progression of Atherosclerosis** **NCCAM**
P.I.: **Howard N. Hodis, M.D.**
INST.: **University of Southern California, Dept. of Medicine, Los Angeles**
GRANT NO.: **5 U01 AT001653-03**
KEYWORDS: **hormone therapy, soy protein, isoflavone-rich, soy protein, postmenopausal women, atherosclerosis, common carotid artery, estrogen, cancer, cardiovascular, CAM**
STUDY TYPE: **Clinical**
AWARD: **$200,000**

The fear and discontent with traditional hormone replacement therapy (HRT) coupled with the interest in natural products has resulted in an increased use of soy protein as a postmenopausal therapeutic alternative by both women and their physicians alike. Evidence from epidemiological and non-humane primate studies indicate that isoflavone-rich soy protein has antiatherogenic activity, evidence supported by a large body of data that indicate mechanistic and biologic plausibility. No studies to knowledge have been published or proposed to determine the long-term effects of soy protein on the progression of atherosclerosis in postmenopausal women. The investigators propose to conduct a 2.5 year, randomized, double-blind, placebo-controlled trial of isoflavone-rich soy protein in 300 healthy postmenopausal women without clinical evidence of cardiovascular disease. They hypothesize that relative to placebo, isoflavone-rich soy protein (supplying genistein, daidzein and glycitein) will reduce the progression of subclinical atherosclerosis in healthy postmenopausal women. The primary end point will be the progression of subclinical atherosclerosis measured as the rate of change in common carotid artery intima-media thickness in computer image processed B-mode ultrasonograms, a well-established noninvasive arterial imaging end point for antiatherosclerosis trials, Isoflavone-rich soy protein may provide a safe and effective alternative approach for extending premenopausal ardioprotection afforded by endogenous estrogen into menopause without the increased risk of thromboembolic events and certain cancers associated with traditional HRT. Since many postmenopausal women are using spy products to maintain their health, it is important to understand whether soy protein has an antiatherogenic effect so that women can make a truly informed decision concerning their expectations of this form of postmenopausal therapy. The question as to whether soy protein is effective in reducing progression of atherosclerosis in postmenopausal women is not only timely, but also of immense medical and financial importance since atherosclerosis remains the number 1 killer of postmenopausal women.

TITLE: **Soy Isoflavones for Menopausal Vasomotor Symptoms** **NCCAM**
P.I.: **Judith Ockene, PhD**
INST.: **University of Massachusetts Medical School, Worcester, MA**
GRANT NO.: **1 R21 AT002522-01A1**
KEYWORDS: **lifespan, reproductive life, menopause, CAM, clinical trial methods**
STUDY TYPE: **Clinical**
AWARD: **$324,190**

Vasomotor symptoms (VMS), including hot flashes and night sweats, affect the majority of menopausal women. Since the results of the Women's Health Initiative were publicized, many women and their health care providers no longer wish to use hormone therapy for VMS. Soy isoflavones have been marketed for reducing VMS, but data are inconclusive as to their effectiveness. Although isoflavones are structurally similar to estrogen and thus bind to estrogen receptors, results from randomized controlled trials of both soy bods and supplements have been mixed. Given the pharmacokinetic characteristics of soy isoflavones,

in particular the half-life (approximately 8 hours), dosing frequency may be critical to their effectiveness in reducing VMS. In addition, no intervention study of VMS has examined whether participants are equol producers. Equol, daidzein's active metabolite, may affect the efficacy of daidzein in reducing VMS intensity. The investigators propose to conduct a small pilot randomized placebo-controlled trial of 180 menopausal women with moderate to severe VMS to examine a range of doses (total daily dose of 100 mg/day and 200 mg/day) and three dosing frequencies (1, 2, and 3 times a day) of capsules containing the primary isoflavones found in soy (daidzein and genistein). Outcomes will include feasibility and preliminary dose evaluation. For feasibility aims they will: 1) assess their ability to recruit and retain participants; 2) measure adherence to capsules and to completing symptoms diaries; 3) modify and test a daily symptoms diary that is more complex than previously used; and 4) test the feasibility and utility of identifying equol producer status. For preliminary dose evaluation aims they will examine VMS as they relate to: 1) isoflavones by dose amount and dose frequency; 2) equol producer status; and 3) in a subgroup, steady state concentrations. These data will provide essential information for optimal study design, methods of data collection, and total daily dose and dosing frequency for a larger, more definitive randomized controlled trial.

MENTAL HEALTH

TITLE: **Health Survey of Two-Spirited Native Americans** **NIMH**
P.I.: **Karina L. Walters, PhD**
INST.: **University of Washington, Seattle, WA**
GRANT NO.: **5 R01 MH65871-04**
KEYWORDS: **mental health, cultural and spiritual coping, HIV risk behaviors, Native American, alcoholism/alcohol abuse, clinical research, human subjects, behavioral & social science**
STUDY TYPE: **clinical**
AWARD: **$175,000**

American Indian and Alaskan Native lesbian, gay, bisexual, transgendered, and two-spirited individuals (two spirits) are a drastically understudied and underserved group, at risk for multiple health and mental health problems. There are no national, quantitative, representative studies of this population on any topic. Building upon solid preliminary data, we will conduct structured survey interviews with 400 two spirits drawn from six sites across the U.S. With these interview data, we will test a theoretical model of stress and coping specific to this population. Sub-aims are to (a) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, and mental health indicators); (b) test the direct associations between trauma and health outcomes; (c) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and (d) examine the mediating role of substance use on the trauma-HIV sexual risk behavior and trauma-mental health relationships. The results will contribute toward the refinement of a sample strategy useful in studying other hidden and stigmatized populations. Through the course of this project, we aim to develop the research infrastructure at the six community agencies comprising our participant recruitment sites in order to facilitate future goals of designing and evaluating interventions to address the urgent needs of two spirits.

TITLE: **Pharmacogenomics and Pharmacogenetics Research Group** **NIGMS**
P.I.: **Julio Licinio, M.D.**
INST.: **University of California, Los Angeles**
GRANT NO.: **2 U01 GM061394-07**
KEYWORDS: **depression, pharmacogenetics, treatment, Hispanics, Mexican-Americans**
STUDY TYPE: **basic**
AWARD: **$50,000**

This is a competitive renewal of our pharmacogenomic study of antidepressant treatment response in Mexican-Americans. We aim at identifying genetic substrates contributing to phenotypic variability in drug response in an ethnically defined, under-represented, and under-studied population. In this application we build on the infrastructure created in the current funding period to substantially enhance our ability to use

the tools of contemporary genomics for prediction of antidepressant responses, by assembling a truly cross disciplinary structure that is greater than the sum of its parts. This will permit us to use a state-of-the-art pharmacogenomic strategy with three specific aims: 1) hypothesis generation, 2) hypothesis testing and 3) replication studies. Together with David Bentley and colleagues at the Sanger Institute we developed combined re-sequencing and genotyping strategies in a large number of candidate genes as a continuation of our existing collaboration. This represents an unparalleled opportunity to pursue a pathway-based approach while simultaneously leveraging a small effort on transcriptome and proteomics studies for gene/pathway discovery. Full-length direct sequencing of 100 genes in 96 individuals (48 best and 48 worst antidepressant responders) will maximize haplotype information in this under-studied population. The results of this sequencing effort, in combination with the existing 105,632 SNPs deposited in dbSNP that are present in candidate genes in our pathways of interest, provide a rich source of polymorphisms for selection of candidates to be used for hypothesis generation. The polymorphisms with the strongest treatment response association will be selected for hypothesis testing. To further confirm findings emerging from hypothesis testing studies, a replication project has been planned with A. Serretti's group (Italy) that has the largest body of published data on antidepressant pharmacogenetics. Our initial funding has supported an ongoing prospective, double-blind trial of two antidepressants with collection of DNA samples from 300 depressed and 300 controls, community engagement, limited genotyping, and a bioinformatics core. We have developed productive collaborations within the PGRN and with other groups, nationally and internationally. All of our data to date have been deposited in PharmGKB. Our depositions into this public database will increase exponentially upon completion of ongoing and new collaborative studies with the Sanger Institute.

TITLE: **Youth Suicide Prevention Using Community-Based, Participatory Research Methods to Design and Implement the Apache Youth Suicide Research and Prevention Program** **IHS**
P.I.: **Maridde J. Craig and John Walkup, M.D.**
INST.: **White Mountain Apache Tribe, Whiteriver, AZ; and Johns Hopkins University School of Medicine, Baltimore, MD**
GRANT NO.: **1 S06 GM074004-01**
KEYWORDS: **adolescent, Native American, mental health, prevention, suicide**
STUDY TYPE: **clinical**
AWARD: **$25,000**

The White Mountain Apache Tribe and Johns Hopkins Center for American Indian Health Native American Research Center in Health proposes to employ community-based, participatory research methods to design and implement the Apache Youth Suicide Research and Prevention Program for the White Mountain Apache Tribe in Whiteriver, Arizona. Rates of suicide among youth and young adults on the White Mountain Apache Reservation have been among the highest in the U.S. of any ethnic group in the past decade. The White Mountain Apache and Johns Hopkins have collaborated for more than 25 years in addressing the health and social priorities of the Tribe, with findings from past work generalized across Indian country and the world. To develop the Apache Youth Suicide Research and Prevention Program we will: (1) develop a surveillance and data collection system for the evaluation of suicidal behavior on the White Mountain Apache Reservation; (2) collect and analyze data from young suicide attempters (<19 years old) to identify key characteristics and determinants of suicidal behavior in this age group; (3) engage community experts in the development of a suicide prevention program that utilizes empirically supported prevention intervention strategies to target key determinants and characteristics in at risk Apache youth; and (4) develop a NIH grant proposal to test the efficacy of the Youth Suicide Prevention Program developed during the period of this award. The outcomes of this work will provide important models for other communities battling this increasing problem among adolescents and young adults.

TITLE: **Osteo-Arthritis Initiative (OAI) -- Baltimore** **NIAMS**
P.I.: **Marc Hochberg, M.D.**
INST.: **University of Maryland School of Medicine, Baltimore**
NUMBER: **N01-AR-2259**
KEYWORDS: **biological markers, osteoarthritis, disease progression**
STUDY TYPE: **clinical**
AWARD: **$67,033**

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (OAI) will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI will support six clinical research centers that will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

TITLE: **Osteo-Arthritis Initiative (OAI) -- Columbus** **NIAMS**
P.I.: **Rebecca Jackson, M.D.**
INST.: **Ohio State University, Columbus**
NUMBER: **N01-AR-2261**
KEYWORDS: **biological markers, osteoarthritis, disease progression**
STUDY TYPE: **clinical**
AWARD: **$524,739**

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (OAI) will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI will support six clinical research centers that will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

TITLE: **Osteo-Arthritis Initiative (OAI) -- Pittsburgh** **NIAMS**
P.I.: **C. Kent Kwoh, M.D.**
INST.: **University of Pittsburgh**
KEYWORDS: **biological markers, osteoarthritis, disease progression**
NUMBER: **N01-AR-2260**
STUDY TYPE: **clinical**
AWARD: **$208,228**

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (OAI) will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for

OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated. The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI will support six clinical research centers that will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

TITLE: **Low-Dose Doxycycline Effects on Osteopenic Bone Loss** **NIDCR**
P.I.: **Jeffrey B. Payne, DDS**
INST.: **University of Nebraska, Lincoln, NE**
GRANT NO.: **5 R01 DE12872-05**
KEYWORDS: **clinical trials, periodontitis, osteoporosis, dental/oral disease, estrogen osteoporosis, skeletal disorder chemotherapy, tetracycline, bone density, bone metabolism**
STUDY TYPE: **translational, clinical**
AWARD: **$315,644**

Osteoporosis represents a major public health problem in the United States. Osteoporosis is associated with decreased systemic bone mineral density (BMD), an increased incidence of vertebrae, wrist and hip fractures, and tooth loss. The dominant pathogenic factor for osteoporosis in postmenopausal women is estrogen (E2) deficiency. In longitudinal NIH-supported clinical trials, we have shown accelerated alveolar crestal bone height and density loss in postmenopausal, E2- deficient women with a periodontitis history relative to E2-sufficient women, and in osteoporotic/osteopenic women versus women with normal lumbar spine BMD. Because of this relationship between E2- deficiency, osteoporosis and oral bone loss, it is desirable to test therapeutic strategies to mitigate alveolar bone loss in postmenopausal women. A recent discovery by Dr. Golub (Co-PI) showed that tetracyclines, including low-dose doxycycline (LDD), by virtue of a non- antimicrobial property, can: a) inhibit host-derived, tissue-destructive matrix metalloproteinases (MMPs), including collagenases, involved in bone resorption; and b) stimulate osteoblast activity and bone formation. These biological properties make tetracyclines compelling candidates for use in postmenopausal women with periodontitis. Therefore, the objective of this research is to investigate the therapeutic potential of LDD in postmenopausal osteopenia and periodontitis, diseases characterized by excess collagen breakdown and bone resorption. The hypothesis of this proposal is that LDD (compared to placebo) can improve radiographic, clinical and biochemical parameters of periodontitis in E2-deficient, osteopenic postmenopausal women with periodontitis. Accordingly, the specific aim of this proposal is to use a 2- year double-blind, placebo-controlled trial of E2-deficient women to determine the effect of LDD on: a) alveolar bone crestal and subcrestal density (measured by computer-assisted densitometric image analysis) and linear alveolar crestal bone height; b) clinical periodontal measurements such as probing depth and relative clinical attachment level; and c) gingival crevicular fluid markers of bone turnover (e.g., C- terminal telopeptide pyridinoline crosslinks [ICTP, a collagen breakdown fragment]). As a secondary aim, the study will evaluate the effect of LDD on systemic bone mineral density at the lumbar spine and femoral neck by dual-energy x-ray absorptiometry (DEXA) and the effect of LDD on serum and urine biochemical markers of bone turnover.

TITLE: **Bone-Sparing by Ca Salts with and without Extra Phosphorus** **NIAMS**
P.I.: **Robert P. Heaney, PhD**
INST.: **Creighton University Dept. of Medicine, Osteoporosis, Omaha, NE**
GRANT NO.: **5 R01 AR048846-03**
KEYWORDS: **osteoporosis, supplementation, menopause**
STUDY TYPE: **clinical**
AWARD: **$75,000**

Bone mineral is basically calcium phosphate, and both elements (Ca and P) are required for bone acquisition. Typical Ca intakes in the U.S. are lower than current recommendations, and typical P intakes, higher. To test the possible importance and value of supplementing both of the components of bone mineral in support of anabolic therapy of osteoporosis, we propose a 1-year randomized trial, comparing, in

two groups of teriparatide-treated postmenopausal osteoporotic women, calcium supplements with and without extra phosphorus (i.e. Ca phosphate vs. Ca carbonate). The principal outcome measure will be change in bone mineral content over the one year of the trial. A secondary outcome is measurement of bone resorption biomarkers so as to assess whether the phosphate salt elevates remodeling relative to the carbonate salt. A finding of superiority of the phosphate-containing Ca supplement would provide evidence leading to a cost-neutral change in Ca sources and a corresponding improvement in osteoporosis co-therapy (and possibly osteoporosis prophylaxis as well).

TITLE: **Bone-Sparing Effects of Soy Phytoestrogens in Menopause** **NIAMS**
P.I.: **Silvina Levis, M.D.**
INST.: **University of Miami School of Medicine, Dept. of Medicine, Miami, FL**
GRANT NO.: **5 R01 AR048932-03**
KEYWORDS: **osteoporosis, menopause, hormone replacement therapy (HRT), prevention, estrogen**
STUDY TYPE: **clinical**
AWARD: **$100,000**

Women will live a third of their lives after menopause. The complications of prolonged estrogen deficiency during the menopausal years are well established. Although hormone replacement therapy (HRT) can spare women some of these complications, the Women's Health Initiative findings indicate significant potential health risks, risks that prompt more and more women to turn from prescribed HRT to over-the-counter products in the hope that soy phytoestrogens and other "estrogens" from natural sources can replace prescription estrogens in terms of benefits while sparing critical side effects. In spite of the fairly widespread and now rapidly growing use of phytoestrogens, major gaps remain in our knowledge of their long-term efficacy and safety. It is proposed to conduct a "Soy Phytoestrogens As Replacement Estrogen (SPARE)" study in young menopausal women to evaluate the effectiveness of a 2-year treatment with purified soy isoflavones in preventing bone loss. The study will also explore the effectiveness of oral isoflavones in preventing menopausal symptoms and other changes associated with estrogen deficiency. The study will characterize the actions of a defined preparation of soy isoflavones in humans and will correlate these actions with the circulating serum levels of the principal isoflavone metabolites, providing new insights on their long-term biological actions. This 5-year study will provide a foundation of knowledge from which menopausal women can begin to make more informed decisions regarding HRT and menopausal signs and symptoms.

NUTRITION

TITLE: **National Food and Nutrient Analysis Program (NFNAP)** **NCI**
INST.: **Interagency Agreement between USDA & NIH**
GRANT NO.: **Y1-CN-5010-01**
KEYWORDS: **nutrition, Latinos, Hispanics, nutrition database**
STUDY TYPE: **national database**
AWARD: **$25,000**

This is a joint NIH-USDA program to expand the current food and nutrient database to include foods commonly consumed by the Hispanic population in the United States. Additional partners include the FDA, the CDC and multiple Institutes and Centers across the NIH. The current database includes 1,000 foods and nutrients consumed by 80% of the population. Given the increasing Hispanic population in the U.S., there is an urgent need to expand the databases in include other foods and nutrients commonly consumed by this ethnic group.

TITLE: **Botanical Supplements for Women's Health** **NCCAM**
P.I.: **Norman R. Farnsworth, PhD**
INST.: **University of Illinois at Chicago**
GRANT NO.: **2 P50 AT000155-06**
KEYWORDS: **menopause, botanicals, dietary supplements, CAM, estrogenic effects**
STUDY TYPE: **basic, clinical**
AWARD: **$100,000**

Since the 1994 DSHEA mandate, botanical dietary supplements (BDSs) are continuously developing into safer and more effective preparations that aid U.S. public health. Since its establishment in 1999, our BOTANICAL CENTER has participated in this development by performing significant (bio-)chemical and clinical research on BDSs that are widely used to restore and/or maintain women's health. The focus of a renewed grant period will continue to be the alleviation of perimenopausal and premenstrual syndrome (PMS) symptoms. Linked to this focus is the central hypothesis that botanicals contain potent secondary plant metabolites that exhibit activities in estrogenic and major CNS (serotonin, GABA, dopamine, and opioid) systems. In close collaboration with the other projects of the CENTER, PROJECT 1 will (Aim 1) evaluate and prioritize select botanicals; (Aim 2) show that they contain phytoconstituents with the desired biological activities and profiles, in vitro and in vivo; isolate and structurally characterize these active principles by modern spectroscopical methods and use them to (Aim 3) standardize the botanicals. The long-term objective of this proposal is to prepare botanical extracts that are chemically and biologically standardized in terms of the bioactive secondary plant metabolite(s), and that are stable for human studies. Combining promising botanicals from the previous grant period with the results of preliminary studies, an initial selection of 12 plants plus two complex herbal mixtures will be evaluated. Primary extracts of a wide polarity range and their solvent partition fractions will be assayed in vitro and in vivo by PROJECTS 2+3, and prioritized using a scoring system that weighs hit numbers, grouping of potency, as well as strengths and concentration of activity. The botanicals with the highest rank will be scaled-up and subjected to an innovative bioassay-guided fractionation procedure (w/PROJECTS 2+3 and CORE B). The major active principles will be obtained through a sequential application of modern chromatography tailored to the specific characteristics of the extracts (HSCCC, Gel/Resin-CC). Modern qualitative and quantitative spectroscopic analysis (1/2D and selective NMR, qNMR, hyphenated MS) will lead to the identification of structures of the major active principles, which ultimately lays the foundation for chemical and biological standardization. Prioritized botanicals will be fully developed into standardized products. Hops will be evaluated in a Phase I clinical study in PROJECT 4.

OBESITY/OVERWEIGHT

TITLE: **PRIDE: Program to Reduce Incontinence by Diet & Exercise** **NIDDK**
P.I.: **Deborah G. Grady, M.D.**
INST.: **University of California, San Francisco, CA**
GRANT NO.: **5U01 DK860-03**
KEYWORDS: **urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral & social science**
STUDY TYPE: **clinical**
AWARD: **$100,000**

Urinary incontinence is a common problem among women that causes distress, diminished quality of life and dramatic limitations in daily functioning. Overweight women are at significantly increased risk of urinary incontinence and over 65% women with incontinence are overweight. Data from short-term, preliminary studies suggest that weight reduction may significantly reduce incontinence episodes. Thus, weight loss may present a promising new approach to urinary incontinence, one likely to produce a cascade of broader health improvements in addition to reductions in frequency of urinary incontinence. Therefore, we propose to randomize 330 overweight and obese women with urinary incontinence (165 at each of two clinical centers) to a 6-month intensive behavioral weight control program or to usual care to determine the short-term effect of weight loss on frequency of incontinence and quality of life, to identify women most likely to benefit from weight loss and to begin to explore the urodynamic mechanisms underlying incontinence improvement following weight loss.

TITLE: **PRIDE: Program to Reduce Incontinence by Diet & Exercise** **NIDDK**
P.I.: **Rena R. Wing, PhD**
INST.: **Miriam Hospital, Providence, RI**
GRANT NO.: **5 U01 DK67861-03**
KEYWORDS: **urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral & social science**
STUDY TYPE: **clinical**
AWARD: **$75,000**

The aims of the study are 1) to determine whether weight loss will reduce the frequency of urinary incontinence in overweight women with incontinence and 2) to determine whether a motivationally-based program will improve weight loss maintenance compared to a skill-based maintenance program.

TITLE: **PRIDE: Program to Reduce Incontinence by Diet & Exercise** **NIDDK**
P.I.: **Frank Franklin, M.D., PhD**
INST.: **University of Alabama, Birmingham**
GRANT NO.: **5 U01 DK067862-03**
KEYWORDS: **urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral & social science**
STUDY TYPE: **clinical**
AWARD: **$75,000**

The specific aims of this study, are to determine whether randomization to a behavioral weight control program results in greater reductions in frequency of incontinence episodes at 6 months compared to usual care and to identify women who are most likely to experience improved incontinence after weight reduction, based on factors such as initial body mass index, body fat distribution and type of incontinence (stress, urge or mixed), have not changed or been modified since funding. The study protocol and interventions have been designed to support the aims of this study. The study design is a multicenter randomized, clinical trial evaluating weight reduction as a treatment for urinary incontinence in 330 overweight and obese women with incontinence. Women will be randomized in a 2-to-1 ratio to either a 6-month intensive behavioral weight reduction program or usual care (no weight reduction intervention) and followed for 18 months. After completing the intensive weight reduction program, a second randomization will be done to test whether an enhanced weight maintenance program results in superior long-term weight loss through 18 months compared to a standard maintenance program. In a subgroup of 100 women, we will perform standard urodynamic studies to allow us to evaluate the mechanism by which weight loss improves incontinence.

TITLE: **Health Outcomes of Weight-Loss: Data Coordinating Center (SHOW/Look AHEAD)** **NIDDK**
P.I.: **Mark A. Espeland, PhD**
INST.: **Wake Forest University, Dept of Public Health Sciences, Winston-Salem, NC**
GRANT NO.: **5 U01 DK57136-07**
KEYWORDS: **obesity, health disparities, Type 2 diabetes, clinical trials, sex differences, weight loss, physical activity, CVD risk factors, behavioral interventions, health promotion, disease prevention**
STUDY TYPE: **randomized clinical trial**
AWARD: **$100,000**

This application describes plans by an experienced group of investigators and staff at the Wake Forest University School of Medicine (WFU) to serve as the Coordinating Center (CoC) for the Study of Health Outcomes of Weight-Loss (SHOW). SHOW is a multicenter randomized trial designed to test whether weight loss interventions can reduce the progression of carotid atherosclerosis and other health outcomes in a cohort of 6000 obese type 2 diabetics. Participants will be randomized to one of 3 intervention arms: intensive lifestyle intervention (diet and exercise), intensive lifestyle intervention plus pharmacotherapy, or community control. The primary outcome is carotid intimamedial thickness. Secondary outcomes include cardiovascular (CV) and cerebrovascular events and death, CV risk factors, and glycemic control. Participants will be recruited over a 3-year period with 4-7 years of intervention and follow-up. WFU plans to operate the CoC for the SHOW trial. In that role, we will provide expert statistical support for sample size, data analyses and interpretation; collaborate in the design of SHOW and provide all supporting study

documents including manuals and data collection forms; design and implement a web-based data management system; plan and support recruitment efforts in the 15 clinics; develop and monitor all quality control efforts; monitor recruitment, retention, the implementation of the intervention, and adherence; subcontract with all Core Facilities (e.g., central laboratory); train and certify staff, perform study administrative duties; and participate in paper writing.

OPTHALMIC DISEASES

TITLE: **Incidence of Late Macular Degeneration in Older Women** **NEI**
P.I.: **Anne L. Coleman, M.D.**
INST.: **University of California, Los Angeles**
GRANT NO.: **5 U10 EY13626-04**
KEYWORDS: **blindness, quality of life, aging, Caucasian women, diabetes, eye disease and disorders of vision, macular degeneration**
STUDY TYPE: **epidemiologic (case-control)**
AWARD: **$230,000**

Age-related macular degeneration is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and the progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors such as diabetes mellitus and prior cataract surgery with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the trajectory of visual decline in older women over a 14- year period. Secondarily, it aims to determine the impact of late ARM on vision-targeted health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision with automated perimetry, intraocular pressure, and uncorrected refractive error. These women also had a refraction and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5% of these women have photographically validated late ARM, 41.5% have early ARM, and 54% have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEIVFQ. In addition, visual acuity and contrast sensitivity will be re-measured. Fundus photographs of both eyes through dilated pupils will be obtained. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-Related Maculopathy Grading System (WARMGS) in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30% of the eyes with ARM and 10% of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

TITLE: **Estrogen Receptors and Maintenance of Lens Transparency** **NEI**
P.I.: **Vicki L. Davis, PhD**
INST.: **Cedars-Sinai Medical Center, Los Angeles**
GRANT NO.: **5 R01 EY014600-03**
KEYWORDS: **ophthalmic diseases, aging, estrogen, cataract, estrogen receptor, lens, receptor expression, eye disorder chemotherapy, eye pharmacology**
STUDY TYPE: **basic**
AWARD: **$132,549**

Epidemiological studies suggest that estrogen may protect against age-related cataracts. The discovery of ocular estrogen receptors (ER) indicates that estrogen protection may result from direct interactions with its receptors in the eye. Studies in our transgenic mouse model validate the concept that estrogen is beneficial for the eye; these mice express a repressor (ERdelta3) that inhibits estrogen action, leading to cortical cataract formation. Although the ERalpha and ERbeta protein and/or RNA have been detected in ocular tissues, there has been no confirmation that these receptors are functional, since there are no known estrogen responsive markers in the eye. Therefore, in this proposal, we will use several transgenic mouse models to investigate the function of ERalpha and ERbeta in the lens. Our specific aims will examine 2 critical questions important for understanding the role of estrogen and its receptors in normal lens physiology and cataractogenesis. 1) Can estrogen induce an ER-mediated response directly in the lens? 2) Are both ERalpha and ERbeta essential for maintenance of lens transparency? First, using ERIN transgenic mice, we will determine whether ERalpha, ERbeta, and ERdelta3 receptors can regulate expression of an estrogen responsive reporter gene in the lens. The ERIN model expresses a beta-galactosidase reporter under the control of 2 consensus estrogen response elements (ERE). The alphalERKO and betaERKO mice provide a means to segregate the individual ER subtypes to determine their individual roles in the lens. Therefore, the ERIN mice will be crossbred with alphaERKO, betaERKO, and ERdelta3 transgenic mice to document that each receptor influences estrogen responsive gene expression in the lens. Next, we will investigate if both ERalpha and ERbeta influence spontaneous and ERdelta3-induced cataract development. We will examine aging alphaERKO, betaERKO, and alphabetaERKO mice to determine if loss or each or both receptors induces lens opacity. To ascertain if cataracts occur in our ERdelta3 mouse model due to inhibition of ERalpha and/or ERbeta activity, the ERKO lines will be crossbred with the ERdelta3 mice. These studies will verify that ERalpha, ERbeta, and ERdelta3 are expressed and functional in the lens. In addition, we will establish if both ERalpha and ERbeta have essential roles in preserving lens transparency. The concept that estrogen can provide protection against age-related cataracts is promising. This study will provide the gateway for future studies to investigate how exposure to various estrogens influence risk of age-related cataracts and the potential of estrogens as a therapy for cataract prevention.

PAIN

TITLE: **Hormonal Cycles in Women: Effects on TMD Pain & Symptoms** **NIDCR**
P.I.: **Linda Leresche, ScD**
INST.: **University of Washington, Department of Oral Medicine**
GRANT NO.: **5 R01 DE016212-02**
KEYWORDS: **TMJ, pain control, estrogen, depression, mental health, mind & body**
STUDY TYPE: **translational**
AWARD: **$150,000**

This project will study the interactions of mind and body related to temporomandibular disorders (TMD), a group of painful conditions involving the muscles of mastication and the temporomandibular joint. These pain problems are about twice as common in women as in men in the community, and prevalence peaks during the reproductive years. The etiology of TMD pain is unknown, but psychological stress, depression and the presence of other somatic complaints have been shown to influence the course of these disorders. Prior research suggests that female reproductive hormones may also influence TMD pain. Two related studies will investigate the cyclic nature of TMD pain in women. Study 1 will assess the relationship of pain to salivary levels of reproductive hormones and to psychological stress across two consecutive menstrual cycles for female TMD patients with normal menstrual cycles, as well as appropriate comparison groups of normally cycling women with episodic headache and normally cycling control women without TMD, headache or other chronic pain problems. Study 2 will manipulate the behavioral and hormonal

factors that are hypothesized to influence TMD pain, comparing the effects of: 1) a continuous oral contraceptive intervention designed to suppress menses and stabilize the hormonal environment, 2) a self-management intervention focused on and timed to the chronobiology of TMD symptoms across the menstrual cycle, and 3) a usual self-management intervention not timed to biological events. The aims of this clinical trial are to shed light on the mechanisms underlying the cyclic nature of TMD pain and symptoms in women, as well as to determine which treatment modality results in the greatest improvement in TMD pain and symptoms.

TITLE: **Pain Management in Temporomandibular Joint Disorders** **NIDCR**
P.I.: **Jennifer Haythornthwaite, PhD**
INST.: **Johns Hopkins University, Baltimore, MD**
GRANT NO.: **5 R01 DE13906-05**
KEYWORDS: **TMD, pain control, behavioral interventions, neurosciences research, dental/oral disease**
STUDY TYPE: **clinical behavioral**
AWARD: **$269,127**

The primary goal of the proposed project is to test the efficacy of psychological interventions, a pharmacological intervention, and the combination of these interventions in reducing pain and improving function in persons with temporomandibular disorders (TMD). Since psychological interventions are costly and require expertise that is frequently unavailable in primary care settings, the proposed project will also examine the efficacy of a minimal contact/self help psychological intervention based on cognitive-behavioral therapy for pain management. In addition to examining the separate and combined effects of psychological and pharmacological interventions for TMD pain, the proposed study will examine whether the minimal contact cognitive-behavioral intervention can accomplish comparable reductions in pain and improvements in function relative to the therapist-administered treatment.

TITLE: **Trigeminal Pain Mechanisms and Control: Mechanisms of Pain Caused by Disruption of Microtubules** **NIDCR**
P.I.: **Jon D. Levine, PhD**
INST.: **University of California at San Francisco, San Francisco, CA**
GRANT NO.: **5 P01 DE08973-15**
KEYWORDS: **pain control mechanism, orofacial neuropathies, neurosciences research, dental/oral disease, neurodegenerative**
STUDY TYPE: **basic**
AWARD: **$168,176**

The chemotherapeutic agent paclitaxel (Taxol) is widely used for the treatment of many different types of carcinomas. At present, the dose of paclitaxel that can be tolerated by patients is limited primarily by the development of a painful peripheral neuropathy characterized by parenthesis, myalgia and arthralgia. Similar dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, including vincristine. Therefore, amelioration of the neuropathic pain might not only reduce the suffering of patients who receive paclitaxel or vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies.

TITLE: **Imaging the Cognitive Modulation of Pain in Fibromyalgia** **NIAMS**
P.I.: **Dane B. Cook, PhD**
INST.: **VA Medical Center, East Orange, NJ**
GRANT NO.: **1 R01 AR050969-01A1**
KEYWORDS: **chronic pain, fibromyalgia, brain imaging, rheumatoid arthritis**
STUDY TYPE: **clinical**
AWARD: **$250,000**

Fibromyalgia (FM) is a disabling disorder characterized by widespread medically unexplained pain. A diagnosis of FM is accompanied by a poor prognosis and less than half of all FM patients experience adequate pain relief. FM patients are often left under treated, resulting in greater functional disability and increased health care utilization. Research aimed at uncovering mechanisms of unexplained pain in FM is needed to guide potential treatment approaches and better understand the pathophysiology of this disorder. Brain imaging data collected in our laboratory have demonstrated augmented fMRI responses to both nonpainful and painful heat, and support the emerging view that abnormalities in central nociceptive processes act to maintain FM pain. However, cognitive processes such as anticipation and attention could also affect brain responses and are known to affect chronic pain outcomes. The broad objectives are to further our understanding of unexplained musculoskeletal pain in FM. fMRI is an objective measure of nociceptive processing, sensitive to sensory and cognitive manipulations. Thus, the specific aims of the project are to: (1) determine whether augmented central processing is unique to FM or is a consequence of chronic pain by comparing FM patients to rheumatoid arthritis patients (RA); (2) determine the influence of pain anticipation on fMRI responses to non-painful stimuli in FM patients compared to healthy and RA controls, and (3) determine the influence of attention to pain on central processing of painful stimuli in FM patients compared to healthy and RA controls. To manipulate anticipation of pain, subjects will be randomly assigned to "pain" and "no pain" conditions. To manipulate attention to pain, subjects will perform the Stroop color word task while receiving either painful or non-painful heat stimuli. The study will be conducted on two separate days. Day one will be conducted in a simulated MRI unit for psychophysical analysis of pain and performance of the Stroop. Day two will consist of functional brain imaging (fMRI) while the subjects receive either nonpainful or painful heat stimuli and perform the Stroop. The investigators hypothesize that FM is a unique chronic pain disorder that involves dysregulated processing of sensory stimuli and that augmented brain responses will not be affected by manipulations of anticipation and attention. This will be a first important step towards understanding the mechanisms of unexplained muscle pain in FM.

PHYSICAL ACTIVITY

TITLE: **Social Cognitive Theory and Physical Activity after Endometrial Cancer Intervention** **NCI**
P.I.: **Karen M. Basen-Engquist, PhD**
INST.: **University of Texas MD Anderson Cancer Center**
GRANT NO.: **5 R01 CA109919-02**
KEYWORDS: **Physical activity, endometrial cancer, social cognitive theory**
STUDY TYPE: **clinical**
AWARD: **$100,000**

Physical activity has been shown to benefit cancer survivors' physical and emotional well-being, however, few studies have focused on the process and determinants of the adoption of physically active lifestyles in cancer survivors populations. The goal of the project is to study predictors of adherence to physical activity in sedentary endometrial cancer survivors who receive an intervention to increase their physical activity. The specific aims of the study are (1) To test a Social Cognitive Theory-based model of physical activity adoption among sedentary endometrial cancer survivors who receive an intervention to increase physical activity; (2) to elucidate the role of cardiorespiratory fitness and somatic sensations during physical activity on self-efficacy; (3) to determine whether intervention dose is related to physical activity adherence; and (4) to test the effects of adherence to physical activity on endometrial cancer survivors' quality of life. Two hundred sixty-seven sedentary Stage I-IIIa endometrial cancer survivors will be recruited to participate in this six-month study. Participants will complete fitness tests, questionnaires, and cognitive tests every two months to assess functional capacity and efficiency, physical activity, and Social Cognitive Theory-related

variables. All participants will receive an intervention to increase their physical activity, consisting of a customized exercise prescription, telephone counseling, and written materials. Results of the study will provide a rigorous test of Social Cognitive Theory as it is applied to physical activity, and will inform the development of effective interventions for cancer survivors.

TITLE: **Young Adult Environmental and Physical Activity Dynamics** **NCI**
P.I.: **Barry M. Popkin, PhD**
INST.: **University of North Carolina Chapel Hill**
GRANT NO.: **5 R01 CA109831-02**
KEYWORDS: **Physical activity, physical environment, cardiovascular disease, race/ethnic differentials, coronary heart disease, prevention**
STUDY TYPE: **clinical**
AWARD: **$100,000**

There is an increasing call for population-wide environmental/policy interventions to increase physical activity despite the lack of large-scale intervention or epidemiological research documenting the benefits of such changes. This longitudinal study will link contemporaneous geographic locations of respondents with physical environment variables and data from an exceptional dataset including quality physical activity data. Four study years (1985, 1992, 1995, and 2001) of the Coronary Artery Risk Development in Young Adults Study [CARDIA] will be used. This is a longitudinal study of the antecedents and risk factors for cardiovascular disease in an ethnicity-, age- and sex-balanced cohort of 5,115 black and white young adults aged 18-30 years at baseline to examine relationships between environmental factors and physical activity. Complex longitudinal and spatial analytical models will be used to explore relationships between environmental factors and physical activity. A critical element addressed will be residential self-selection, an issue of increasing concern as scholars attempt to understand how the environment affects physical activity. The investigators will model physical activity as a function of covariates, some of which may be endogenous choices made by the individual. The investigators will examine race/ethnic differentials in these effects and the impact of "the environment" shifts over time and through the lifecycle. The focus will be on examining how modifiable environmental factors will affect physical activity patterns among underserved communities and consequently will reduce ethnic and socioeconomic differentials in health status. The longitudinal analysis and the vast array of environmental measures used, coupled with the very high quality physical activity measures of CARDIA, allow us to capture the effects of the environment (and changes in location) on physical activity shifts. No study heretofore has had large-scale groupings and in-depth environmental measures over time to examine these issues in a dynamic manner.

TITLE: **Mediators and Moderators of Exercise Behavior Change** **NCI**
P.I.: **Angela Bryan, PhD**
INST.: **University of Colorado, Boulder**
GRANT NO.: **5 R01 CA109858-02**
KEYWORDS: **exercise behavior, cancer, cardiovascular disease, Type II diabetes mellitus, physical activity, race/ethnicity, behavioral & social science, nutrition, prevention**
STUDY TYPE: **clinical**
AWARD: **$100,000**

Rates of cancer and cardiovascular disease have shown very little improvement over the past two decades, and the incidence of Type II diabetes mellitus is increasing at an alarming rate. Recent reports estimate that approximately 30% of total cancer deaths are related to poor exercise and nutrition, and other reports have suggested that, when taking into consideration both cardiovascular disease and cancer, inactivity contributes to as many as 250,000 premature deaths per year. Despite the benefit of regular physical activity in the prevention of cancer and other debilitating illnesses, 75% of the U.S. population do not get the recommended amount of physical activity as defined by 30 minutes of moderate intensity physical activity 5 or more days per week, and 40% of the population is completely sedentary. The objective of the proposed research is to understand the mediators and moderators of a well tested, individually tailored, print-based intervention to increase exercise behavior among sedentary adults. Using a randomized, controlled intervention trial, the proposed study will address three primary and one secondary hypotheses: 1) A previously tested and validated exercise promotion intervention is successful at helping sedentary

individuals initiate and maintain a moderate intensity physical activity regimen, as compared to a health and wellness control intervention, 2) Increases in positive attitudes, perceived normative support, self-efficacy, and intentions to exercise will mediate the effectiveness of the intervention, 3) That increased positive mood, and better temperature, stress, and lactate regulation immediately after exercise challenge (assessed in the laboratory) will moderate the effectiveness of the intervention, and 4) Secondarily, the investigators will test whether gender, race/ethnicity, and two recently suggested genetic factors (BDNF and OPRM1) moderate the effectiveness of the intervention. The rigorous assessment of how and for whom an exercise promotion intervention is effective will provide information for future development of intervention strategies and content, as well as allow the targeting of exercise content to individuals for whom it is most likely to be effective.

TITLE: **Angiogenesis and Mechanisms of Exercise Training in Peripheral Arterial Disease (PAD)** **NHLBI**
P.I.: **Brian H. Annex, M.D.**
INST.: **Medical Center, Durham, NC**
GRANT NO.: **5 R01 HL075752-03**
KEYWORDS: **artery, atherosclerosis, exercise, behavioral & social science, cardiovascular, chronic pain conditions**
STUDY TYPE: **clinical**
AWARD: **$250,000**

Peripheral arterial disease (PAD) impairs arterial blood flow to the legs and is a major indicator of systemic atherosclerosis. PAD affects 5% of the US population over 50. Approximately 1/3 of patients with PAD have typical claudication, defined as pain in one or both legs on walking that is relieved by rest. Patients with claudication have a marked impairment in exercise performance similar to patients with NYHA class III heart failure. Goals of treatment for PAD patients include risk-factor modification and antiplatelet drug therapy to address increased cardiovascular mortality risk. Supervised exercise training is the most efficacious treatment to improve walking capacity, demonstrated in many (small) randomized trials. Neither the pathophysiology of claudication nor the mechanism(s) by which exercise training improves walking times in persons with IC are completely understood. It is unknown how long-term exercise training effects skeletal muscle or to what extent skeletal muscle abnormalities in PAD are reversible. Women have been largely underrepresented in mechanistic studies of IC and exercise training. There is an urgent need for clinical research directed towards defining the basis of the exercise training changes induced in PAD patients in order to: 1) provide insights into the general pathophysiology of the exercise impairment in PAD; 2) permit scientifically plausible and testable modifications to currently prescribed exercise regiments to better employ this critical therapeutic modality, and 3) identify novel targets from pharmacotherapy that are capable of inducing the repertoire of molecular responses induced by exercise training.

REPRODUCTIVE HEALTH/DEVELOPMENTAL BIOLOGY

TITLE: **ORWH-NICHD Leiomyoma Tissue Bank** **NICHD**
P.I.: **James Segars, M.D.**
INST.: **NICHD**
ID Number: **Z01 HD008737**
KEYWORDS: **minority health, African American women, etiology, uterine fibroids (leiomyoma), reproductive health, benign tumors, gynecology**
AWARD: **$93,000**

Health of 30-50% of women in the U.S. is adversely affected by uterine leiomyoma (fibroids). Uterine fibroids are a health disparity issue that disproportionately affects African American women. Research into causes and treatment has lagged behind other disciplines, in part due to lack of available tissues, since surgical samples are often not made available to scientists. To address the problem of tissue availability, and promote research on this condition, this project proposes to establish a fibroid tissue bank as an initiative in the intramural program of NICHD. This tissue bank will provide samples to NIH-funded investigators and DoD-funded investigators to support work on this condition. The Leiomyoma Tissue

ORWH-NICHD Leiomyoma Tissue Bank Cont'd. **NICHD**

Bank (LTB) will be physically located in space assigned to Dr. Segars of NICHD. The LTB will be structured after RStaR-banks for endometrium and ovary established by the Specialized Cooperative Program in Reproductive Research. Computerization of sample inventory will be performed with software provided by NICHD.

TITLE: **Protein Tyrosine Kinases in Leiomyomata Uteri** **NICHD**
P.I.: **Jean Wang, PhD**
INST.: **University of California, San Diego**
GRANT NO.: **5 R01 HD046225-03**
KEYWORDS: **Protein tyrosine kinases, tumor growth, uterine myometrium, leiomyoma**
STUDY TYPE: **basic**
AWARD: **$75,000**

In this application, the investigators propose that female sex hormones stimulate the expression and/or activation of protein tyrosine kinases to promote uterine cell proliferation and tumor growth, and predict that inhibition of protein tyrosine kinases involved in the proliferation of uterine cells would halt the growth of uterine leiomyomata. This study will survey the expression and activity of protein tyrosine kinases in normal uterine myometrium and leiomyoma specimens procured from women in different ages and racial/ethnic groups. The investigator plans to create a microarray that is suitable for profiling the expression of all 90 human protein tyrosine kinase genes. A strength of the application is the creation of the microarray, which is important and promises to have wide-scale application beyond the study of uterine leiomyomata. Results from this study may identify protein tyrosine kinases that are important for proliferation of uterine leiomyomata.

TITLE: **Finding Genes for Uterine Fibroids** **NICHD**
P.I.: **Cynthia Morton, PhD**
INST.: **Brigham & Women's Hospital**
GRANT NO.: **5 R01 HD046226-03**
KEYWORDS: **Uterine fibroids, cytogenetic, uterine leiomyomata, African American women, genetics**
STUDY TYPE: **translational**
AWARD: **$75,000**

Although the majority of uterine leiomyomata are karyotypically normal, cytogenetic abnormalities are found in 25-40% of the tumors. This application proposes to perform a genome-wide scan to identify genes that predispose women to develop uterine leiomyomata and examine the relationship between genes that are involved in the pathogenesis of uterine leiomyomata. In an overall effort to understand the genetic contributions to the etiology, growth, and natural history of these tumors, correlation of genetic data from the genome-wide scan with environmental factors is planned. A strength of the application includes the recruitment and enrollment plan that is comprehensive with a special emphasis on African American women, the most severely affected segment of the population. This well-written study may facilitate understanding of the genetic pathways involved in the formation of uterine leiomyomata, which may ultimately lead to improved treatment options for affected women.

TITLE: **Estrogen Dependency of Uterine Leiomyoma** **NICHD**
P.I.: **Ayman Al-Hendy, M.D., PhD**
INST.: **University of Texas Medical Branch, Galveston**
GRANT NO.: **5 R01 HD046228-03**
KEYWORDS: **Estrogen receptor, immune response, recombinant adenovirus, selective estrogen receptor modulator, leiomyoma, fibroid tumors**
STUDY TYPE: **basic**
AWARD: **$75,000**

The hormone dependent phenotype of uterine leiomyomata suggests that interventions targeting the estrogen receptor-signaling pathway may have therapeutic efficacy. This application plans to investigate the immune response and safety of single versus repeated recombinant adenovirus treatment alone or in combination with a selective estrogen receptor modulator (SERM) in mice, rat, and human leiomyoma cells. The strength and overall conceptual framework of this work is to test the validity and regulatory

mechanisms of gene therapy as an alternative to non-surgical treatment for uterine leiomyomata as well as to further elucidate the molecular mechanisms of estrogen dependency of uterine leiomyomata. This highly innovative research will add to our understanding of the molecular mechanisms of estrogen-dependence in this common uterine tumor and may open a new area of investigation and treatment of uterine leiomyomata.

TITLE: **Molecular Etiology of Leiomyoma Uteri** **NICHD**
P.I.: **Cheryl Walker, PhD**
INST.: **University of Texas MD Anderson Cancer Center**
GRANT NO.: **5 R01 HD046282-03**
KEYWORDS: **leiomyoma, tumor suppressor gene, estrogen receptor signaling, fibroid tumors, genetics**
STUDY TYPE: **basic**
AWARD: **$75,000**

The goal of this application is to address the molecular regulation of uterine leiomyomata by identifying the mechanisms responsible for differential cell cycle regulation in uterine leiomyomata that may underlie inter-tumor heterogeneity and responsiveness. The investigator proposes to examine whether a well-defined cascade of molecular and genetic events in an identified tumor suppressor gene plays a role in estrogen receptor signaling and cell cycle control in rat and human leiomyoma cells. Strengths of this application include its sound and well-integrated specific aims. Results generated from these experiments may help elucidate how defective cell cycle regulation and estrogen receptor signaling contribute to the pathophysiology of uterine leiomyomata. This study may further advance our current understanding of the molecular mechanisms that play a role in the etiology and phenotypic heterogeneity observed in these tumors.

TITLE: **Regulation of Uterine Fibroids by CCN5** **NICHD**
P.I.: **John Castellot, PhD**
INST.: **Tufts University School of Medicine**
GRANT NO.: **5 R01 HD046251-03**
KEYWORDS: **estradiol, extracellular matrix, gene interactions, smooth muscle, fibroid tumors, estrogen**
STUDY TYPE: **basic**
AWARD: **$75,000**

This application proposes a research project that will elucidate the cellular, molecular, and biochemical mechanisms regulating the proliferation and motility of human uterine smooth muscle cells. The investigator has determined that estrogen induces a growth arrest specific gene that inhibits motility and proliferation in cultured smooth muscle cells. This project will examine the pathophysiology of uterine leiomyomata from the point of view of specified gene interactions with estradiol and extracellular matrix. Strengths include the tightly focused and logical progression of experiments in animal models and human cells. Conceptually, the discovery of a gene as a mediator of estrogen-related regulation of uterine smooth muscle growth may help explain the estrogen sensitivity of uterine leiomyomata and provide a therapeutic basis for controlling formation and growth of these tumors.

TITLE: **Reactive Oxygen Species Regulate Smooth Muscle Growth** **NICHD**
P.I.: **Romana Nowak, PhD**
INST.: **University of Illinois**
GRANT NO.: **5 R01 HD046227-03**
KEYWORDS: **smooth muscle, obesity, hypertension, African American women, fibroid tumors**
STUDY TYPE: **basic**
AWARD: **$75,000**

This application plans to investigate the key agents in the signaling pathway of smooth muscle cell proliferation that can be targeted by therapeutic agents. The investigator proposes that hormones related to obesity and hypertension, especially in African American women, may play a role in the pathogenesis of uterine leiomyomata. Animal models and human cell lines will be used in the study. A strength of the application is the novel hypothesis that uterine leiomyomata are a family of proliferative conditions, and

that these tumors develop as a response to injury, particularly hypoxia, that oxidative stress promotes vascular smooth muscle cell proliferation and hypertrophy, and that proliferation is the result of growth factors primarily and steroid hormones secondarily. Results obtained from this research may suggest a challenge to the existing paradigm that hormonal modulation is the key to development of uterine leiomyomata.

TITLE: **Leiomyomata Uteri: Apoptosis and Cell Survival Pathways** **NICHD**
P.I.: **Gregory Christman, M.D.**
INST.: **University of Michigan**
GRANT NO.: **5 R01 HD046249-03**
KEYWORDS: **cytoxic gene therapy, dietary, estrogen alpha-receptor antagonist, gonadotropin releasing hormone agonist, leiomyoma, fibroid tumors**
STUDY TYPE: **basic**
AWARD: **$75,000**

This application proposes to study the effect of exposure to cytotoxic gene therapy, dietary estrogen alpha-receptor antagonist, and gonadotropin releasing hormone agonist on leiomyoma cell proliferation and apoptosis in animal models and human cell lines. The overall hypothesis is that smooth muscle cell tumors have numerous cell-to-cell communications that make them uniquely susceptible to cell death via a bystander effect, which makes them a promising target for molecular therapy. Strengths of the application include its clinical relevance, the logical and innovative approach to developing novel therapeutic modalities, and verifying their effects on the molecular processes involved in cellular proliferation and apoptosis. Program staff will work with the applicant to address any identified weaknesses. Understanding the apoptosis and cell survival pathways active in uterine leiomyomata may allow the investigators to better promote long-term tumor regression in response to therapeutic agents.

TITLE: **Estrogen Biosynthesis and Uterine Leiomyomata** **NICHD**
P.I.: **Serdar Bulun, M.D.**
INST.: **University of Illinois**
GRANT NO.: **5 R01 HD046260-03**
KEYWORDS: **aromatase expression, estrogen biosynthesis, myometrium, fibroid tumors**
STUDY TYPE: **basic**
AWARD: **$75,000**

In this application, the investigator proposes to determine the cellular and molecular mechanisms responsible for induction of normal and aberrant aromatase expression in uterine leiomyomata. The underlying rationale is underscored by the role of estrogen in the growth of uterine leiomyomata and the central role that aromatase expression plays in estrogen biosynthesis. The investigator plans to focus the investigation on the molecular mechanisms that may be involved in the induction of aromatase leading to estrogen biosynthesis within the myometrium/leiomyoma tissue. Major strengths of the proposal include the experience of the investigator and the well-developed experimental plan. Program staff will work with the applicant to address any identified weaknesses. Results obtained from this study may facilitate our understanding about how locally produced estrogen plays a critical role in the pathogenesis of uterine leiomyomata.

TITLE: **Intermediate Outcomes of Hysterectomy and Alternatives** **AHRQ**
P.I.: **Miriam Kuppermann, PhD**
INST.: **University of California, San Francisco**
GRANT NO.: **5 R01 HS11657-04**
KEYWORDS: **hysterectomy, quality of life, pelvic pain, endometriosis, fibroid tumors, chronic pain conditions, decision making, hysterectomy, uterus disorder, chronic pain, endometriosis, leiomyoma, urinary incontinence, women's health**
STUDY TYPE: **outcome research**
AWARD: **$250,000**

The proposed application expands on our existing prospective longitudinal study of 811 women with non-cancerous uterine conditions for which hysterectomy is a reasonable treatment option: abnormal uterine bleeding, symptomatic uterine leiomyomata, and pelvic pain/endometriosis. The principal aims of the

proposed study are to 1) determine whether and how intermediate-term (4-8 year) clinical and quality of life outcomes differ by treatment group (hysterectomy, uterus-preserving surgery, or non-surgical treatments) for their uterine conditions; and 2) develop predictive models of treatment choice and satisfaction from a broad array of domains. The proposed expansion of the existing study is motivated by two main factors. First, by increasing the size of our cohort by an additional 700 we will extend the mean duration of follow-up from 1.7 to 4.1 years, and we will obtain at least four years of follow-up data on over 976 women. The increased sample at four years will allow the investigators to accrue an adequate number of women undergoing hysterectomy and non-surgical treatments to support a statistically meaningful comparison. Because symptoms for women with noncancerous uterine conditions typically extend from the early 40?s to menopause, including intermediate-term, face this decision, providing useful information will help equip women and their physicians to make informed, shared decisions. Second, we will enhance our measures of sexual functioning, depression, and incontinence, and include assessments of newly available alternative treatments. These additions reflect changes in the understanding of the role of these factors in the management of non-cancerous uterine conditions since the inception of the original study. The results of this study are central to the long-term goal of improving decision making in the management of non-cancerous uterine conditions. The findings that emerge from the proposed study will be relevant to the development of evidence-based guidelines and the creation of decision-assisting tools to help women with non-cancerous uterine conditions make informed choices regarding their treatment during their decade of risk for hysterectomy.

TITLE: **Pregnancy and Drug Metabolizing Enzymes and Transporters (OPRU)** **NICHD**
P.I.: **Steve N. Caritis, M.D.**
INST.: **Magee-Womens Research Institute, Pittsburgh**
GRANT NO: **5 U10 HD047905-02**
KEYWORDS: **women, pregnancy, drugs, drug metabolism and transport, clinical trials, genetics**
STUDY TYPE: **basic, clinical**
AWARD: **$50,000**

The purpose of this research is to establish an Obstetric-Fetal-Pharmacology Research Unit (OPRU) at the University of Pittsburgh and to summarize the components of the applicant's OPRU. They will demonstrate their willingness to cooperate with other OPRUs to establish a Network of OPRUs to identify and study common problems related to the use of pharmacologic agents during pregnancy. The investigators provide three protocols for assessment by the Network for future exploration. The Pittsburgh OPRU is composed of a large clinical facility (Magee-Women's Hospital) with more than 8000 deliveries and a wide array of women with medical or obstetric complications. A CRC satellite at Magee provides an optimal site for recruitment and study of pregnant women. These clinical facilities are linked to the Center for Clinical Pharmacology (CCP), which provides a core laboratory for classical pharmacology analyses and a pharmacogenetic laboratory for genotyping, mRNA expression and sequencing endpoint measurements. A proteomics laboratory is also linked to the CCP. In addition to these clinical and analytical resources is a breeding rhesus monkey colony housed at Magee-Women's Hospital. A basic science component completes the Pittsburgh OPRU. A diverse group of basic scientists and clinical researchers has been interacting through the CCP and will add considerable breadth and depth to their OPRU. The leadership of the Pittsburgh OPRU provides a diverse and experienced group of researchers with a long history of collaboration and investigation in the area of maternal-fetal pharmacology. The leadership has experience in collaborative endeavors and is prepared to cooperate with other OPRUs to conduct collaborative research.

TITLE: **Washington Obstetric-Fetal Pharmacology Research Unit (OPRU)** **NICHD**
P.I.: **Menachem Miodovnik, M.D.**
INST.: **Georgetown University, Washington, DC**
GRANT NO: **5 U10 HD047890-02**
KEYWORDS: **women, pregnancy, drugs, epilepsy, anticonvulsants, clinical trials, genetics**
STUDY TYPE: **basic, clinical**
AWARD: **$50,000**

The Washington Obstetric Pharmacology Research Unit (WOPRU) represents a collaboration among two universities and four medical centers in the nation's capitol that is uniquely positioned to use population pharmacokinetic, pharmacokinetic-pharmacodynamic, clinical trials simulation, cutting edge in vivo and in vitro techniques to assess clinical pharmacology of important therapeutic agents and their effects in pregnant women and their offspring. Specifically, the WOPRU combines the basic research resources of Georgetown University (GU) (lead agency) and George Washington University (GWU) with the clinical strengths of MedStar Health (Washington Hospital Center [WHC] and Georgetown University Hospital [GUH]), GWU Hospital, and Children's National Medical Center (CNMC). These hospitals are strategically placed throughout the DC metropolitan area, and are closely associated with the respective surrounding communities. The WOPRU obstetricians deliver over 7,000 babies from women who represent a broad spectrum of social, economic, ethnic, racial and cultural backgrounds with a large proportion of these pregnancies being high risk. The WOPRU institutions have an excellent track record of providing care and recruiting patients into clinical trials from this diverse community. The faculty of the WOPRU represent a team of highly motivated basic scientists and clinical investigators who are enthusiastically approaching the prospect of becoming a new center for OPRU. They are experienced investigators in a multitude of basic science and clinical disciplines with a unique combination of strengths in pharmacometrics, pharmacodynamics, pharmacogenetics, drug metabolism, therapeutic drug monitoring, proteomics, genomics and biostatistics in conjunction with significant experience in multi-center clinical trials. The administration, and the basic science and clinical investigators of the WOPRU institutions are unanimous in their eagerness to support and participate in the future OPRU network.

TITLE: **UW Obstetric-Fetal Pharmacology Research Unit (OPRU)** **NICHD**
P.I.: **Mary F. Hebert, PharmD**
INST.: **University of Washington OPRU**
GRANT NO: **5 U10 HD047892-02**
KEYWORDS: **Women, pregnancy, drugs, diabetes, anti-diabetes drugs, drug metabolism, clinical trials, genetics**
STUDY TYPE: **basic, clinical**
AWARD: **$50,000**

The overall objective of this research is to establish an Obstetric-Fetal Pharmacology Unit at the University of Washington. The major goal of the pharmacology unit will be to characterize the pharmacokinetics and pharmacodynamics of drugs that are of therapeutic value during pregnancy and whose clinical pharmacology is altered by the pregnant state. The general research focus will be cytochrome P450 enzymes and membrane transporters. There is an appropriate environment and resources at the University of Washington for establishing a successful and productive Obstetric-Fetal Pharmacology Research Unit. The following translational research studies that integrate the investigators strengths in clinical and basic sciences are proposed to evaluate the following study aims. 1. To determine whether the in vivo activities of CYP2C9 and organic cation transporter (OCT) are altered through stages of pregnancy using the following phenotype markers: glyburide for CYP2C9 and metformin for OCT. Phase I (population pharmacokinetic analysis) and Phase II (pharmacokinetic /pharmacodynamic analysis) studies are proposed to investigate the effects of pregnancy on the aforementioned drug-metabolizing enzymes and transporters (second and third trimesters vs. 3 months postpartum period). 2. To determine the efficacy and safety of insulin vs. glyburide vs. glyburide plus metformin for treatment of gestational diabetes mellitus. A Phase III efficacy and safety trial is proposed to evaluate the effects of gestational diabetes as well as the treatments on maternal, fetal and infant / child developmental outcomes.

TITLE: **Obstetric-Fetal Pharmacology Research Units Network (OPRU)** **NICHD**
P.I.: **Gary D. Hankins, M.D.**
INST.: **University of Texas Medical Branch, Galveston, Texas**
GRANT NO: **5 U10 HD047891-02**
KEYWORDS: **Women, pregnancy, drugs, diabetes, anti-diabetes drugs, clinical trials**
STUDY TYPE: **basic, clinical**
AWARD: **$50,000**

The University of Texas Medical Branch (UTMB) will participate as a member of the Obstetric-Fetal Pharmacology Research Units (OPRU) Network. The principal investigator is responsible for the proposed clinical trial on the use of hypoglycemic drugs in the treatment of diabetes during pregnancy. Over 12,000 pregnant women are cared for annually within the RMCHP clinic system, approximately 7,000 of whom deliver at UTMB. The investigators have expertise in utilizing human placenta and derived preparations in the investigations and in placental receptors, their natural ligands and mediated responses, as well as the mechanism of hCG release from trophoblast tissue. They have investigated the effects of in vitro and in vivo chronic administration of opiates on placental physiology and maternal-neonatal outcome. Utilizing dual perfusion of placental lobule, they demonstrated the influence of efflux protein and placental metabolic enzymes on the PK for placental transfer of opiates. They identified placental aromatase as a drug-metabolizing enzyme and are investigating its polymorphism. One of the investigators is responsible for coordinating the baboon studies to be conducted at the Southwest National Primate Research Center (SNPRC) in San Antonio. A population of normal and diabetic baboons will be studied. The Department of Ob/Gyn has scientists with expertise in areas relevant to this RFA including infection, vascular physiology, and placental functions. The Division of Neonatology, the GCRC, and other departments at UTMB will provide support for this project.

TITLE: **Impact of Sex Differences and Pregnancy in Drug Disposition–Adverse Effects** **NICHD**
P.I.: **Menachem Miodovnik, M.D.**
INST.: **Georgetown University, Washington, DC**
GRANT NO.: **5U10HD047890-02S1**
KEYWORDS: **sex differences, drug disposition, pharmacology, obstetrics**
STUDY TYPE: **literature review, ancillary study**
AWARD: **$75,000**

Men and women differ in response to drug treatment. Anatomical, physiological, and molecular differences between the sexes account for differences in clinical therapeutics. To design safe and effective drug treatment, it is essential to understand how men and women differ in disposition of and response to drugs. Additionally, it is important to understand how sex differences influences disposition and responses to drugs in pregnancy. This project would critically evaluate adverse effects of drugs in men, women and during pregnancy. The study would be completed in a year. It would primarily be a literature review pulling together adverse effects data, though the investigator would also use the FDA adverse events files and explore using the similar files in the WHO adverse events system housed in Uppsala, Sweden.

TITLE: **Gestational Hypothyroidism: Is the Current Treatment Regimen Adequate? Single Dose and Steady State Pharmacokinetics Based on State-of-the-Art Analytical Methods** **NICHD**
P.I.: **Menachem Miodovnik, M.D.**
INST.: **Georgetown University, Washington, DC**
GRANT NO.: **5 U10HD047890-02S2**
KEYWORDS: **hypothyroidism, pregnancy, pharmacokinetics**
STUDY TYPE: **clinical, ancillary study**
AWARD: **$25,000**

Hypothyroidism during pregnancy present clinicians with a unique challenge, optimal dosing regimens developed and validated for non-pregnant women cannot be extrapolated to pregnancy. Hypothyroidism in pregnancy is associated with higher rates of complications such as spontaneous abortions, preeclampsia, stillbirth, and prematurity. Low thyroid hormone (TH), especially thyroxine (T4), is also associated with adverse effects on fetal growth and development and is critical for normal brain development. Because the fetal thyroid is not fully formed until gestational week (GW) 16, during the first half of pregnancy the fetus

Gestational Hypothyroidism: Is the Current Treatment Regimen Cont'd. **NICHD**

totally depends on maternal supply of TH. After GW 16, the fetus continues to partially rely on maternal thyroid hormone supply until delivery. Hypothyroid mothers who are not appropriately supplemented will not provide adequate thyroxin to the baby. Therefore, early identification of hypothyroidism in pregnant women is extremely important. Recent studies have shown that standard immunoassays (IAs) consistently overestimate thyroid hormone concentrations during pregnancy. Using current generally accepted IA methods, it is estimated that as many as 50 percent of pregnant hypothyroid women could be missed - which could result in neurobehavioral deficits in thousands of babies. There is no evidence-based treatment of hypothyroidism in pregnancy. Currently patient treatment is determined by thyroid stimulating hormone (TSH) levels. For appropriate LT4 supplementation of hypothyroid women in pregnancy, thyroid hormone measurements should be based on state of the art detection methods. The investigators' objectives are:

- To estimate LT4 PK parameters in pregnant women already receiving LT4 to treat their hypothyroidism.
- To compare 1st to 3rd trimester TH PK in LT4-treated hypothyroid women, and compare these to same subject post-partum levels, and to PK during lactation.
- To measure, in LT4-treated women, FT4, T4 and T3 trough steady state levels on gestation weeks 8-10, 22-24, 32
- Single dose studies using stable isotope

TITLE: **Development and Differentiation in Reproductive Axis** **NICHD**
Cooperative Reproductive Sciences Research at Minority Institutions
P.I.: **Director–David R. Mann, PhD, Morehouse School of Medicine, Atlanta, GA**
Co-director/Partner–Tony M. Plant, PhD, University of Pittsburgh, Specialized Cooperative Centers Programs in Reproductive Research, Pittsburgh, PA
GRANT NO.: **5 U54 HD41749-05**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation**
STUDY TYPE: **basic science, translational, clinical**
AWARD: **$250,000**

The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new, and/or the enhancement of ongoing, basic science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health. The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core. Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant. Grant No. 1–1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann. Grant No. 2--1U54HD41749-010002 (Role of Prohibition in Follicular Development), Winston E. Thompson. Grant No. 3--1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran. Grant No. 4--1U54HD41749-010004 (SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.

TITLE: **The Biologic Effects of Androgens in Men and Women** **NICHD**
RFA: **Cooperative Reproductive Sciences Research at Minority Institutions**
P.I.: **Shalender Bhasin, M.D.**
INST.: **Charles R. Drew University of Medicine and Science**
GRANT NO.: **5 U54 HD041748-03**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, genetics, minority health**
STUDY TYPE: **basic science, translational, clinical**
AWARD: **$200,000**

The Drew Center would serve to strengthen an existing, established, investigative effort between Charles R. Drew University and UCLA. The role of testosterone in normal female physiology is poorly understood and this center would serve to increase knowledge of the characterization of this hormone in sexual function, body composition and strength, and cognitive ability in women. One project uses the model of

hormone deficient women. Randomized treatment with varying doses of testosterone is proposed to address these important biological questions. Another project will test the hypothesis that female patients with panhypopituitarism would benefit from physiological testosterone replacement. A third project will use an animal model to examine the genetic factors, beyond hormonal effects, that regulate sex differentiation between male and female brains. The fourth project focuses on androgen-dependent stem cell differentiation. Strengths of the Center include the expertise and experience of the investigative team, its clinical approach to examine whether testosterone replacement in physiological range can produce meaningful improvements in quality of life, and its unique approach to investigating the molecular basis of sex differentiation.

TITLE: **MMC/PSU Cooperative Center for Research in Reproduction** **NICHD**
RFA: **Cooperative Reproductive Sciences Research at Minority Institutions**
P.I.: **Ponjola Coney, M.D.**
INST.: **Meharry Medical College, Memphis, TN**
GRANT NO.: **5 U54 HD044315-03**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, fibroid tumors, estrogen**
STUDY TYPE: **basic science, translational, clinical**
AWARD: **$200,000**

The Meharry Center would serve to facilitate the development of a reproductive science research center at Meharry Medical College through a strong collaborative partnership with Pennsylvania State University. Studies outlined in these projects will generate knowledge and assess outcomes across the lifespan of women of different ages and racial/ethnic groups: (1) the role of sex steroid hormones as determinants of bone mineral density in African American females, (2) the influence of oral contraceptives on the growth of uterine fibroids, and (3) the efficacy and safety of metformin and lifestyle factors in the amelioration of polycystic ovary syndrome (PCOS) and its symptomatology in both adolescent and adult females. The overall objective is to determine whether ovarian production of estrogens and progesterone differ among women of diverse racial/ethnic groups and whether these determinants are responsible for racial differences in several positive and negative health outcomes. Strengths of the Center include the innovative aspects of the proposed projects, their experimental designs, and the comparisons of lifestyle interventions and therapeutic regimens.

TITLE: **Mechanisms of aPL Antibody-Induced Pregnancy Loss** **NIAMS**
P.I.: **Jane E. Salmon, M.D.**
INST.: **Hospital for Special Surgery, New York**
GRANT NO.: **2 R01 AR38889-14**
KEYWORDS: **Antiphospholipid Antibody Syndrome, autoantibodies, autoimmune disease, miscarriage, complement**
STUDY TYPE: **basic, interdisciplinary**
AWARD: **$100,000**

The antiphospholipid syndrome (APS), characterized by thrombosis and pregnancy loss that occurs in the presence of antiphospholipid (aPL) antibodies, is a leading cause of miscarriage and maternal and fetal morbidity. Pregnancy complications in women with APS include fetal death, preeclampsia, and intrauterine growth restriction (IUGR). The pathogenic mechanisms that lead to injury in vivo are incompletely understood and the therapy for pregnant women with APS is only partially successful. Our studies in a murine model of APS, induced by passive transfer of human Apl antibodies, indicate that complement activation plays an essential and causative role in fetal loss and growth restriction. In addition, treatment with heparin, the standard therapy for pregnant patients with APS, prevents complement activation and protects mice from pregnancy complications induced by aPL antibodies, while anticoagulants that do not inhibit complement do not protect pregnancies. These studies indicate that APS is an inflammatory disease and, they suggest that complement inhibitory therapy might be an effective treatment. Our overall goals are to use the murine model of APS to determine how complement is activated, which complement products mediate the clinical complications associated with aPL antibodies, and the relative role of complement

activation within the overall inflammatory cascade. In addition, we propose to test the hypothesis that activation of complement at the maternal-fetal interface plays an etiologic role in IUGR. The aims are: Aim 1. To determine which complement components and receptors are necessary or sufficient to mediate aPL antibody-induced placental injury, fetal loss and/or IUGR. (a) To identify the pathways that initiate complement activation and lead(s) to complement deposition in deciduas and poor pregnancy outcomes; (b) To identify the complement activation products and receptors that mediate fetal injury; (c) To assess the role of murine complement regulatory proteins in the control of local complement activation. Aim 2. To define the role of aPL antibody-mediated complement activation within the overall inflammatory cascade in order to identify complement-dependent vs. complement-independent mechanisms, (a) To define the contribution of FcγR to aPL antibody-mediated injury; (b) To define the cellular and cytokine mediators which contribute to complement activation in deciduas, to IUGR and to fetal loss. The proposed study, together with their ongoing work to define the role of complement and cytokines in pregnancy complications in APS patients, will provide insights into the mechanisms by which complement induces disease and define targets for interventions to prevent aPL antibody-associated fetal demise and IUGR. Additionally, understanding how aPL antibodies "cause" pregnancy loss may translate into new concepts about maternal-fetal tolerance and miscarriages in general and benefit women with non-aPL-related pregnancy complications.

TITLE: **American Indian Women and Childbearing Experiences** **NINR**
P.I.: **Janelle F. Sagmiller-Palacios, BSN**
INST.: **University of California, San Francisco**
GRANT NO.: **1 F31 NR009627-01**
KEYWORDS: **American Indian, maternal child health, childbearing, vulnerable populations, adolescents, minority**
STUDY TYPE: **clinical**
AWARD: **$41,527**

Early childbearing is a common and poorly understood event among the American Indian population. In 2002 American Indian early childbearing rates of 53.8 per 1,000 live births were higher than total U.S. rates of (42.9) and White rates of (28.6). Childbearing American Indian women typically have significantly worse maternal/child outcomes compared to other groups. This pilot study is designed to explore, retrospectively, the early childbearing (prior to 18 years of age) experiences of American Indian women who currently live in urban areas. This interpretive study seeks to understand the lived experiences of early childbearing for American Indian women. Early childbearing experiences to be examined are: 1) decisions for bearing children early in life; 2) cultural values and beliefs associated with early childbearing; and 3) support structures and barriers. Twenty women will be drawn from the Native American Health Centers located in Oakland and San Francisco, California. Audiotapes will be transcribed verbatim. This study addresses an important area of research related to understanding the needs of vulnerable populations. Future work will target identified issues from this study, enabling American Indian communities to promote healthy maternal and child outcomes and facilitate postponement of early childbearing.

VIOLENCE

TITLE: **Impact of Domestic Violence on Cancer Treatment** **NCI**
P.I.: **Jeanne E. Hathaway, M.D.**
INST.: **Harvard University, School of Public Health, Cambridge, MA**
GRANT NO.: **1 R03 CA119198-01A1**
KEYWORDS: **violence, domestic, against women; cancer; behavioral research; minority women**
STUDY TYPE: **clinical**
AWARD: **$7,936**

Domestic violence (DV) is experienced by one to three million Americans annually and has been shown to disproportionately impact the health and health care access of women. DV has also been associated with cervical neoplasia and key risk factors for cancer, including smoking and drinking. Anecdotal reports

further indicate that DV may delay the diagnosis of cancer, interfere with cancer treatment, and negatively impact women's health during cancer treatment. Despite this evidence, no research has focused on the relationship between DV and cancer. Research design and specific aims: This exploratory study aims to conduct in-depth interviews with a culturally diverse sample of individuals who have experienced abuse by an intimate partner while in cancer treatment (n = 32). Interviews will be semi-structured and conducted in English or Spanish. Interviews will focus on the effects of DV on cancer development, identification, and treatment, and participants' opinions as to how oncology and other health care providers can best identify, support, and protect patients facing both cancer and DV. Subjects will be recruited through oncology centers, a hospital-based DV program, cancer resource centers, local newspapers, and flyers posted in participating hospitals and the community. Interviews will be analyzed using grounded theory methodology. Contribution and long-term objective: This will be the first known study to explore the impact of DV on any chronic disease, including cancer. Study findings will be used in educating oncology and other health care providers about the impact of DV on cancer treatment and formulating efforts to address DV among oncology patients. Findings from this study may ultimately contribute towards improved health care and safety of individuals facing both cancer and domestic violence.