FY 2004 ORWH-SUPPORTED RESEARCH INITIATIVES

AGING

TITLE: **Phytoestrogens and Aging: Dose, Time and Tissue** **NIA**
P.I.: **William Helferich, Ph.D.**
INSTITUTION: **University of Illinois, Department of Food Science & Human Nutrition**
GRANT NO.: **1 P01 AG024387-01**
KEYWORDS: **Aging, dietary supplements, breast cancer, estrogen, nutrition**
STUDY TYPE: **Basic**
AWARD: **195,000**

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: **Modulation of Age-related Changes in the Auditory System** **NIA**
P.I.: **James F. Willott, Ph.D.**
INSTITUTION: **University of South Florida**
GRANT NO.: **2 R01 AG007554-15**
KEYWORDS: **Sensorineural hearing loss, neuron loss, age, sex hormones, presbycusis, behavioral & social science, estrogen**
STUDY TYPE: **Basic**
AWARD: **$315,250**

The current project has been investigating a method that dramatically ameliorates age-related hearing loss in several inbred strains of mice that serve as models for presbycusis and other forms of progressive sensorineural hearing loss. The treatment involves an augmented acoustic environment (AAE), an extended period of nontraumatic acoustic stimulation for 12 hours each day. Positive effects of AAE treatment include slowing progressive elevation of auditory brainstem response (ABR) thresholds, diminished loss of outer hair cells and spiral ganglion cells, lessened age-related reduction of volume and neuron loss in the anterior ventral cochlear nucleus (AVCN), increased amplitude of the acoustic startle response, and stronger prepulse inhibition (PPI; indicative of the behavioral salience of sounds). However, in demonstrating these findings, the current project has revealed that the effects of AAE treatment are complicated by several factors including sex, frequency spectrum of the AAE; and age or degree of progressive hearing loss at initiation of AAE treatment. The continuation project addresses these factors, focusing on histopathology of the cochlea and AVCN using D2 and B6 mice. Aim 1 will evaluate an observed sex effect in B6 mice: females between about 6-12 months of age (when fertility and estrogen are declining) exhibit an acceleration in the rate and severity of hearing loss compared to males. Findings stemming from this aim can help us to better understand sex-related factors that may modulate presbycusis in humans. Aim 2 will elucidate variables responsible for the positive effects of AAE treatment on cochlear tissue using histological methods. The goal is to gain additional insight into mechanisms associated with AAE effects. Aim 3 will study the role of sex hormones and other variables involved in central AAE effects, including the death in AVCN neurons in AAE-treated male B6 mice and neuron protection observed in females. The findings will have implications with respect to possible effects of the acoustic environment (e.g., amplification) on the central auditory system. Aim 4 will evaluate in greater detail the effects of very early initiation of AAE treatment, which has potential clinical implications. The proposed continuation project can help us to better understand progressive sensorineural hearing loss and factors that modulate it, such as sex hormones and age

at intervention. The ultimate goal is to develop new approaches for amelioration and treatment of presbycusis and other hearing disorders.

TITLE: **End of Life Care in Assisted Living Facilities** **NINR**
P.I.: **Juliana C. Cartwright, Ph.D.**
INSTITUTION: **Oregon Health Sciences University**
GRANT NO.: **1 R03 NR008921-01**
KEYWORDS: **Lifespan, frail elderly, rural health, aging**
STUDY TYPE: **Clinical**
AWARD: **$75,499**

The purpose of this study is to address the absence of descriptive knowledge about end-of-life (EOL) care in the fastest growing, yet understudied, congregate residential setting for frail older adults, assisted living facilities (ALF). Nationally it is estimated that death accounts for 28% of the annual turnover in ALF residents. Increasingly, dying ALF residents are enrolled in hospice programs. Despite projections that ALFs will surpass nursing homes in occupancy within several years, and estimates that the current national population of 1 million ALF residents will double by 2020, there is limited information on EOL care and hospice involvement in ALFs. Specifically, this study will examine the perspectives of ALP staff and hospice nurses on: 1) how EOL care is provided for ALF residents and 2) facilitators and barriers to EOL care in ALFs. A qualitative descriptive design will be used. Face-to-face semi-structured interviews will be conducted with a purposeful sampling of up to 36 ALF and hospice nurses in both rural and urban sites in Oregon. In addition, documents used in EOL care in ALFs will also be analyzed (e.g., flow sheets, protocols). Qualitative content analysis will include the following components: open coding of text data, constant comparative analysis of text data and documents, negative case analysis, theoretical memos, and document trails. Key characteristics of the care activities, similarities and differences in how the activities are performed, and related challenges and barriers will be identified. The end product of this study will be a detailed description of how EOL care happens for ALP residents, from the perspectives of the staffs that provide or supervise this care. The findings in combination with the investigator's earlier findings from dying residents and their families, will be the basis for developing and testing a model intervention aimed at improving EOL care in ALFs in subsequent research.

TITLE: **A Fall Prevention Program for High Risk Elderly Women** **NINR**
P.I.: **Jean F. Wyman, PhD, RN**
INSTITUTION: **University of Minnesota, Minneapolis, MN**
GRANT NO.: **5 R01 NR005107-05**
KEYWORDS: **injury prevention, nursing intervention, aging**
TYPE STUDY: **Clinical**
AWARD: **$100,000**

The long-term objective of this study is to develop cost-effective, community-based strategies for the prevention of falls in high-risk elderly women. Specific aims include: 1) Test the efficacy of a fall prevention program for high risk elderly women on fall rates over one and two years; 2) Determine the effects of the fall prevention program on postural competence, functional performance, and a variety of other outcome measures; and 3) Identify demographic, clinical, personal, functional, and postural competence variables that predict long-term exercise adherence for participants in the fall prevention program. The participants will be 250 community-dwelling women who are aged 70 and over, mentally intact, ambulatory, with postural instability and at least one other fall risk factor, not currently involved in regular exercise, and medically stable with physician approval for independent exercise participation. This study will provide information on the efficacy and cost of simple interventions designed to prevent falls and fall-related injuries, reduce preclinical disability, maintain long-term exercise adherence, and improve quality of life for older women.

TITLE: **Health, Illness, and Social Life at Older Ages** **NIA**
National Social Life Health and Aging Project
P.I.: **Linda Waite, PhD**
INSTITUTION: **Department of Sociology, Center on Aging, University of Chicago, IL**
GRANT NO.: **1 R01 AG021487**
KEYWORDS: **sexuality, aging, mental health, prevention, behavioral & social science**
TYPE STUDY: **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.

ALCOHOL AND OTHER SUBSTANCE ABUSE

TITLE: **Screening & Brief Intervention of Problem Drinking Women** **NIAAA**
P.I.: **Grace Chang, M.D.**
INSTITUTION: **Brigham and Women's Hospital**
GRANT NO.: **1 R01 AA014678-01A1**
KEYWORDS: **Problem-drinking women, alcohol abuse, dependence, randomized trial, behavioral & social science, diabetes, drug abuse, hypertension, infertility**
STUDY TYPE: **Clinical**
AWARD: **$100,000**

Early identification and intervention among problem-drinking women may avert the more severe, adverse consequences of alcohol abuse and dependence. Among nonpregnant women of childbearing age, the use of alcohol and, in particular, the riskier practices of frequent and binge drinking have not changed since 1995. Moreover, 12% of women 60 years and older regularly drink in excess of recommended amounts, and as a group are underscreened and underdiagnosed, despite being the largest group of health care users in the United States. Screening and intervention, while generally effective, have not been adequately tested among women who account for only 27% of brief intervention trial subjects since 1995, despite the NIH guidelines on inclusion of women in clinical trials. This is concerning, as women in general are more vulnerable to alcohol's negative effects due to differences in metabolism. The purpose of this randomized trial is to test the effectiveness of screening and brief intervention for risk drinking by nonpregnant women with specific medical problems exacerbated by excessive alcohol consumption. The medical problems are female factor infertility, hypertension, and diabetes, conditions that are costly to treat and difficult to manage. Five hundred fifty-two nonpregnant women with risk drinking (exceeding NIAAA sensible drinking limits of 7 drinks a week or 1-2 drinks per episode) and infertility, hypertension, or diabetes will be randomized to receive either a nurse practitioner delivered brief intervention using Personal Steps to a Healthy Choice: A Woman's Guide or medical treatment as usual. The specific aim of this randomized clinical trial is to test the hypothesis that 45% of the women who receive the medically oriented brief intervention and 30% of the control group will achieve NIAAA sensible drinking limits in the 12 months after study enrollment.

TITLE: **Alcohol Pharmacogenetics in Mexican Americans** **NIAAA**
P.I.: **Yu-Jui Yvonne Wan, Ph.D.**
INSTITUTION: **The University of Kansas Medical Center**
GRANT NO.: **2 R01 AA012081-05A1**

KEYWORDS: **Aldehyde dehydrogenase, alcohol dehydrogenase, Mexican American, alcohol pharmacogenetics, substance abuse, minority health, alcoholism**
STUDY TYPE: **Basic**
AWARD: **$100,000**

Representing one of the fastest growing ethnic groups in the United States, Hispanics accounted for 12% of the nation's population by March 2000, and suffer from higher rates of alcohol related problems as compared with those from other ethnic backgrounds (e.g., Caucasians and African Americans). This notwithstanding, genetic factors that might contribute to such risks remain poorly understood. Building upon the research infrastructure that has been established, this research will systematically explore and examine genetic mechanisms for alcoholism in Mexican Americans. This ongoing research program has started to identify unique genetic patterns that might be in part responsible for the heightened risk for alcoholism and alcohol associated health problems in this population. These include (I) extremely low allele frequency for both ALDH2*2 (aldehyde dehydrogenase) and ADH2*2 (alcohol dehydrogenase); (2) a relatively high rate of ADH3*2 and CYP2E1 c2 (cytochrome P4502E1) alleles; (3) association of ADH3*2, ADH2* 1, DRD2 (dopamine receptor -141C Del/Ins) and serotonin transporter gene-linked polymorphic region (5-HTTLPR) with alcoholism; (4) a strong association of ADH3*2 and ADH2*1 alleles with binge drinking; and (5) association of the DRD2 Taq1 A and 1B alleles with early age of onset for drinking. In this new funding cycle, they investigators plan to further pursue and clarify the meaning of these findings. Specifically, they will (1) expand the study to include Mexican American women with alcohol problems; (2) further examine the role of these polymorphisms, as well as their potential interactions, in relation to risks for alcoholism in Mexican American populations; (3) examine the role of these risks in relationship with the severity of alcoholism i.e. binge drinking and early onset of drinking; (4) characterize and determine the haplotype of DRD2 in association with drinking in Mexican Americans, and assess the relative advantage of haplotype vs. allelic analysis in delineating risk factors contributory to the development of alcoholism. This study will be the first to systematically examine how genetic factors modulate alcohol dependence and abuse in Mexican Americans. Results derived from such a study should not only provide for a better understanding of alcohol use and abuse among Mexican Americans, but also contribute towards a knowledge base regarding ethnic differences in alcohol pharmacogenetics and mechanisms that might be responsible for the high rate of alcoholism in this minority population.

TITLE: **Reducing Alcohol and Risks Among Young Females** **NIAAA**
P.I.: **Lydia N. O'Donnell**
INSTITUTION: **Education Development Center, Inc, Newton. MA**
GRANT NO.: **5 R01 AA014515-02**
KEYWORDS: **alcohol, African American, Latina adolescent females, HIV/ AIDS, alcoholism, basic & social science, infectious diseases, minority health**
TYPE STUDY: **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 7th grade and more than half by spring of 10th 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).

CANCER

TITLE: **Culture and Cancer Disparities: The Case of Latino Women** **NCI**
P.I.: **Hector Betancourt, Ph.D.**
INSTITUTION: **Linda Loma University**

GRANT NO.: **1 R21 CA101867-01A1**
KEYWORDS: **Breast cancer, cervical cancer, screening, health disparities, Minority sub-populations: Latinas, behavioral & social science**
STUDY TYPE: **Basic**
AWARD: **$162,000**

The aims of this research are to identify aspects of culture associated with variations in breast and cervical cancer screening among Latino women, to develop psychometrically appropriate instruments to measure those cultural variables in English and Spanish, and to examine hypothesized relationships among the identified cultural factors, relevant psychological processes, and cancer screening. Although the focus is on culture, relations to other factors (e.g., age, access to health care, and SES) will also be examined. The research is guided by an approach to the study of culture proposed by the investigators to study the role of culture in psychological functioning and behavior. The instruments to be developed are also expected to contribute to the long-term goal of developing a model that may effectively guide research and intervention concerning not only ethnic disparities in cancer screening but in health behavior in general, with Latino as well as with other culturally diverse populations. Although the immediate focus is on Latino women, Anglo (non-Latino White) women are included as the mainstream comparison group in order to satisfy methodological and practical requirements associated with the comparative study of culture. Participants will be recruited from the population of Latino and Anglo women living in San Bernardino County, Southern California, or any of the surrounding counties in Region 5 of the California Statewide Cancer reporting system. Three distinct methodologies will be utilized. First, the methods for the study of subjective culture will be used to identify specific aspects of culture relevant to cancer screening among Latino and Anglo women. Content analyses of open-ended interviews and focus groups will be performed to identify the relevant aspects of culture and to generate items for the cultural instruments to be developed. Second, conventional psychometric procedures and statistical techniques will be applied to the development and validation of quantitative instruments to measure the cultural factors identified as relevant to cancer screening. Finally, survey methodology and multivariate quantitative methods of analyses will be used to test a hypothesis concerning the relationships among cultural factors, mediating psychological processes, and breast/cervical cancer screening in Latino as well as mainstream Anglo women.

TITLE: **Modulation of a Breast Cancer Pathway by Pregnancy** **NCI**
P.I.: **Teresa A. Rose-Hellekant, DVM, Ph.D.**
INSTITUTION: **University of Wisconsin, Madison**
GRANT NO.: **1 R21 CA106284-01**
KEYWORDS: **Breast cancer, transgenic mice, TGFa expression, estrogen, prolactin, cervical cancer**
STUDY TYPE: **Basic**
AWARD: **$133,650**

Full-term pregnancy early in life reduces the lifetime risk of breast cancer in women, and in rodents protects against chemically induced mammary cancer, suggesting that rodents may serve as a good model for this effect in humans. However, the effect of pregnancy on transgene-induced carcinogenesis cannot yet be determined in transgenic mice. Traditional transgenic mouse models of mammary cancer employ gene-targeting elements that are upregulated by hormones at puberty, during pregnancy and lactation; the upregulation of transgene expression by pregnancy complicate attempts to study the effects of pregnancy on transgene-induced mammary cancer. In addition, transgene expression in traditional transgenic mice occurs in nearly all mammary epithelial cells, and is active throughout life. This feature does not mimic the spatial pattern of carcinogenic gene alterations in human breast, which typically is focal rather than widespread. Our purpose is to develop a novel transgenic approach that can be used to precisely and independently regulate when transgene expression is "turned on" in the mammary epithelium (specifically, after the completion of pregnancy), and in a focal pattern that mimics the upregulation of breast cancer relevant genes in human disease. To accomplish these goals, the investigators will establish transgenic mice with following characteristics: (1) timing of onset of TGFa expression is regulatable, (2) TGFa expression is activated irreversibly in a controllable fraction of mammary epithelial cells, and (3) TGFa is under the control of an estrogen and prolactin nonresponsive promoter that permits evaluation of the effect on lesion development of hormonal modulation. This application has the following specific aims: Aim 1. Develop transgenic mice that

permit manipulation of TGFa expression in mammary epithelium. Aim 2. Establish how prior pregnancy affects TGFa -induced mammary tumorigenesis.

TITLE: **Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines** **NCI**
P.I.: **Douglas R. Lowy, MD**
INSTITUTION: **NCI, Bethesda, MD**
GRANT NO.: **1 Z01 BC09052**
KEYWORDS: **human papillomavirus, cervical cancer, vaccine development, STDs**
TYPE STUDY: **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.

CARDIOVASCULAR DISEASE

TITLE: **Genetics of Early Onset-Stroke** **NINDS**
P.I.: **Steven J. Kittner, MD**
INSTITUTION: **University of Maryland, School of Medicine, Dept. of Neurology, Baltimore, MD**
GRANT NO.: **5 R01 NS045012-02**
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**
TYPE STUDY: **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: **Altered Glucose and Lipid Metabolism In Obesity and CVD** **NHLBI**
P.I.: **Maureen J. Charron**
INSTITUTION: **Albert Einstein College of Medicine, Bronx, NY**
GRANT NO.: **5 R01 HL073163-02**
KEYWORDS: **metabolic disturbances, cardiovascular disease, insulin-stimulated GLUT4 transporter, diabetes, genetics, obesity, prevention**
TYPE STUDY: **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.

CRANIOFACIAL

TITLE: **Brief Focused Treatment for TMD: Mechanisms of Action** **NIDCR**
P.I.: **Mark D. Litt**
INSTITUTION: **University of Connecticut, School of Medicine, CT**
GRANT NO.: **5 R01 DE014607-02**
KEYWORDS: **temporomandibular disorders (TMD), pain, coping, mood, cortisol, cytokines, behavioral & social science, dental/oral disease, chronic pain conditions**
TYPE STUDY: **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 (N--106) 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**
INSTITUTION: **University of Michigan at Ann Arbor, MI**
GRANT NO.: **5 R01 DE 015396-02**
KEYWORDS: **temporomandibular, pathogenesis, candidate gene, estrogen, dental/oral disease, genetics, chronic pain conditions**
TYPE STUDY: **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**
INSTITUTION: **University of Maryland, Baltimore, MD**
GRANT NO.: **5 R01 DE 015386-02**
KEYWORDS: **temporomandibular, fibromyalgia, neurons, musculoskeletal, gender, dental/oral disease, chronic pain conditions**
TYPE STUDY: **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**
INSTITUTION: **Texas A&M University Health Science Center, TX**
GRANT NO.: **5 R01 DE 015372-02**
KEYWORDS: **gene, macrophage, rheumatoid factor, autoimmune, dental/oral disease, estrogen, TMJ disorders**
TYPE STUDY: **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 RIII 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 Sjogren's Syndrome** **NIDCR**
P.I.: **John Greenspan, Troy Daniels**
INSTITUTION: **University of California, San Francisco, CA**
GRANT NO.: **N01 DE32636**
KEYWORDS: **research registry, Sjogren's syndrome, international, dental/oral disease**

TYPE STUDY: **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.

DIABETES

TITLE: **The Role of Inflammation and Parity on GDM and Type 2 DM** **NIDDK**
P.I.: **Wanda Nicholson, M.D.**
INSTITUTION: **Johns Hopkins Hospital**
GRANT NO.: **1 K23 DK067944-01**
KEYWORDS: **Type 2 diabetes mellitus, gestational diabetes mellitus, inflammation, risk factors, clinical study**
STUDY TYPE: **Clinical**
AWARD: **$100,000**

The investigator will study the role of inflammatory markers as predictors of gestational diabetes mellitus (GDM) and incident Type 2 diabetes mellitus (Type 2 DM), to complete advanced training in the conduct of longitudinal studies, and to transition to an independent career in clinical research. Parity has been previously linked to Type 2 DM; however, the underlying mechanism for this association is unclear. Recently, markers of inflammation (e.g. C-reactive protein) have emerged as independent predictors of Type 2 DM. No studies have examined whether the association of parity with Type 2DM is mediated by the presence of inflammation. Moreover, it is unclear whether inflammatory markers are also predictors of GDM. The investigator proposes to determine the effect of parity and inflammatory markers on prevalent and incident cases of Type 2 DM through cross-sectional and case-cohort analyses of the NHANES III and ARIC data, respectively. In addition, a prospective case-cohort study will assess inflammatory markers as risk predictors of GDM. This proposal will provide an in-depth examination of the role of parity and inflammatory markers in the pathogenesis of GDM and Type 2 DM. During this award, the investigator will gain new skills and knowledge in the research methods for prospective study design, multivariate assessment of risk factors and longitudinal data analysis. The combination of observational research, primary data collection and advanced educational training will provide the basis for further prospective studies integrating the relation of parity and inflammation to GDM and Type 2 DM. This award will give the researcher the dedicated time and experience needed to develop into an independent clinical investigator.

TITLE: **Estrogen Effects in Insulin Target and Granulosa Cells** **NIDDK**
P.I.: **Jerrold Olefsky, M.D.**
INSTITUTION: **University of California, San Diego**
GRANT NO.: **1 R01 DK068606-01**
KEYWORDS: **Estrogen, estrogen receptors, TNF-alpha, insulin resistance, osteoporosis, diabetes, obesity**
STUDY TYPE: **Basic**
AWARD: **$100,000**

High fat intake is a major environmental factor leading to decreased insulin sensitivity contributing to the rising incidence of interrelated insulin resistant diseases such as Syndrome X, PCOS, Type 2 diabetes mellitus, and obesity. Their investigators have demonstrated that estrogenized women and female rodents are protected from fat-induced insulin resistance, whereas, males, and estrogen deficient females are fully susceptible to these adverse effects of fat. In this application, the investigators plan a broad based, *in vivo* and *in vitro* approach to elucidate the mechanisms of fat-induced insulin resistance and the protective effects of estrogens, using various novel animal model systems, 3T3-L1 adipocytes *in vitro*, and the non-classical insulin target tissue ovarian granulose cells (GCs). An underlying hypothesis in this application is that excess fat metabolism due to elevated FFA levels, or high fat diets, leads to activation of the "inflammatory pathway" and that specific serine/ threonine kinases in this pathway such as PKC theta, IKK beta, or JNK, or genes induced as a result of NfkappaB activation, feedback on the insulin signaling system to cause insulin resistance. Preliminary data show that treatment of 3T3-LI adipocytes *in vitro* with FFAs leads to a marked state of cellular insulin resistance, and the investigator will exploit this novel system to conduct new studies aimed at elucidating the molecular mechanisms of FFA induced insulin resistance and estrogen's protection against these effects. Finally, since the investigators

hypothesize that GCs from insulin resistant animals and women (particularly PCOS) can be insulin/IGF-I resistant with functional consequences, they propose an extensive series of studies in GCs prepared from normal rats and insulin resistant rodents, to determine whether FFA treatment causes insulin resistance in these cells, as it does in insulin target cells, and to identify the underlying mechanisms. The investigators will also study the basic signaling systems for insulin, IGF-I and FSH in these cells. Taken together the results of these studies should greatly enhance understanding of the mechanisms of fat-induced insulin resistance, in classic and non-classic insulin target tissues, and also elucidate the mechanisms underlying the protective effects of estrogens. These studies should also highlight the role of inflammatory pathway activation in these pathophysiologic events and this may have potential therapeutic implications for new treatment approaches.

TITLE: **Diabetes Prevention Program Outcomes Study(DPPOS)** **NIDDK**
P.I.: **Sarah Fowler, PhD**
INSTITUTION: **George Washington University**
GRANT NO.: **5 U01 DK048489-11**
KEYWORDS: **diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, prevention, cardiovascular disease**
TYPE STUDY: **Clinical**
AWARD: **$300,000**

While the primary goal of the Diabetes Prevention Program (DPP) was to prevent the development of diabetes, an important secondary goal was to decrease the rate of cardiovascular disease and its risk factors. These clinically important outcomes were considered as secondary during the DPP due to a lack of sufficient power in the time allotted to the study to detect potential differences between the treatment groups (ongoing analyses of the DPP data suggest that there are significant differences between the groups with regard to some CVD risk factors). Following the early conclusion of the DPP, the lifestyle and metformin arms were kept on their study interventions. Due to the marked effect of lifestyle in preventing or delaying type 2 diabetes, placebo and metformin participants were also offered the same lifestyle 16 session curriculum provided to the intensive lifestyle group during what was named the 'bridge period.' The DPP cohort being followed in the DPPOS, is the largest study population with pre-diabetes, and the only population with Type 2 diabetes studied from time of onset. The study cohort will provide insights regarding the clinical course of these metabolic disorders and will provide information on the persistence of the prevention or delay of type 2 diabetes. In addition, the DPP is the longest follow-up study of sustained weight loss ever conducted. Of major interest is the outcome of continued lifestyle and long term weight loss, and metformin intervention in the gender specific and minority sub-groups during the DPPOS.

GASTROENTEROLOGY

TITLE: **Improving IBS Outcomes** **NINR**
P.I.: **Margaret M. Heitkemper, PhD**
INSTITUTION: **University of Washington, Seattle, WA**
GRANT NO.: **5 R01 NR04142-07**
KEYWORDS: **irritable bowel syndrome (IBS), polymorphisms, gender, serotonin, behavioral & social science, digestive disease, chronic pain conditions**
TYPE STUDY: **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, Ph.D.**
INSTITUTION: **RAND Corporation, Santa Monica, California**
GRANT NO.: **1 U01 DK 070234-01**
KEYWORDS: **urinary frequency, bladder pain, patient screening, survey research, quality of life, endometriosis, interstitial cystitis, chronic pain conditions, urologic disease**
TYPE STUDY: **Epidemiological**
AWARD: **$350,000**

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: **Risk Factors for Decline in Renal Function** **NIDDK**
P.I.: **Gary Curhan, M.D.**
INSTITUTION: **Channing Laboratory**
GRANT NO.: **1 R01 DK066574-01A1**
KEYWORDS: **Chronic renal failure, analgesic, disease risk, epidemiology, cardiovascular, genetics, hypertension, kidney disease, prevention**
STUDY TYPE: **Clinical**
AWARD: **$100,000**

Renal failure is a life-threatening and costly medical condition. End-stage renal disease, defined as severe renal dysfunction requiring chronic dialysis or kidney transplantation, is increasing in prevalence and has an annual mortality rate exceeding 20%. Less severe loss of renal function also has important health consequences. Mild to moderate reductions in renal function and microalbuminuria are important predictors of cardiovascular disease and death, in high-risk groups as well as in the general population. The risk of adverse outcomes increases with decreasing renal function. Even in the absence of known risk factors for renal function decline, such as hypertension or diabetes, kidney dysfunction may develop slowly over decades. Slowing or preventing decline in renal function may favorably impact morbidity and mortality. Genetic factors, biological processes (such as inflammation) and environmental factors (such as analgesic use) may contribute to renal function decline. Heightened activity of the renin-angiotensin system (RAS), particularly of angiotensin II, is an important mediator of renal pathophysiology. Thus, genes related

to the RAS system may have important long-term effects on renal function. Chronic inflammation may adversely affect the kidney by causing vascular disease and fibrosis. Analgesics are the most commonly used drugs in the US, and chronic analgesic use may be an important, preventable cause of renal dysfunction. The primary objective of this study is to examine prospective risk factors for renal function decline, defined as decline in estimated glomerular filtration rate (using serum creatinine) and development of microalbuminuria, among 5000 participants in two large female cohorts: the Nurses' Health Study I (NHS I) and the Nurses' Health Study II (NHS II). Stored and newly collected blood and urine specimens will permit repeated measurements of renal function and urine albumin and will allow us to examine changes over a period of 19 years in NHS I and 11 years in NHS II. Mixed-effects regression will be used to analyze the slope of renal function in the exposed and unexposed groups during the long-term follow-up. This study will provide: 1) prospective data on risk factors for renal function decline; 2) threshold levels of safe cumulative dose of individual classes of analgesics; 3) population-based incidence rates of renal dysfunction and rate of renal function decline in younger and older women; and 4) an important resource for future long-term studies of renal function decline.

TITLE: **The Function of the Urethera in Continent Women** **NICHD**
P.I.: **Kimberly Kenton, M.D.**
INSTITUTION: **Loyola University of Chicago**
GRANT NO.: **1 K23 HD047325-01A1**
KEYWORDS: **Career development and training, patient-oriented research, clinical trials, urologic disorders, urethral function, and urinary incontinence, prevention, urologic disease**
STUDY TYPE: **Clinical**
AWARD: **$97,054**

This application requests funds for two purposes: career development and research. The applicant plans to obtain a Master of Science in Clinical Research Design and Statistical Analysis from the University of Michigan. The career goals include short and long-term goals. Short-term goals include the obtaining the Master's degree and beginning an innovative well-designed patient-oriented research project under the mentorship of a highly productive clinical researcher. The long-term goals include developing into an independent patient-oriented researcher with expertise in electrodiagnosis and urethral function, enhancing research abilities with a better understanding of methodology and design designing follow-up studies to prevent and treat neuromuscular injuries to the urethral sphincter, submission of an RO1 to fund such studies, and developing research mentoring skills to begin training the next generation of patient-oriented clinical researchers. The specific aims of the research plan are: 1. To acquire high-quality neuromuscular signals from the urethra using concentric needle EMG (with quantitative motor unit analysis) and current perception threshold testing to test the null hypothesis that there are no differences in urethral neuromuscular function in: a: Caucasian and African American women; b: Continent and stress incontinent women; and c: Continent nulliparous and parous women. 2. To establish quantitative parameters of urethral sphincter function in women of various races. Normative ranges will be calculated for EMG, current perception thresholds, and urethral pressures for Caucasian and African American women. These data can then be used by other centers as reference data.

TITLE: **Weight Reduction for Incontinence Network (WIN)** **NIDDK**
P.I.: **Deborah G. Grady, MD, (Rena Wing, Ph.D., Frank Franklin, Ph.D.)**
INSTITUTION: **University of California, San Francisco, CA, Miriam Hospital, Providence, R.I. and University of Alabama, Birmingham**
GRANT NO.: **5 U01 DK67860-02, DK067861-02, DKDK067862-02**
KEYWORDS: **urinary incontinence, obesity, behavior, quality of life, urologic disease, behavioral & social science**
TYPE STUDY: **Clinical**
AWARD: **$250,000**

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.

HIV/ AIDS

TITLE: **Impact of Delivery Models in HIV Health Care** **FIC**
P.I.: **Ximena L. Burbano, MD**
INSTITUTION: **Fundacion Santa, Bogota**
GRANT NO.: **5 R01 TW006218-02**
KEYWORDS: **HIV/AIDS, health services research, prevention, infectious diseases**
TYPE STUDY: **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, MD**
INSTITUTION: **University of Nairobi, Kenya**
GRANT NO.: **5 R01 TW006640-02**
KEYWORDS: **HIV/AIDS, postpartum, counseling, prevention, topical microbicides**
TYPE STUDY: **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, MD**
INSTITUTION: **University of California, School of Public Health, Berkeley, CA**
GRANT NO.: **3 D43 TW000003-05**
KEYWORDS: **training, virology, HIV/AIDS, infectious diseases**
TYPE STUDY: **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, MD**
INSTITUTION: **Well Medical College of Cornell University, Dept. of Medicine, New York, NY**
GRANT NO.: **3 D43 TW000018-16S5**
KEYWORDS: **infectious diseases, epidemiology, biosocial, HIV/AIDS, treatment and prevention, rural health**
TYPE STUDY: **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, MD, 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, MD, PhD**
INSTITUTION: **University of Washington, College of Medicine, Seattle, WA**
GRANT NO.: **5 D43 TW000007-17**
KEYWORDS: **HIV/AIDS, international, prevention, treatment, immunology, infectious diseases, vaccine development**
TYPE STUDY: **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.

IMMUNITY/AUTOIMMUNITY

TITLE: **Innate and Adaptive Regulatory T cells (Treg) in Immune Tolerization of RA** **NIAID**
P.I.: **Salvatore Albani, M.D., Ph.D.**
INSTITUTION: **University of California, San Diego**
GRANT NO.: **1 R21 AI059957-01**
KEYWORDS: **Autoimmune, rheumatoid arthritis, regulatory T cells**
STUDY TYPE: **Clinical**
AWARD: **$230,375**

It has been suggested that two categories of Treg can be identified by phenotypical and functional characteristics. "Innate" and "adaptive" Treg would cooperate in limiting potentially noxious inflammatory processes. This regulatory function may be impaired in autoimmunity. Its restoration could provide novel therapeutic approaches. This project aims to unravel the role which may pertain to Treg function in induction of tolerance to an antigenic peptide (dnaJP1) in rheumatoid arthritis (RA). One hundred five samples from RA patients treated in the context of a Phase I (completed) and a Phase II (ongoing) clinical trial with dnaJP1 or placebo have already been collected at the beginning of treatment and at monthly intervals. The investigators will test whether mucosal tolerization to a peptide is associated with emergence of cells with a regulatory phenotype. They will also determine if a proportion of Treg are dnaJP1-specific, and if numbers and functional characteristics of these cells change as a consequence of immunotherapy. The specific aims are: Specific Aim 1: To characterize "innate" and "adaptive" Treg in serial samples obtained from a tolerization trial in rheumatoid arthritis and to explore their functional role in the tolerization process. SA1a: Peripheral blood mononuclear cells (PBMC), synovial fluid mononuclear cells (SFMC) and T cells obtained from synovial membranes of RA patients will be evaluated by FACS analysis for phenotypical markers characteristic of T regulatory T cells. In particular, levels of CD25, CD4, CTLA4 and CCR4 will be studied. "Innate" and "adaptive" T cells will be differentiated based an a set of phenotypical and functional variables, including levels of CD25 expression and quantification on sorted cells by real time PCR (TaqMan) gene expression of several molecules putatively involved in Treg function. These genes will include IL-10, TGF beta, IL-4, FOXP3, CTLA. Samples obtained will be also tested in *in vitro* studies to explore regulatory properties of "innate" and "adaptive" Treg on T cell responses to recall antigens as well as to antigens (gp39, dnaJPl and p205) putatively involved in the pathogenic process. Specific Aim 1b: Clinical information will be compared with immunological data. Specific Aim 2: To investigate whether some Treg have specificity for dnaJpl and whether functional and phenotypical characteristics of dnaJP1-specific Treg are associated with the course of the tolerization process. Functional characteristics of sorted cells will be evaluated by TaqMan.

TITLE: **Mitochondrial Dysfunction in Patients with SLE** **NIAID**
P.I.: **Andras, Perl, M.D., Ph.D.**
INSTITUTION: **SUNY Upstate Medical University**
GRANT NO.: **1 R01 AI061066-01**
KEYWORDS: **Autoimmune, lupus, rheumatoid arthritis**
STUDY TYPE: **Basic/Clinical**
AWARD **$152,000**

Abnormal T cell activation and cell death underlie the pathology of systemic lupus erythematosus (SLE). Immune responses resulting in activation, proliferation, or programmed cell death are dependent on controlled production of reactive oxygen intermediates (ROI) and ATP in mitochondria. In turn, synthesis of ATP and containment of cell death-inducing factors within the mitochondria are dependent on the mitochondrial transmembrane potent which is subject to regulation by oxidation-reduction equilibrium of ROI, pyridine nucleotides (NADH/NAD + NADPH/NADP) and GSH levels. Mitochondrial hyper-polarization and transient ATP depletion have been identified in the investigators laboratory as early and reversible steps in normal T cell activation and apoptosis. By contrast, T lymphocytes of patients with SLE exhibit persistent mitochondrial hyperpolarization, cytoplasmic alkalinization, increased ROT production, as well as diminished levels of intracellular glutathione and ATP. Oxidative stress affects expression and signaling through the T-cell receptor, cell death receptors, and CD38 as well as activity of redox-sensitive caspases and transcription factors mediating lymphokine production. Mitochondrial

dysfunction leading to ATP depletion may be ultimately responsible for diminished activation-induced apoptosis and sensitize lupus T cells to necrosis. The investigators recently discovered that T cell activation-induced mitochondrial hyperpolarization is mediated by Ca2+- and ROI-dependent production of nitric oxide (NO). This proposal is focused on understanding the mechanism of persistent mitochondrial hyperpolarization in lupus T cells. Specific Aim 1 will further characterize the role of mitochondrial signal processing, with an emphasis on production of NO and ROI, cytoplasmic alkalinization, and Ca fluxes with respect to aberrant T cell activation and cell death in patients with lupus and healthy and rheumatoid arthritis controls. Specific Aim 2 will assess functioning of isolated mitochondria and metabolic pathways connected to regulation, production, and synthesis of ATP and pyridine nucleotides. Specific Aim 3 will assess coordinate changes in gene expression involved in T-cell activation, apoptosis, and metabolism to delineate pathways contributing to or affected by mitochondrial hyperpolarization in SLE. Specific Aim 4 will systematically validate signaling pathways located upstream and downstream of mitochondrial hyperpolarization and identify signals capable of normalizing mitochondrial dysfunction in lupus T cells. Thus, checkpoints of mitochondrial hyperpolarization could represent novel targets of pharmacological intervention in patients with SLE.

TITLE: **Sex-based Differences in Anti-viral Immunity and SLE** **NIAID**
P.I.: **Sally R. Sarawar, PhD**
INSTITUTION: **LaJolla Institute**
GRANT NO.: **5 R21 AI51862-04**
KEYWORDS: **Lupus, autoimmunity, EBV, animal research, genetics**
TYPE STUDY: **Basic**
AWARD: **$50,000**

SLE is a prevalent autoimmune disease with a significantly higher SLE is a prevalent autoimmune disease with a significantly higher incidence in females than in males. Studies on the etiology of SLE indicate that both genetic and environmental factors influence disease penetrance. A strong correlation between SLE and previous infection with Epstein Barr virus (EBV), but not with other viruses has been reported. However, some studies have failed to find evidence of a viral etiology for SLE. This may be due to the high prevalence of EBV infection, unknown host/virus parameters, and the fact that multiple genetic loci control susceptibility to SLE. New Zealand mice are susceptible to SLE, and genetic loci that control disease susceptibility in these mice has been identified. C57/BL6 congenic mouse strains carrying one or more of three of the susceptibility loci designated SLE 1, 2, and 3 have been generated. It has been shown that the presence of at least two loci is necessary for high disease penetrance. We propose that a mouse viral homologue of EBV could substitute for the presence of a second locus, and could trigger disease in mice congenic for a single locus. We also suggest that this effect may differ in males and females, due, in part, to the more vigorous response to infection in the latter. We have a mouse model of gammaherpesvirus infection, which closely resembles EBV infection in humans and, like EBV, is able to induce non-specific B cell activation and autoantibody production, but does not induce overt autoimmune disease in C57BL/6 mice. In the present study, we will determine whether there are sex-based differences in the immune response to MHV-68 infection. We will determine whether infection of susceptible mice, bearing one or more SLE susceptibility locus, with MHV-68 can induce or exacerbate autoimmune disease and whether this effect differs in male and female mice. We will also determine whether there are genes whose expression is similarly modified by the presence of disease loci and the viral infection and whether their expression correlates with the induction of autoimmune disease.

TITLE: **Mechanism Regulating Neutrophil Activation in Pregnancy** **NIAID**
P.I.: **Howard R. Petty, PhD**
INSTITUTION: **Wayne State University**
GRANT NO.: **5 R01 AI51789-04**
KEYWORDS: **autoimmunity, rheumatoid arthritis, pregnancy**
TYPE STUDY: **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, MD**
INSTITUTION: **Albert Einstein College of Medicine**
GRANT NO.: **5 R01 AI51767-03**
KEYWORDS: **autoimmunity, hormones, animal models, estrogen**
TYPE STUDY: **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, MD**
INSTITUTION: **Hospital for Special Surgery, New York, NY**
GRANT NO.: **5 R01 AR049772-02**
KEYWORDS: **thrombosis, pregnancy loss, systemic lupus erythematosus, antiphospholipid antibodies, genetic polymorphisms, recurrent fetal loss, poor fetal outcome, placentas, autoimmune diseases, genetics, prevention**
TYPE STUDY: **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, MD**
INSTITUTION: **John Hopkins University, MD**
GRANT NO.: **5 R01 AR49125-03**
KEYWORDS: **Systemic Lupus Erythematosus, cognitive dysfunction, basic behavioral, behavioral & social science, brain disorders, depression, fibromyalgia, mental health**
TYPE STUDY: **Clinical**
AWARD: **$80,000**

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: **Identifying Genes for Neuropsychiatric Lupus** **NIAMS**
P.I.: **Nilamadhab Mishra, MD**
INSTITUTION: **Wake Forest University, NC**
GRANT NO.: **5 R21 AR49153-03**
KEYWORDS: **systemic lupus erythematosus, gene expression, cerebellum, hippocampus, immunopathology, autoantibody, autoimmune disorder, cytokine, histopathology, messenger RNA, basic behavioral, behavioral & social science, brain disorders**
TYPE STUDY: **Basic**
AWARD: **$40,000**

In brief, this project will examine the genes responsible for neurologic disturbances in murine models of SLE by microarray analysis. Systemic lupus erythematosus (SLE) is a chronic, idiopathic autoimmune disease characterized by episodic flares and progression of disease, substantial morbidity and mortality. It is a multisystern rheumatic disease with a wide variety of associated clinical neurological and psychiatric syndromes including cognitive, behavioral, affective, and/or

motor manifestations that may effect up to 75 percent of SLE patients. Both morbidity and mortality remain high because of lack of understanding of the underlying mechanisms related to abnormal central nervous system (CNS) function. Although the gene responsible for neurological disturbances in SLE is not finely dissected out, preliminary studies in mouse models of lupus suggests aberrant cytokine gene expression in hippocampus and cerebellum are responsible for the neurological deficit.

TITLE: **Antibodies to NR2 in SLE** **NIAMS**
P.I.: **Betty Diamond, MD**
INSTITUTION: **Yeshiva University, NY**
GRANT NO.: **5 R01 AR49126-03**
KEYWORDS: **NMDA receptor, antibody, cognition disorder, systemic lupus erythematosus, glutamate receptor, inhibitor/antagonist, human tissue, brain disorders**
TYPE STUDY: **Clinical**
AWARD: **$60,000**

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: **Brain Cell Death in MRL Mice: Targets and Mechanisms** **NIAMS**
P.I.: **Boris Sakic, PhD**
INSTITUTION: **McMaster University, Ontario Canada**
GRANT NO.: **5 R21 AR49163-03**
KEYWORDS: **Systemic Lupus Erythematosus, brain cell death, autoimmune disease, basic behavioral, behavioral & social science, brain disorders, prevention**
TYPE STUDY: **Basic**
AWARD: **$20,000**

This research will elucidate pathogenic mechanisms of neuropsychiatric systemic lupus erythematosus by studying neuroimmunologic disease in autoimmune MIRL-lpr mice. Lymphoid cell infiltration into the choroid plexus, neuronal atrophy, CSF neurotoxicity and an anxiety/depressive behavioral state in MRL-lpr mice suggest that cytotoxic cells and metabolites in the CSF accelerate apoptosis in limbic regions, thus accounting for altered performance in tasks reflective of emotional reactivity and motivation. The project aims to examine: 1. Whether DNA fragmentation involves neurons, glial and/or endothelial cells (will be achieved by combining immunofluorescence with TUNEL staining). 2. Whether population of periventricular brain stem cells is susceptible to neurotoxic effects of CSIF (will be achieved by culturing neurospheres and assessing the effects of incubation with CSF from MRL-lpr mice). 3. Whether brain cell death involves apoptotic pathways (will be achieved by examining nuclear morphology with electron microscopy, by detecting DNA laddering with chemilumnescent method and caspase activation with immunohistochemistry). 4. Whether immunosuppression prevents neurodegeneration and CSF neurotoxocity.

TITLE: **Virginia Mason/UCHSC Autoimmune Center** **NIAID**
P.I.: **George S. Eisenbarth, MD**
INSTITUTION: **University of Colorado, Denver, CO**
GRANT NO.: **5 U19 AI50864-04**
KEYWORDS: **autoimmunity, diabetes, Rheumatoid Arthritis, genetics, prevention**
TYPE STUDY: **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, MD**
INSTITUTION: **Scripps Research Institute, La Jolla, CA**
GRANT NO.: **5 U19 AI51973-04**
KEYWORDS: **autoimmunity, diabetes, autoimmune disease CD antigen, CD40 molecule, antibody inhibitor, antigen antibody reaction, autoimmune disorder, cooperative study, disease /disorder prevention /control, immunotherapy**
TYPE STUDY: **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, MD**
INSTITUTION: **Oklahoma Medical Research Foundation, Oklahoma, OK**
GRANT NO.: **5 R01 AR48045-04**
KEYWORDS: **Scleroderma, immune response, autoimmunity, autoimmune disease, Raynaud's disease, autoantibody, scleroderma, ribonucleoprotein, immunodiffusion, western blotting**
TYPE STUDY: **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**
INSTITUTION: **University of Connecticut, Farmington, CT**
GRANT NO.: **5 R01 AR48082-04**
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**
TYPE STUDY: **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 micorarray 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, MD**
INSTITUTION: **Oklahoma Medical Research Foundation**
GRANT NO.: **5 R01 AI31584-11**
KEYWORDS: **Systemic Lupus Erythematosus, Epstein-Barr virus, Epstein Barr virus, systemic lupus erythematosus, B lymphocyte, autoimmune disorder, cytomegalovirus**
TYPE STUDY: **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-I (EBNAI), which contains a peptide sequence that inhibits antigen presentation and class I HLA-dependent cytotoxic T cell responses. Preliminary data show that EBNA-I 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-I humoral immune response, of EBNA-I expression in B cells, and of EBNA-I sequence variants. We plan to use the Early-Immediate antigen-I (EI-I) 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-I 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: **Registry and Repository of African Americans with Rheumatoid Arthritis** **NIAMS**
P.I.: **Larry Moreland, MD**
INSTITUTION: **University of Alabama at Birmingham, Birmingham, AL**
GRANT NO.: **1 N01 AR002247-000**

KEYWORDS: **African American, Rheumatoid Arthritis, autoimmunity, autoimmune disease, genetics, minority health**
TYPE STUDY: **Clinical**
AWARD: **$200,000**

This 5 year project will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis and establish a registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3 years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast U.S. will gather data, which will provide a resource for investigators interested in the genetics of RA in AA. The CLEAR registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor- alpha [TNF-alpha]/lymphotoxin (LT)- alpha, interleukin-1 (IL-1), and IL-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3 years disease duration in AA.

TITLE: **UCSF Autoimmunity Center of Excellence** **NIAID**
P.I.: **David Wofsy, MD**
INSTITUTION: **University of California, San Francisco, CA**
GRANT NO.: **5 U19 Ai056388-02**
KEYWORDS: **immunology, molecular biology, autoimmune diseases, clinical trials, immunotherapies, murine lupus, lupus nephritis, diabetes, multiple sclerosis, prevention, urologic disease**
TYPE STUDY: **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** **NIAID**
P.I.: **Samia J. Khoury, MD**
INSTITUTION: **Brigham and Women's Hospital**
GRANT NO.: **5 U19 AI046130-06**
KEYWORDS: **autoimmune disease, prevention, autoimmune disorder, immunotherapy, clinical research**
TYPE STUDY: **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** **NIAID**
P.I.: **Ignacio Sanz, MD**
INSTITUTION: **University of Rochester**
GRANT NO.: **5 U19 AI056390-02**
KEYWORDS: **Diabetes Mellitus, Multiple Sclerosis, Systemic Lupus Erythematosus, autoimmune diseases, pathogenesis, disease-specific autoantibodies**
TYPE STUDY: **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** **NIAID**
P.I.: **Eugene W. St, Clair, MD**
INSTITUTION: **Duke University**
GRANT NO.: **5 U19 AI056363-02**
KEYWORDS: **B cell responses, immunotherapy, autoimmune diseases, lupus, arthritis**
TYPE STUDY: **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 a (TNFa), 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 TNFa 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-TNFa) 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** **NIAID**
P.I.: **Robert H. Carter, MD**
INSTITUTION: **University of Alabama at Birmingham**
GRANT NO.: **5 U19 AI056542-02**
KEYWORDS: **translational therapies, immunology, autoimmune diseases, autoimmune disorder, autoimmunity, cooperative study, clinical research**
TYPE STUDY: **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, MD**
INSTITUTION: **UCSF/ VAMC, Dept. of Medicine, San Francisco, CA**
GRANT NO.: **5 R03 EY014962-02**
KEYWORDS: **graves' disease, hyperthyroidism, autoantibodies, ophthalmopathy, animal model, autoimmune disease exophthalmic goiter, eye disorder, hormone receptor, hormone regulation /control mechanism, hyperthyroidism, thyrotropin**
TYPE STUDY: **Basic**
AWARD: **$126,000**

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'-like animal model to investigate critical issues of Graves' disease as is Graves' ophthalmopathy as follows: 1. Graves' ophthalmopathy in the Graves'-like 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: **Sex in Viral Myocarditis** **NIAID**
P.I.: **Sally A. Huber, PhD**
INSTITUTION: **University of Vermont**
GRANT NO.: **5 R21 AI51850-03**
KEYWORDS: **autoimmunity, myocarditis, hormones, host defense responses, autoimmune disease, infectious diseases**
TYPE STUDY: **Translational**
AWARD: **$50,000**

Myocarditis is an inflammatory disease of the myocardium. Approximately 65% of cases follow recent enterovirus infections and occur in males. As in humans, CVB3 infections cause severe myocarditis in male, but not virgin female mice. Androgens (progesterone and testosterone) increase virus receptor expression on cardiac myocytes while 17-beta-estradiol treatment does not. Since lymphocytes also express CVB3 receptors, we hypothesize that hormones might modulate lymphocyte expression of these molecules as well. Cytokine release differs between male and female lymphocytes with male cells producing interferon (IFN)gamma and female cells producing interleukin (IL)-10. We hypothesize that viruses, which have repetitive symmetry of the virus capsid, cross-link important cell surface molecules on lymphocytes and cause rapid non-antigen-specific lymphocyte activation. These studies may provide new insights as to how viruses affect developing host defense responses and how hormones can modulate this initial response.

TITLE: **Seroprevalience/Incidence of Genital Herpes** **FIC**
P.I.: **Edith Nakku-Joloba**
INSTITUTION: **New Mulago Hospital, Uganda**

GRANT NO.: **5 R01 TW006672-02**
KEYWORDS: **herpes, epidemiology, infectious diseases, prevention, rural health, vaccine related**
TYPE STUDY: **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.

MENOPAUSE

TITLE: **Effects of Botanicals on Cognition in Midlife Women** **NCCAM**
P.I.: **Pauline Maki, Ph.D.**
INSTITUTION: **University of Illinois at Chicago**
GRANT NO.: **1 R21 AT001868-01A1**
KEYWORDS: **Lifespan, menopausal transition and postmenopausal years, interdisciplinary, CAM, estrogen**
STUDY TYPE: **Basic/Clinical**
AWARD: **$194,837**

The broad, long-term objective of this program of research is to better understand the effects of hormone therapy (HT) and alternative botanical supplements on cognition and brain functioning in early postmenopausal women. The specific aims of this research project are to quantify and compare the effects of the botanical menopausal treatments, black cohosh and red clover, and standard HT, Prempro® (conjugated equine estrogen plus medroxyprogesterone acetate), on neuropsychological and neuroimaging outcomes. The proposed design is a randomized, double-blind, placebo-controlled clinical trial. The cognitive study is conducted as an ancillary study to the NIH-funded study, *A Phase II, Randomized, Double -Blind, Placebo-Controlled Study to Determine the Efficacy of Black Cohosh, Red Clover and Prempro in the Management of Hot Flashes.* Participants will include up to 28 women in each study arm - placebo, Prempro®, black cohosh, and red clover - for a total of up to 112. The primary outcome measures will be scores on standardized neuropsychological tests and patterns of brain activation during performance of verbal memory tests. Before treatment and at the end of the 12-month treatment period, participants will complete a 1.5-hour battery of neuropsychological tests that have been shown in previous studies to be sensitive to the effects of HT and menopausal symptoms. Half of the participants (n = 60) will also complete neuroimaging assessments using functional magnetic resonance imaging (fMRI) before and after the 12-month treatment period. The tasks performed in

the MRI scanner will be verbal and figural memory tasks shown to be sensitive to HT in midlife women. Findings of group differences in the patterns of brain activation (i.e., regional blood flow changes) will point to the brain areas subserving any treatment-related improvements in memory performance. Recent findings of significant health risks associated with Prempro® heighten the need for research into the effects of alternative therapies for menopausal symptoms on cognitive outcomes.

TITLE: **The Study of Women's Health Across the Nation (SWAN III)** **NIA**
P.I.: **Kim Sutton-Tyrrell**
INSTITUTION: **University of Pittsburgh**
GRANT NO.: **U01 AG012553**
KEYWORDS: **Aging, hormones, menopause, minorities, reproductive aging, risk factors, CAM, diabetes, hypertension, kidney-incontinence, behavioral & social science, cardiovascular**
TYPE STUDY: **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 followup. 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, MD**
INSTITUTION: **University of Southern California, Dept. of Medicine, Los Angeles, CA**
GRANT NO.: **5 U01 AT001653-02**
KEYWORDS: **hormone therapy, soy protein, isoflavine-rich soy protein, postmenopausal women, atherosclerosis, common carotid artery, estrogen, cancer, cardiovascular, CAM**
TYPE STUDY: **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.

MENTAL HEALTH

TITLE: **Evidence-based Practice Report on Eating Disorders** **AHRQ**
P.I.: **Kathryn Lohr, Ph.D.**
INSTITUTION: **Research Triangle Institute – University of North Carolina,**
GRANT NO.:
KEYWORDS: **Eating disorders, sex, gender analysis, mental health**
STUDY TYPE: **Policy Analysis**
AWARD: **$250,000**

Eating Disorders primarily affect young girls and women, but can affect males so sex and gender-based differences will be evaluated in this report. In terms of major areas of focus for this report, three types of eating disorders will be evaluated: bulimia nervosa, anorexia nervosa and binge eating. Evidence will be reviewed relating to whether one type of treatment or combination of treatment modalities is more effective for these disorders. Identification of predictors of increased relapse risk or hospital readmission will be assessed, and what variables improve both short and long-term patient outcomes.

TITLE: **Estrogen Influences on Neural Precursor Cell Development** **NIMH**
P.I.: **C Dominique Toran-Allerand, M.D., ScD**
INSTITUTION: **Columbia University, College of Physicians and Surgeons**
GRANT NO.: **1 R21 MH071381-01**
KEYWORDS: **Estrogen, cognition, depression, mood disorders, aging, Alzheimer's disease, neurobiology, brain, receptors, drug target, mental health, neurodegenerative**
STUDY TYPE: **Basic**
AWARD: **$222,179**

The proposed studies are designed to obtain preliminary data concerning the actions of estrogen on the development of progenitor cells of the adult rat hippocampal dentate gyrus. 17β-estradiol reportedly enhances granule cell neurogenesis (the formation of new neurons) in the adult female rat hippocampal dentate gyrus. The cellular mechanisms and estrogen receptor(s) mediating this hormonal action are not known. The investigators have shown that 17β -estradiol and its transcriptionally inactive, natural stereoisomer 17a -estradiol elicit rapid and transient activation of the mitogen-activated protein kinase and phosphatidylinositol 3"-kinase-Akt signaling pathways in postnatal rodent neocortical cultures and neural progenitor cells of the adult rat hippocampal dentate gyrus. These responses appear to be mediated by a putative estrogen receptor (ER), "ER-X", which is distinct from the intranuclear estrogen receptors ER-a and ER- β. "ER-X" is plasma membrane associated and developmentally regulated and returns following ischemic brain injury. Progenitor cells of the adult rat hippocampal gyrus are enriched in "ER-X" protein and lack ER-a and ER-fl mRNA and protein. The investigators propose a series of integrated and complimentary cell biological and biochemical analyses to compare the actions of 17a - and 17β-estradiol on the

development of progenitor cells. They hypothesize that "ER-X" and 17a-estradiol, its preferred ligand, play an important role in the development and remodeling of the hippocampus. This hypothesis will be tested by focusing on the effectiveness of 17a -estradiol in comparison with 17β-estradiol with respect to (i) neurogenesis, (ii) neuronal differentiation, and (iii) the intracellular signaling pathways that mediate these actions. The expression of "ER-X" in the adult hippocampal dentate gyrus suggests that its developmental role could be reactivated to enhance functional hippocampal remodeling in the course of disorders of cognition, mood, and affect, such as major depression and bipolar disorder, conditions that may be associated with estrogen, since they are more frequent in females. Unlike 17β-estradiol, 17a-estradiol has little affinity for ER-a or ER-β and may be more effective and therapeutically safer. The results of these experiments will enable drug development and treatment of children and adults of both sexes without fear of undesirable effects mediated by ER-a or ER-β.

TITLE: **Brain LC-PUFAs and Maternal Mental Health** **NIMH**
P.I.: **Beth Levant, Ph.D.**
INSTITUTION: **University of Kansas Medical Center**
GRANT NO.: **1 R01 MH71599-01**
KEYWORDS: **Long chain polyunsaturated fatty acid, docosahexaenoic acid, depression, psychosis, brain DHA, pregnancy and lactation, basic behavioral, mental health**
STUDY TYPE: **Basic**
AWARD: **$243,827**

Alterations in brain long chain polyunsaturated fatty acid (LC-PUFA) composition, particularly decreased docosahexaenoic acid (DHA), are implicated as a contributing factor in depression and psychosis. Preliminary data indicates that pregnancy and lactation can deplete the maternal brain of DHA. Accordingly, these studies are designed to test the hypothesis that depletion of maternal brain DHA during pregnancy and lactation contributes to postpartum mental illness. The Specific Aims will use a rat model to: 1. Determine the effects of pregnancy and lactation on levels of maternal brain DHA and other LC-PUFA. Manipulation of dietary fatty acid content will be used to alter maternal brain DHA levels. LC-PUFA will be assessed in four brain regions associated with depression and psychosis, as well as in erythrocytes. These studies will establish a rodent model with which to study the effects of depleted brain DHA levels following pregnancy and lactation on neurochemical parameters associated with depression and psychosis in humans. 2. Determine the effects of reduced brain DHA in the postpartum period on maternal hypothalamic-pituitary-adrenal (HPA) axis activity and regulation. Regulation of the HPA axis will be assessed using a modification of the dexamethasone suppression test. The affinity and density of cerebral cortical corticotrophin releasing factor1 (CRF1) receptors will also be quantified. 3. Determine the effects of reduced brain DHA in the postpartum period on monoamine neurochemistry. The concentrations of serotonin, norepinephrine, and dopamine (and their respective metabolites) will be measured in brain regions relevant to depression or psychosis. The affinity and density of receptors most strongly implicated in depression or psychosis (5-HT1A, 5-TH2A, p, D2, and D_) will also be quantified. 4. Determine the effects of reduced brain DHA in the postpartum period on expression of brain-derived neurotrophic factor (BDNF) in hippocampus. Hippocampal expression of the BDNF gene, which is decreased in animal models of depression, will be measured by RNAse protectionassay. These experiments will determine whether reproductive activity and the resulting alterations in maternal brain LC-PUFA content are likely to contribute to postpartum mental illness in women. Findings will point to causes of postpartum mental illness and thus the identification of women at risk and the elimination of risk factors. These findings will also suggest novel treatments for such illnesses when they occur.

TITLE: **Health Survey of Two-Spirited Native Americans** **NIMH**
P.I.: **Karina L. Walters, PhD**
INSTITUTION: **University of Washington, Seattle, WA**
GRANT NO.: **5 R01 MH65871-03**
KEYWORDS: **mental health, cultural and spiritual coping, HIV risk behaviors, Native American, alcoholism/alcohol abuse, clinical research, human subjects, behavioral & social science**
TYPE STUDY: **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.

MUSCULOSKELETAL SYSTEMS

TITLE: **Regulation of PTH Activity in Bone by B-arrestin** **NIAMS**
P.I.: **Mary L. Bouxsein, Ph.D.**
INSTITUTION: **Beth Israel Deaconess Medical Center**
GRANT NO.: **1 R01 AR049265-01A1**
KEYWORDS: **Osteoporosis, parathyroid hormone, anabolic therapy**
STUDY TYPE: **Basic**
AWARD: **$ 99,999**

Parathyroid hormone (PTH) is a major regulator of mineral homeostasis and bone metabolism. Intermittent PTH therapy is approved for treatment of osteoporosis, yet the cellular mechanisms underlying the biologic effects of PTH are not completely understood, including the molecular basis for the observation that low-dose, intermittent administration of PTH elicits net bone formation, whereas continuous administration of high-dose PTH causes predominantly bone loss. The biological actions of PTH are mediated by a G protein-coupled receptor (PTH1R). The investigators demonstrated that a cytoplasmic molecule, β-arrestin2 (β-arr2), regulates the activity of PTH1R and its agonists *in vitro* by promoting rapid endocytosis of ligand-receptor complexes and by inhibiting CAMP signaling in response to agonists. In this revised application, the investigators present preliminary data showing that compared to wild-type mice, β-arr2 null mice have reduced bone mass and an altered bone response following intermittent PTH administration. In addition, osteoblasts from mice null for β-arr2 exhibit increased and sustained CAMP signaling in response to PTH. The investigators therefore hypothesize that β-arrestin2 is a key modulator of the biologic activity of PTH in bone. The investigators will pursue three specific aims to test this hypothesis: 1) Determine the role of β-arr2 in regulating the anabolic response of bone to intermittent PTH, by determining the response of ovariectomized β-arr2 KO and WT mice to intermittent PTH therapy. 2) Determine the cellular and molecular mechanisms of PTH biologic activity in primary osteoblastic cell cultures from β-arrestin2 KO mice. 3) Determine the effects of targeted overexpression of β-arrestin2 in osteoblasts on the skeletal response to intermittent and continuous PTH administration in ovariectomized and intact mice, respectively. In summary, the overall goal of this project is to improve our understanding of the mechanisms regulating the biologic activity of PTH in bone. By conducting complementary *in vivo*, *ex vivo*, and *in vitro* experiments in mice deficient for β-arrestin2 and in mice overexpressing β-arrestin2 specifically in bone, the investigators will provide novel insights into potential mechanisms that underlie the distinct skeletal response to intermittent versus continuous PTH administration. Information gained from the proposed studies will be instrumental for the development of new PTH1R ligands with improved signaling and biologic activity profiles for treatment of osteoporosis and other metabolic bone disorders.

TITLE: **Osteo-Arthritis Initiative** **NIAMS**
P.I.: **Michael Nevett, Ph.D., Coordinating Center (University of California, SF) (University of Maryland School of Medicine, Baltimore; March Hochberg, M.D., Ohio State University, Columbus; Rebecca Jackson, M.D., University**

of Pittsburgh; C. Kent Kwoh, M.D. and Memorial Hospital of Rhode Island, Pawtucket; Annlouise Assaf, Ph.D., F.A.H.A.)
KEYWORDS: **biological markers, osteoarthritis, disease progression**
TYPE STUDY: **Clinical**
AWARD: **$800,000**

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**
INSTITUTION: **University of Nebraska, Lincoln, NE**
GRANT NO.: **5 R01 DE12872-04**
KEYWORDS: **clinical trials, periodontitis, osteoporosis, dental/oral disease, estrogen osteoporosis, skeletal disorder chemotherapy, tetracycline, bone density, bone metabolism**
TYPE STUDY: **Translational, Clinical**
AWARD: **$384,609**

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**
INSTITUTION: **Creighton University Dept. of Medicine, Osteoporosis, Omaha, NE**
GRANT NO.: **5 R01 AR048846-02**
KEYWORDS: **osteoporosis, supplementation, menopause**
TYPE STUDY: **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, MD**
INSTITUTION: **University of Miami School of Medicine, Dept. of Medicine, Miami, FL**
GRANT NO.: **5 R01 AR048932-02**
KEYWORDS: **osteoporosis, menopause, hormone replacement therapy (HRT), prevention, estrogen**
TYPE STUDY: **Clinical**
AWARD: **$100,000**

Women will live a third of their lives after menopause. The complications of prolonged estrogen deficiency during the menopausal years is 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.

OBESITY/OVERWEIGHT

TITLE: **Longitudinal Assessment of Bariatric Surgery (Expansive)** **NIDDK**
P.I.: **Steven H. Belle, M.D.**
INSTITUTION: **University of Pittsburgh**
GRANT NO.: **5 U01 DK066557-02**
KEYWORDS: **Bariatric surgery, obesity, gender differences, behavioral & social science, digestive diseases**
STUDY TYPE: **Clinical**
AWARD: **$300,000**

The Bariatric Surgery Clinical Research Consortium (BSCRC) is being established to "facilitate coordinated clinical, epidemiological, and behavioral research in the field of bariatric surgery". The Consortium will include 4-6 collaborating clinical centers, a NIDDK Project Scientist and a Data

Coordinating Center (DCC). This Consortium will work cooperatively to create a core information base, collected under a common protocol, on patients undergoing bariatric surgery and a non-surgical control group. The Consortium members will also participate in 1-2 clinical research projects each year. The DCC will work with the BSCRC members to support all aspects of study design, study conduct, and data analysis for the central information core and each clinical research project. The DCC will develop a distributed data entry system and will maintain a secure, central database of clinical, laboratory, and surgical information, and serum and tissue sample inventories. The DCC will identify and contract with central laboratory(ies) and either coordinate with the Central NIDDK Biosample Repository or identify and contract with another repository. The DCC will develop safety and efficacy analysis plans and will prepare materials for presentations at BSCRC-related meetings, scientific conferences, and for publications and regulatory bodies. The DCC will coordinate all activities of the Consortium, including meetings and conference calls for the Executive Committee, Steering Committee, subcommittees, and presentations to the Data and Safety Monitoring Board. Finally, they will share data collected for the BSCRC with the wider scientific community and archive all data, study intervention materials, and coordinate archiving all specimens at the end of the study.

TITLE: **Look AHEAD (Action For Health in Diabetes)** **NIDDK**
INSTITUTION: **Wake Forest University (coordinating center), Winston Salem, NC Johns Hopkins University, Baylor College of Medicine, University of Colorado Health, University of Washington, University of Tennessee, St. Lukes-Roosevelt Institute, University of Alabama at Birmingham, The Miriam Hospital, Pennington Biomedical Research, University of Texas Health Science, University of Minnesota, University of Pittsburgh, Massachusetts General Hospital, University of California Los Angeles, University of Pennsylvania, Southwest American Indian Center (12 clinical centers)**
GRANT NO.: **5 U01 DK57136-06**
KEYWORDS: **Type 2 diabetes, obesity, cardiovascular, cerebrovascular, neurosciences research, behavior, behavior & social science, brain disorders, coronary heart disease, stroke**
TYPE STUDY: **Clinical**
AWARD: **$100,000**

Look Ahead is a multicenter randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. The Look AHEAD trial will enroll 5,000 obese patients with type 2 diabetes over a 2.5 year period. Participants will be randomly assigned to one of two interventions, the Lifestyle Intervention or Diabetes Support and Education, and will be followed for a total period of up to 11.5 years. The primary aim of Look AHEAD is to study the effects of the two interventions on major cardiovascular events: heart attack, stroke and cardiovascular death. Look AHEAD also will investigate the impact of the interventions on other cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include: diabetes control and complications, fitness, general health, health-related quality of life and psychological outcomes. The cost and cost effectiveness of the Lifestyle Intervention relative to Diabetes Support and Education will be assessed.

OPTHALMIC DISEASES

TITLE: **Incidence of Late Macular Degeneration in Older Women** **NEI**
P.I.: **Anne L. Coleman, MD**
INSTITUTION: **UCLA**
GRANT NO.: **5 U10 EY13626-03**
KEYWORDS: **blindness, quality of life, aging, Caucasian women, diabetes, eye disease and disorders of vision, macular degeneration**
TYPE STUDY: **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**
INSTITUTION: **Cedars-Sinai Medical Center, Los Angeles CA**
GRANT NO.: **5 R01 EY014600-02**
KEYWORDS: **ophthalmic diseases, aging, estrogen, cataract, estrogen receptor, lens, receptor expression, eye disorder chemotherapy, eye pharmacology**
TYPE STUDY: **Basic**
AWARD: **$131,297**

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 alphaERKO 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: **Mast Cell Role in Masseter Muscle Repair** **NIDCR**
P.I.: **Joyce A. Morris-Wiman, Ph.D.**
INSTITUTION: **University of Florida**
GRANT NO.: **1 R21 DE016317-01**
KEYWORDS: **TMJ, pain, inflammation, dental/oral disease**
STUDY TYPE: **Basic**
AWARD: **150,000**

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: **Hormonal Cycles in Women: Effects on TMD Pain & Symptoms** **NIDCR**
P.I.: **Linda Leresche, ScD**
INSTITUTION: **University of Washington, Department of Oral Medicine**
GRANT NO.: **1 R01 DE016212-01**
KEYWORDS: **TMJ, pain control, estrogen, depression, mental health, mind & body**
STUDY TYPE: **Translational**
AWARD: **130,000**

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: **Twin Study of Chronic Widespread Pain** **NIAMS**
P.I.: **Niloofar Afari, Ph.D.**
INSTITUTION: **Harbor View Medical Center Seattle, WA**
GRANT NO.: **1 R01 AR051524-01**
KEYWORDS: **Chronic pain, fibromyalgia, chronic fatigue syndrome, genetics**
STUDY TYPE: **Clinical**
AWARD: **$ 99,999**

Chronic widespread pain (CWP) occurs in 4-13% of people and is one of the defining characteristics of Fibromyalgia (FM). Although tender points were originally considered as essential to the diagnosis of FM, it is now felt that they reflect pain severity and distress, and that FM lies at one end of the CWP continuum. To truly understand the pathogenesis of CWP, it would be optimal to study the entire spectrum of individuals who have this symptom. Another critical issue in the mechanistic study of CWP is what to study. Over the past two decades, FM researchers have described abnormalities in various components of the central nervous system as well as high rates of psychological co-morbidities and other chronic multisymptom illnesses. The role and significance of each of these factors in predisposing to the illness, directly causing the symptoms or occurring as a consequence of the condition, are unclear. The complexity of FM and the continuum of CWP have led investigators to develop a theoretical model of CWP that is synergistic and multidimensional predisposing factors are of particular interest in this model since these represent premorbid risk or protective factors that relate to the development of CWP. Further, predisposing factors can be differentiated from illness-associated features that occur as a consequence of the condition. A co-twin control study is a powerful means for examining specific hypotheses about the etiology and consequences of CWP derived from the theoretical model. Twenty-one MZ and 21 DZ twin pairs discordant for CWP, along with 22 MZ and DZ pain-free control twin pairs will be recruited from the population-based University of Washington Twin Registry. Twin pairs will undergo an intensive evaluation of the autonomic nervous system (ANS) function, hypothalamic-pituitary-adrenal (HPA) axis function, exercise capacity, sleep and activity levels, evoked pain processing, and psychiatric and psychosocial factors involved in CWP. There are 2 specific aims: 1) Assess similarities and differences in ANS function, HPA axis function, exercise capacity, sleep and activity levels, evoked pressure pain sensitivity, and psychiatric and psychosocial factors between female twins with CWP and their pain-free co-twins. 2) Determine if the association between CWP and the above illness characteristics is due to confounding by genetics or common environmental factors by comparing CWP-discordant MZ female twin pairs with CWP-discordant DZ and pain-free MZ and DZ pairs. Additionally, investigating the pattern of differences between twin groups can help to distinguish factors that are predisposing to CWP and those that occur after the onset of the illness.

TITLE: **Pain Management in Temporomandibular Joint Disorders** **NIDCR**
P.I.: **Jennifer Haythornthwaite, PhD**
INSTITUTION: **Johns Hopkins University, Baltimore, MD**
GRANT NO.: **5 R01 DE13906-04**
KEYWORDS: **TMD, pain control, behavioral interventions, neurosciences research, dental/oral disease**
TYPE STUDY: **Clinical Behavioral**
AWARD: **$341,705**

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

TITLE: **Sex Differences in Opioid Analgesia** **NIDA**
P.I.: **Anne Z. Murphy, PhD**
INSTITUTION: **University of Maryland School of Medicine, Baltimore, MD**
GRANT NO.: **5 R01 DA016272-03**
KEYWORDS: **opioids, gender, pain, analgesia**
TYPE STUDY: **Basic**
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 animal models of acute pain, the effective dose of morphine is approximately 5-10x 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 (PAG) and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. The major hypothesis is that the opiate-sensitive intrinsic and extrinsic circuitry of the PAG 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. 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. 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: **Trigeminal Pain Mechanisms and Control** **NIDCR**
P.I.: **Jon D. Levine, PhD**
INSTITUTION: **University of California at San Francisco, San Francisco, CA**
GRANT NO.: **5 P01 DE08973-14**
KEYWORDS: **pain control mechanism, orofacial neuropathies, neurosciences research, dental/oral disease, neurodegenerative**
TYPE STUDY: **Basic**
AWARD: **$163,734**

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.

PHYSICAL ACTIVITY

TITLE: **Social Cognitive Theory and PA after Endometrial Cancer Intervention** **NCI**
P.I.: **Basen-Engquist, Karen M.**
INSTITUTION: **University of Texas MD Anderson Cancer Center**
GRANT NO.: **1R01CA109919-01**
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.: **Popkin, Barry M.**
INSTITUTION: **University of North Carolina Chapel Hill**
GRANT NO.: **1R01CA109831-01**
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.: **Bryan, Angela**
INSTITUTION: **University of Colorado, Boulder**
GRANT NO.: **1R01CA109858-01**
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: **Physical Activity Adherence in Black Women Over 65** **NINR**
P.I.: **Karen J. Anderson, M.S.**
INSTITUTION: **University of Nebraska**
GRANT NO.: **1 F31 NR008969-01**
KEYWORDS: **Health promotion, black women, physical activity, older women, behavioral & social science, minority health**
STUDY TYPE: **Clinical**
AWARD: **$34,228**

The proposed dissertation study will be guided by Healthy People 2010 objectives in the Physical Activity Focus Area. The overall purpose of this study is to improve the health status of African American women 65- 85 through promoting adherence to healthy lifestyle behaviors, specifically physical activity. The specific aim of this study is to determine the impact of a physical activity intervention on self-efficacy for overcoming barriers and adherence to physical activity in this target population. A 2-group, comparative experimental design with repeated measures at

baseline, six months, and 1-year follow-up period on selected psychosocial and physiological outcomes per the conceptual model and hypotheses will be implemented. The candidate proposes to investigate the effects of a physical activity intervention on self-efficacy to overcome barriers and promote adherence to physical activity among in older African American women, a priority area for Healthy People 2010.

TITLE: **Heart to Heart: An Exercise Intervention for Rural Women** **NINR**
P.I.: **Cindy K. Perry, M.S.N.**
INSTITUTION: **Oregon Health and Science University**
GRANT NO.: **1 F31 NR008656-01A1**
KEYWORDS: **Rural residency status, cardiovascular disease, exercise and women's cardiovascular disease, prevention**
STUDY TYPE: **Clinical**
AWARD: **$31,569**

Women's participation in regular exercise is a major factor in preventing heart disease, the leading cause of death in women. Only 15% of adults exercise at the recommended level and the percentage for rural women is even less. Heart-to-heart (HTH) is an innovative intervention designed to increase exercise in rural women at risk of developing coronary heart disease. The specific aims of this research project are to: (1) Determine the magnitude of change in exercise adherence and cardiorespiratory fitness and whether this magnitude differs for rural women in HTH and rural women in the control group; (2) Examine the magnitude of change in self-efficacy, stage of change, and social support and whether this change differs for rural women in HTH and rural women in the control group; (3) Examine whether self-efficacy, stage of change, and social support mediate the relationship between HTH and the outcome variables of exercise adherence and cardiorespiratory fitness; (4) Describe HTH participants' experiences with the intervention. Data from exercise logs will measure adherence, a 12-minute walk test will measure fitness, and self-report data will measure self-efficacy, social support, and group cohesion. Quantitative data will be analyzed with ANOVA, hierarchical regression and effect sizes. Qualitative data will be analyzed with qualitative content analysis

TITLE: **Angiogenesis and Mechanisms of Exercise Training in PAD** **NHLBI**
P.I.: **Brian H. Annex**
INSTITUTION: **Medical Center, Durham, NC**
GRANT NO.: **5 R01 HL075752-02**
KEYWORDS: **artery, atherosclerosis, exercise, behavioral & social science, cardiovascular, chronic pain conditions**
TYPE STUDY: **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: **Evidence-based Practice Report on Assisted Reproductive Technology** **AHRQ**
KEYWORDS: **Reproduction, infertility, pregnancy, perinatal period, conditioning**
STUDY TYPE: **Policy analysis**
AWARD: **$150,000**

Increasingly, assisted reproductive technologies (ART) are being employed to overcome infertility. Based on current reports, there appears to be an association between ART and adverse outcomes related to infant and child health. A careful evidence-based practice report is needed in order to disentangle treatment and infertility effects, especially to address the unique methodological challenges that are specific to this area of research. It is fairly well documented that ART results in greater numbers of multiple-gestation pregnancies, but the underlying causes are not well understood. More careful measures are needed for such outcomes as perinatal morbidities, birth defects, and developmental disabilities

TITLE: **Protein Tyrosine Kinases in Leiomyomata Uteri** **NICHD**
P.I.: **Jean Wang, PhD**
INSTITUTION: **University of California, San Diego**
GRANT NO.: **5RO1 HD046225-02**
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**
INSTITUTION: **Brigham & Women's Hospital**
GRANT NO.: **1RO1 HD046226-02**
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, MD, PhD**
INSTITUTION: **University of Texas Medical Branch, Galveston**
GRANT NO.: **5RO1 HD046228-02**

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**
INSTITUTION: **University of Texas MD Anderson Cancer Center**
GRANT NO.: **1RO1 HD046282-02**
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**
INSTITUTION: **Tufts University School of Medicine**
GRANT NO.: **1RO1 HD046251-02**
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**
INSTITUTION: **University of Illinois**
GRANT NO.: **1RO1 HD046227-02**

KEYWORDS: **Smooth muscle, obesity, hypertension, and 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, MD**
INSTITUTION: **University of Michigan**
GRANT NO.: **1RO1 HD046249-02**
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, MD**
INSTITUTION: **University of Illinois**
GRANT NO.: **1RO1 HD046260-01**
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: **Pregnancy and Drug Metabolizing Enzymes and Transporters** **NICHD**
P.I.: **Steve N. Caritis**
INSTITUTION: **Magee-Women's Corporation**
GRANT NO: **1 U10 HD047905-01**
KEYWORDS: **Women, pregnancy, drugs, drug metabolism and transport, clinical trials, genetics**

STUDY TYPE: **Basic/Clinical**
AWARD: **$350,000**

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** **NICHD**
P.I.: **Menachem Miodovnik**
INSTITUTION: **Georgetown University**
GRANT NO: **1 U10 HD047890-01**
KEYWORDS: **Women, pregnancy, drugs, epilepsy, anticonvulsants, clinical trials, genetics**
STUDY TYPE: **Basic/Clinical**
AWARD: **$150,000**

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** **NICHD**
P.I.: **Mary F. Hebert**
INSTITUTION: **University of Washington OPRU**
GRANT NO: **1 U10 HD047892-01**
KEYWORDS: **Women, pregnancy, drugs, diabetes, anti-diabetes drugs, drug metabolism, clinical trials, genetics**

STUDY TYPE: **Basic/Clinical**
AWARD: **$150,000**

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** **NICHD**
P.I.: **Gary D. Hankins**
INSTITUTION: **University of Texas Medical Branch, Galverston, Texas**
GRANT NO: **1 U10 HD047891-01**
KEYWORDS: **Women, pregnancy, drugs, diabetes, anti-diabetes drugs, clinical trials**
STUDY TYPE: **Basic/clinical**
AWARD: **$150,000**

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: **Regulation of the Contraction in Human Uterus** **NICHD**
P.I.: **Victor Fomin, Ph.D.**
INSTITUTION: **Indiana University School of Medicine**
GRANT NO.: **1 R03 HD045802-01A1**
KEYWORDS: **Pregnancy, parturition, prematurity, uterus, contraction, labor**
STUDY TYPE: **Basic**
AWARD: **$100,000**

Preterm uterine contractions or insufficient contractile activity during labor result either in miscarriage or in emergency cesarean section. A proper understanding of the mechanisms of uterine contraction and its cellular regulation is essential in finding ways to treat these uterine functional pathologies. Although the mechanisms of uterine smooth muscle contraction are generally understood, the factors responsible for the initiation of labor and the mechanisms by

which the uterus maintains its contractility during labor are largely unknown. A growing body of evidence suggests that protein kinase C (PKC) plays an important role in regulation of contraction in a number of smooth muscles. However, its role in regulation of myometrium (uterine smooth muscle) is still controversial. Experimental results show both stimulatory and inhibitory effects of PKC on myometrial contraction. This complex mode of PKC action on rnyometrium can be explained by diversity within the PKC family of proteins, consisting of 12 known isoenzymes (isoforms). The investigators recently showed that 7 of the isoforms are expressed in human non-pregnant myometrium, while in late pregnancy two more, PKCβI and PKCβII are expressed. They have also shown a progressive increase n PKCa expression during pregnancy. The investigators hypothesize that different isoforms of PKC play specific stimulatory or inhibitory, roles in regulating contraction of human myometrium. Early in the contraction-relaxation cycle some PKC isoforms can stimulate contractile pathways, and later other isoforms can decrease the rate of contraction, thus contributing to the muscle relaxation. Firstly, individual PKC isoforms will be depleted in myometrial cell line and muscle strips of human pregnant myometrium using isoform-specific anti-sense oligodeoxynucleotides (ODN). Secondly, the impact of this procedure on the intracellular free Ca concentration in the cell line and on the intracellular free Ca and the contraction of the muscle strip will be elucidated by measuring these parameters in the cells and the muscle strip. Knowing a crucial role of intracellular Ca ([Ca2+) in uterine contraction, the effect of the PKC depletion on [Ca2+] force relationship will be analyzed. This will help to better understand how PKC affects the uterine contraction during pregnancy. Within the scope of this proposal the investigators will concentrate on elucidation of the role(s) of PKCa and β as the isoforms expressed differently in pregnancy.

TITLE: **Molecular Mechanisms of Ovarian Follicular Activation** **NICHD**
P.I.: **Joanne Fortune, Ph.D.**
INSTITUTION: **Cornell University**
GRANT NO.: **1 R03 HD045815-01A1**
KEYWORDS: **Reproduction, infertility, aging, ovarian follicles, contraception, genetics**
STUDY TYPE: **Basic**
AWARD: **$99,999**

In female mammals most oocytes reside in primordial follicles in a resting stage. Little is known about the mechanisms that regulate the movement of these follicles into the growing pool (follicle activation). The pool of resting primordial follicles is a resource, as yet untapped, that could be exploited as a source of material to provide alternative methods for alleviating infertility in women and propagating valuable domestic animals and endangered species. It is likely that a delicate balance among various factors, both stimulators and inhibitors, regulates follicular activation and growth *in vivo*. To date, efforts to determine the signals that initiate follicle growth have consisted of testing individual "candidates" to determine if they promote or inhibit follicle activation. Although progress has been made using this approach, that progress has been slow. The investigators will develop a complementary approach, based on recent advances in molecular techniques, to determine specific genes that are turned on or off during the activation of follicles. In Specific Aim #1 suppressive subtractive hybridization (SSH) will be used to test the hypothesis that specific genes are turned on (or off) during follicle activation. Candidate genes will be determined by comparing freshly isolated pieces of bovine ovarian cortex (highly enriched for primordial follicles) with cortical pieces cultured for 2 days (in which 90% of follicles have activated and become primary). Cattle provide an excellent model for human follicular development and SSH are ideally suited for the detection of rare and novel sequences in two closely related cell types/tissues. Specific Aim #2 is designed to test candidate genes identified in Specific Aim #1 for a potential role in follicle activation by using *in situ* hybridization to localize differentially expressed sequences in freshly isolated vs. cultured bovine cortical pieces. At the end of two years, the investigators expect to have identified a number of candidate genes that will provide important clues to the genetic regulation of follicle activation. Elucidation of these fundamental mechanisms has practical implications for the development of new contraceptive technologies and alleviation of infertility.

TITLE: **Role of Neutralizing Antibodies in Transmission of SHIV** **NICHD**
P.I.: **Nancy L. Haigwood, Ph.D.**
INSTITUTION: **Seattle Biomedical Research Institute**

GRANT NO.: **2 R01 HD038653-04A1**
KEYWORDS: **HIV, sexually transmitted disease, prevention, mother to child transmission**
STUDY TYPE: **Clinical**
AWARD: **$99,999**

Maternal neutralizing antibodies (NAbs) may play a role in determining whether an infant becomes infected during Mother to Child Transmission (MTCT). Higher levels of both autologous and heterologous NAbs are associated with non-transmission. Although single-dose or multiple-dose nevirapine has limited transmission dramatically, there is growing concern over the development and persistence of drug-resistant viruses in the infants that could limit future treatment, raising interest in testing vaccines or immunotherapies during the early breastfeeding period, when postpartum transmission risk is highest. The focus of this research is to expand on the findings of the investigators previous study. They established a perinatal SHIV transmission model in M. nemestrina, where they have observed extraordinary virus control in infected and exposed newborn macaques. This model allows a detailed analysis of transmitted variants, passive transfer of maternal IgG and NAbs, and the development of autologous de novo responses in newborns. The research will explore the role of preexisting NAbs in limiting infection and facilitating tie novo antiviral immunity. The researchers hypothesize that the presence of moderate to high levels of NAbs (IgG) at the time of oral SHIV exposure will limit infection or pathogenesis in newborns by reducing the infectivity or number of variants that are transmitted. To test this concept, they will challenge newborns orally with SHIV in the presence of NAbs that are closely matched to the challenge virus versus mismatched NAbs. They will compare the development of de nova responses to SHIV with responses to hepatitis B vaccine given to the infant macaques in the absence of passive immunity. Understanding the potential and limitations of natural immunity will aid in the conceptual and optimal design of vaccines and immunotherapies that can further limit MTCT. 1. Characterize the transmitted viruses and the *de novo* antiviral responses in exposed infants with highly controlled SHIV infection and determine their profiles of neutralization sensitivity and resistance to passively acquired maternal IgG. 2. Test the antiviral effects of IgG (SHIVIG) as a model for maternal antibodies in limiting infection, by comparing neutralizing IgG matched to the challenge virus *versus* mismatched IgG with limited or no neutralizing activity against the challenge virus. 3. Determine whether the presence of neutralizing versus non-neutralizing IgG affects the magnitude or timing of *de novo* NAbs in infected infants. Investigate possible mechanisms of action in the development of accelerated NAb responses and other antiviral immune responses.

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 HD41749-04**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation**
TYPE STUDY: **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: **Intermediate Outcomes of Hysterectomy and Alternatives** **AHRQ**

P.I.: **Miriam Kuppermann, PhD**
INSTITUTION: **University of California San Francisco**
GRANT NO.: **5 R01 HS11657-03**
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**
TYPE STUDY: **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: **The Biologic Effects of Androgens in Men and Women** **NICHD**
RFA: **Cooperative Reproductive Sciences Research at Minority Institutions (RFA HD-02-012)**
P.I.: **Shalender Bhasin, MD**
INSTITUTION: **Charles R. Drew University of Medicine and Science**
GRANT NO.: **5 U54 HD041748-02**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, genetics, minority health**
TYPE STUDY: **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 (RFA HD-02-012)**
P.I.: **Ponjola Coney, MD**
INSTITUTION: **Meharry Medical College**
GRANT NO.: **5 U54 HD044315-02**
KEYWORDS: **reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation, fibroid tumors, estrogen**
TYPE STUDY: **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: **Collaborative Research Initiative** **NICHD**
P.I.: **Linda C. Guidice, MD, PhD**
INSTITUTION: **Stanford University, Palo Alto, CA**
GRANT NO.: **U54 HD 31398-08**
KEYWORDS: **endometriosis, genetics, infertility, chronic pain conditions, estrogen**
TYPE STUDY: **translational**
AWARD: **$150,000**

Endometriosis is a benign, estrogen-dependent, gynecologic disorder that is clinically associated with pelvic pain and infertility and is diagnosed by direct visualization during surgery. Pelvic endometriosis, and thus, eutopic endometrium (i.e. endometrium within the uterus) is presumed abnormal in women with the disease. The abnormality extends to uterine receptivity, supported by high implantation failure and poor pregnancy rates in IVF cycles in women with disease. Recently, using a global gene profiling approach, we identified candidate genes for uterine receptivity in normally cycling women without endometriosis and in women with mild/moderate endometriosis, through a collaborative, multi-center study. The current collaborative research initiative will lay the foundation for clinical translation of the data collected to date, with the following goals: diagnosis of a receptive endometrium for fertility: diagnosis of a non-receptive endometrium in women with endometriosis and infertility; diagnosis of endometriosis; and diagnosis of the stage (severity) of endometriosis in the pelvis.

TITLE: **Prevalence and Etiological Predictors of Vulvodynia** **NICHD**
P.I.: **Bernard L. Harlow, PhD**
INSTITUTION: **Brigham & Women's Hospital, Boston, MA**
GRANT NO.: **5 R01 HD38428-05**
KEYWORDS: **vulvodynia, survey, controls, cases, cytokines, pain (chronic)**
TYPE STUDY: **Clinical**
AWARD: **$100,000**

Vulvodynia is a syndrome of unexplained vulvar itching, burning, and/or pain that causes major physical and psychological distress. It is diagnosis of exclusion when vulvar discomfort becomes chronic over many months and the presence of any other remediable cause, such as infection or dermatitis, is ruled out. The two major subtypes of vulvodynia- generalized vulvar dysesthesia and vestibulodynia- are often misclassified. Few descriptive or etiologic epidemiological studies have been performed. Thus, the prevalence and incidence in the general population is unknown and no preventable exposures have been identified. A recent NIH sponsored consensus conference

stressed the need to determine the prevalence of vulvodynia and conduct population-based observational studies to identify modifiable risk factors. The applicant has conducted a population-based prevalence survey in more than 400 women that achieved a 70% response rate and found that 18% of women reported a lifetime history of chronic vulvar symptoms that lasted three months or longer. Approximately 8% of all women surveyed were currently experiencing these symptoms. In addition, the applicant conducted a pilot case-control study of 31 women diagnosed with either dysesthetic vulvodynia or vestibulodynia, or a combination of the two within the last five years and compared them to 31 similarly aged health women identified from the general population. Cases were, on average, three times more likely to report medical treatments or surgical procedures for conditions that may have influenced perineal pain, or a greater frequency of condom use and use of talcum powder in the genital area that may have lead to mucosal abrasion and inflammation. A survey is being conducted on 16,000 women 20-59 years of age fro the general population to estimate the age-specific prevalence of vulvodynia. From this sample, the applicant will identify 400 cases of vulvodynia, verified through a two-step screening process, and a sample of 400 frequency matched age and county of residence controls. Structured interviews will assess a wide spectrum of exposures related to trauma. A subsample of 80 cases and 80 controls will receive a clinical examination to confirm the presence or absence of vulvodynia, and also will provide a vaginal lavage and vulvar swab specimen for the assessment of cytokines and the culturing of microbiological organisms. It is hypothesized that various types of vulvar trauma may precede the spontaneous and evoked vulvar pain experienced by women with vulvodynia and that vulvodynia may be a variant of a specific type of Complex Regional Pain Syndrome that is consistent with sensory disturbances such as mechanical allodynia.

TITLE: **Vulvodynia Prevalence and Efficacy of 4 Interventions** **NICHD**
P.I.: **Gloria A. Bachmann, MD**
INSTITUTION: **UMDNJ-RWJ Medical School, New Brunswick, NJ**
GRANT NO.: **5 R01 HD40119-05**
KEYWORDS: **vulvodynia, chronic pain syndrome, clinical, epidemiology, outcomes, chronic pain, cognitive behavior therapy, diet therapy, female reproductive system disorder, amitriptyline, corticosteroid, cost effectiveness, hormone therapy, behavioral /social science research, women's health**
TYPE STUDY: **Clinical**
AWARD: **$100,000**

Vulvodynia is a complex, multi-factorial chronic pain syndrome which is associated with significant distress and interpersonal. Vulvar vestibulitis and dyspareunia are two common, although not well-understood clinical components or sub-types of vulvodynia. Chronic vulvar pain is experienced by, according to recent surveys, about 10-15% of the female population between 18 and 80. Pathophysiologic findings have not been convincing for the role of any specific antibody or etiological mechanism, although several have been proposed including aberrant somatosensory processing in the peripheral or central inflammatory process. The epidemiology and predictors of vulvodynia have similarly not been well- articulated in the literature. One study suggested that the disorder may be largely limited to white, middle-aged women, although sampling and data gathering limitations cloud the assessment of these findings. Thirdly, many centers have begun emphasizing surgical treatments for vulvar vestibulitis, although these approach is rejected by about 1/3 of women at the outset. The vestibulectomy procedure also leads to definite worsening of the condition in about 10% of cases. This grant will propose to examine efficacy, outcomes and cost-effectiveness associated with four non-surgical interventions for vulvodynia. In general, the women's Health Research Section of RWJMS is committed to offering minimally- invasive services and treatments to a broad diversity of women in the central northeast region. The investigators previous experience and that of the co-PI's make this site uniquely well-prepared to offer a broad range of dissemination and educational experiences, both locally and nationally, in the final years of the grant cycle. The investigators plan to arrange and host an international consensus conference (something they have done twice recently in other areas of relevance), and to disseminate findings obtained from this and similar conferences broadly. They will also disseminate any questionnaires and treatment manuals developed in the context of this grant via website or other appropriate electronic or non-electronic form. The investigators will develop patient education and public information materials, which will also be distributed in the most accessible

and least costly form. The ultimate goal is to share findings from this and related research with the broadest cross-spectrum of women that we can.