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Allergy and Immunology

Senior Research Staff

Edward Zoratti, M.D.

Research Summary

Principal Investigator: Zoratti, Edward, M.D.
Inner City Asthma Consortium

The objectives of the Inner City Asthma Consortium are to implement a long range scientific plan to reduce asthma severity and prevent asthma among inner city children and to identify the mechanisms involved in the immunopathogenesis of asthma in these populations. The specific objectives are to: 1) conduct clinical trials to evaluate the safety and efficacy of promising immune based therapies in reducing asthma severity and preventing disease onset in minority children residing in inner cities in the United States; 2) conduct research to delineate the underlying mechanisms of such therapies as an integral part of the clinical trials undertaken by the Consortium; 3) conduct clinical studies on the immunopathogenesis of asthma onset, progression and severity ; and 4) develop and validate surrogate / biomarkers to measure disease stage, progression and therapeutic effect.

Cardiology/Cardiovascular Research

Senior Research Staff

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Research Summaries

Principal Investigator: Guerrero, Mayra, M.D.
Personalized Risk Information Services Manager (Subcontract) (NIH R01 HL096624-01)

With the Institute of Medicine's call for a more evidence-based, efficient, patient-centered healthcare system, this study proposes to test the impact of a new mechanism for eliciting informed consent from patients undergoing percutaneous coronary intervention (PCI) on patients' comprehension of procedural risks/benefits and upon clinicians' use of effective strategies to minimize the risk of bleeding at the time of PCI. Bleeding is the most common, non-cardiac complication of PCI and is strongly associated with myocardial infarction (heart attack), stroke, increased length of stay/costs and death. While important adjunctive therapies exist to minimize the risk of bleeding, in current practice, these therapies are most often applied to patients at low risk for bleeding and least often applied to those at the highest risk - a risk-treatment paradox. Our proposal seeks to clarify patients' risk of bleeding at the time of PCI so that these adjunctive therapies can be most rationally applied to those at highest risk to support safer, more cost-effective, patient-centered care. To accomplish this, the infrastructure of the informed consent process at participating study centers will be transformed by deploying a novel, web-based system - the personalized risk information services manager (PRISM) - that generates individualized consent forms with estimates of risks and outcomes using validated multivariable models from contemporary practice. Using a pre/post study design at 6 institutions, supplemented with a case control matching methodology, the impact of this new mechanism for eliciting informed consent from patients undergoing PCI will be evaluated by explicitly testing whether PRISM: a) improves the quality of the informed consent process, b) supports the more rational use of Bleeding Avoidance Therapies among those at the highest risk for bleeding, c) decreases bleeding events at the time, or within 1 month, of PCI and d) supports a more cost-effective model of PCI. This project tests a paradigmatic shift in the practice of medicine that is directly aligned with the strategic directions of the NHLBI to translate new knowledge into routine clinical care. Given the unprecedented investment of NHLBI and the ARRA Stimulus Package in supporting comparative effectiveness reIT infrastructure, whether it can improve patients¿ experience with health care, lead to more rational medical decision-making or whether it is even economically feasible to redesign healthcare delivery in this direction. Towards this end, our team has developed the personalized risk information services manager (PRISM; www.cardioscience.org; username: guest, password: guest), an entirely new paradigm for delivering patient-specific outcomes projections at the interface of patient care.3,4 A particularly compelling opportunity to test the impact of

evidence-based, patient-centered care is at the time of acquiring informed consent for percutaneous coronary interventions (PCI). While >1,000,000 PCI procedures are performed annually, and although multiple riskprediction models are available,5-10 these models are never used to present patients with estimates of their risk for PCI complications or to guide periprocedural management. A particularly important opportunity to influence care at the time of PCI is management of bleeding risk. Bleeding is common, morbid, and costly, occurring in 2-6% of patients undergoing PCR with wide institutional variability. Major bleeding events also result in a 3-4 day increase in length of stay,11 in turn increasing hospitalization costs by $6,000-8,000.12 Bleeding is also associated with morbid events including non-fatal MI, stroke, and death. Importantly, peri-procedural bleeding risk is modifiable, as there are established bleeding avoidance therapies (BATs) including effective anticoagulation treatments (e.g., bivalirudin), vascular closure devices, and radial access techniques that can mitigate the risk. However, these interventions can be costly, mandating a rational strategy to apply them in higher risk patients, while avoiding them in patients at lower risk. In partnership with the National Cardiovascular Data Registry(R) (NCDR(R)), our group developed and validated a clinical risk model to estimate individual patient risk for post-PCI bleeding using a large nationally representative database of >300,000 patients from >400 hospitals.13 To address this opportunity to improve the quality of informed consent, and to realize the Institute of Medicine¿s goal of delivering safer, more efficient, evidence-based, patient-centered care, we will 1) implement PRISM-generated, individualized informed consent documents at 6 high-volume PCI hospitals and 2) test its association with the quality of informed consent. We will also examine the association of PRISM-generated consents with 3) the use of BATs in those with the greatest potential to benefit (i.e. those at the highest risk for bleeding) Finally, we will integrate all of these goals by formally assessing the cost-effectiveness of PCI after introducing PRISM into practice.

Principal Investigator: Lanfear, David, M.D.
Pharmocogenetics of the B-type Natriuretic Peptide Pathway (NIH 1K23HLO 85124)

The over all goal of this project is to generate predictors of the efficacy and toxicity of intravenously administered recombinant BNP. Our approach is to systematically evaluate genetic variants in candidate genes in the BNP pathway that are known to mediate its effects or clearance. We will assess polymorphisms within these candidate genes based on functional variants described in published literature, variants which are judged to plausibly have functional consequences, as well as ‘tag’ variants with linkage to other variants or haplotype blocks. We will then relate genotype and haplotype to both pharmacokinetic parameters as well as clinical measures of response to therapy among heart failure patients receiving exogenous BNP. As a step toward mechanistic understanding we will also assess the association of sequence variants with expression level of the candidate genes using real-time PCR, and protein quantity and localization using immunohistochemistry, in target human tissue (kidney). In this fashion we will be able to definitively identify functional, predictive variants in these genes and to develop decision models for genetic based prediction of response to therapy in terms of both efficacy and toxicity. This will not only enhance the current understanding of BNP

system biology, but the resulting tools will set the ground work for clinical validation, leading to BNP therapy that can be optimally targeted to those with the highest likelihood of favorable response while avoiding those with excess risk of adverse event.

Principal Investigator: Nour, Khaled, M.D.
Prospective Multicenter Imaging Study for Evaluation of Chest Pain (Subcontract) (NIH R01HL098237)

Prospective Multicenter Imaging Study for Evaluation of Chest Pain
Millions of Americans develop chest pain suggestive of coronary heart disease each year and often require non-invasive diagnostic testing. However, currently available tests are imprecise, robust evidence regarding optimal test choice is limited, and testing costs are rising disproportionately. Further, the role of new technology such as coronary computed tomographic angiography (CTA) is uncertain. In response, the "PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE)" Trial will test the hypothesis that an initial 'anatomic' testing strategy (using CTA) is clinically superior to usual care or an initial 'functional' stress testing strategy (using physician-selected stress imaging (echocardiography or nuclear) or exercise electrocardiography)) in low-intermediate coronary artery risk patients with chest pain, and will reduce the composite primary endpoint of death, myocardial infarction, major peri-procedural complications and hospitalization for unstable angina. This 150 site pragmatic trial will randomize 10,000 symptomatic patients with clinically determined, low-intermediate risk for CAD over 24 months. All subsequent diagnostic and therapeutic management will be based on the latest clinical practice guideline recommendations and will be at the discretion of the treating care team. Patients will be followed for up to 48 months (median 2.5 years). The trial design is carefully constructed to ensure the broadest possible applicability of results by incorporating the full spectrum of practice settings, caregiver specialties, and types of tests which are immediately relevant to the clinical decisions needed to care for the vast majority of chest pain patients nationwide. Projecting a 9% event rate in the functional testing or usual care arm, enrollment of 5,000 patients in each testing arm will provide 90% power for detecting a 20% relative reduction in the composite primary endpoint. Secondary endpoints include components of the primary endpoint as well as 1) medical costs, resource utilization, cost effectiveness; 2) health related quality of life. This proposal includes the lead Clinical Coordinating Center (CCC; Pamela S Douglas, PI), a Statistical and Data Coordinating Center (SDCC; Kerry L Lee, PI), an Economics and Quality of Life (EQOL; Daniel B Mark, PI), and a Diagnostic Test Core (Dx Core; Udo Hoffmann, PI). This experienced multi-speciality team will deliver the integrated services vital to PROMISE trial, including faculty and operational leadership, imaging and testing expertise, site management, patient follow up, statistical analysis and data management. Although costs of care are extremely important, only demonstration of clinical superiority in real-world settings will change practice or justify use and reimbursement of a new technology such as CTA. PROMISE, as the first large randomized comparison of two diagnostic testing strategies for patients with suspected CAD, will provide the critical evidence regarding clinical outcomes and costs of alternative approaches necessary to shape clinical practice recommendations and health care policy in patients with chest pain for years to come. PUBLIC HEALTH RELEVANCE: Project narrative The PROMISE

("PROspective Multicenter Imaging Study for Evaluation of Chest Pain) Trial is a 10,000 patient multicenter, randomized trial which will identify the best diagnostic approach for people with chest pain and suspected heart disease. It will determine whether coronary computed tomographic angiography (CTA) is superior to usual cardiac stress testing in improving subsequent health outcomes and reducing medical costs for up to 4 years. By determining the impact of diagnostic testing on patient health, PROMISE's results will define care and shape health policy for the millions of symptomatic people referred for stress testing each year, determine the value of stunning new technologic advances such as CTA, and address rising health care costs.

Endocrinology & Metabolism

Senior Research Staff

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Fred Whitehouse, M.D.

Research Summaries

Principal Investigator: Thomas, Abraham, M.D.
Prevention of Cardiovascular Disease in Diabetes Mellitus (NIH N01-HC-95181)

The purpose of this program is to conduct a multicenter randomized trial assessing the effect on macrovascular morbidity and mortality in persons with Type 2 diabetes mellitus of the following pharmacologic strategies:

1. Intensive glycemic control using a non-insulin-resistance-lowering drug regimen compared with conventional glycemic control using a non-insulin-resistance-lowering drug regimen
2. Intensive glycemic control using an insulin-resistance-lowering drug regimen compared with conventional glycemic control using a non-insulin-resistance-lowering drug regimen
3. Intensive glycemic control using an insulin-resistance-lowering drug regimen compared with intensive glycemic control using a non-insulin-resistance-lowering drug regimen
4. Intensive compared with conventional levels of lipid and blood pressure control

Principal Investigator: Whitehouse, Fred, M.D.
Epidemiology of Diabetes Interventions and Complications (N01-DK-6-2203)

The Epidemiology of Diabetes Intervention and Complications (EDIC) is primarily an epidemiologic investigation, especially for the study of macro vascular disease in IDDM, and it also takes advantage of intention to treat analyses based on previous involvement of the study population in the DCCT.

General Internal Medicine

Senior Research Staff

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Eric Scher, M.D., Interim Chair
Keoki Williams, M.D.

Research Summaries

Principal Investigator: Williams, Keoki, M.D.
Pharmacogenomics of Inhaled Corticosteroid Responsiveness in Patients with Asthma (NIH R01 AI079139)

Inhaled corticosteroids (ICS) are considered first-line therapy for the management and control of patients with persistent asthma. Use of inhaled steroids has been associated with reduced airway responsiveness, improved lung function, diminished symptoms, and fewer exacerbations. However studies show considerable inter-subject variability in ICS response with only 33 per cent to 50 per cent of patients demonstrating substantial improvement in forced expiratory volume in 1 second (FEV1) following therapy. It has also been estimated that corticosteroid resistance accounts for half of all asthma-related health care costs. Therefore understanding the factors that contribute to corticosteroid resistance is both clinical and economically important. African-American patients, in particular, appear less likely to respond to corticosteroid therapy when compared with white patients. However, it is not currently known whether this difference results from genetic or environmental factors, or whether differences exist in inhaled steroid responsiveness (i.e., the recommended route of therapy). This question is of particular importance, since African-American patients suffer disproportionately from asthma-related complications. To date there have been studies examining potential mechanisms of corticosteroid responsiveness, but none have addressed inhaled corticosteroid responsiveness, nor were these studies designed to identify potentially causative genetic factors at a population-level. Therefore in this application we first plan to assess differences in inhaled corticosteroid responsiveness (i.e., improvement in FEV1) between African-American and white patients with asthma following 6 weeks of inhaled beclomethasone diproprionate (BD) treatment. Second, we will seek to identify genetic loci associated with ICS responsiveness in this cohort treated with BD for 6 weeks. The diversity of our cohort is a distinct advantage, as it allows us to use both association analysis and admixture mapping to jointly identify loci associated with steroid response. Next, we will take advantage of our ability to assess ICS exposure and clinical outcomes longitudinally in our patient population so as to assess for pharmacogenomic interactions on asthma exacerbations (i.e., asthma-related emergency department visits, asthma-related hospitalizations, and oral steroid bursts) in this same group. Lastly, we will validate observed drug x gene interactions on asthma exacerbations in a separate, larger cohort of patients with asthma. This latter group will also come from our screened asthma population and will comprise those for whom we have both DNA and clinical data (i.e., historic ICS exposure measures and clinical outcomes). Therefore, in this application we

plan to identify a set of genetic polymorphisms associated with ICS responsiveness as defined by both an improvement in pulmonary function and an alteration in exacerbation-related clinical outcomes. PUBLIC HEALTH RELEVANCE: Inhaled corticosteroids (ICS) are considered first-line treatment for persistent asthma, yet little is known about the genetic factors that influence response to this therapy. This has particular importance to African American patients who suffer disproportionately from asthma complications and who may be less likely to respond to treatment. This study seeks to quantify response to ICS therapy in African American and white patients, as well as use cutting-edge genetic techniques to look for markers that predict treatment response. Knowledge gained from this study may help clinicians select asthma treatments most likely to work for their patients, as well as provide insight for future asthma therapeutics.

Principal Investigator: Williams, Keoki, M.D.
The Clinical Effectiveness of Pharmacy Adherence Information For Diabetes Control (NIH 5R01DK064695-08)

Nonadherence to medications is common among patients with diabetes and contributes to suboptimal control of glycemic and lipid plasma levels. Adherence is not routinely measured in clinical practice because no valid, feasible methods have been readily available. The lack of medication adherence information contributes to clinician failure to identify and address patient nonadherence and to clinical inertia and poor health outcomes. Existing electronic prescribing systems hold the potential to display medication adherence information. We propose a 2-arm cluster-randomized trial to test the effectiveness of providing PCPs with both adherence measurements and an adherence clinic to improve adherence to diabetic and lipid-lowering drugs. This adherence clinic will consist of a pharmacist and nurse trained in motivational interviewing (Ml) techniques to improve adherence to medications. Adherence indices will be generated by linking e-prescribing information with pharmacy data. The trial will be conducted among 1,436 patients with diabetes and poor blood glycemic and/or lipid control. Primary care providers will be randomized to 1 of the following 2 study arms: 1) usual care--PCPs will write prescriptions electronically but will not be provided patient adherence information or Ml support; and 2) intervention--PCPs will be provided adherence information and adherence prompts electronically plus physicians and patients will receive support from an adherence clinic. Our intervention uses as theoretical behavioral framework elements of the Chronic Care Model, Self-Determination Theory, and the Health Belief Model. The study will use qualitative methods to guide intervention design and implementation and will include both process evaluation and treatment fidelity measures. The intervention will be tailored to patients' adherence and goal levels. Outcomes will include adherence to diabetes and lipid-lowering medications; cholesterol and glycated hemoglobin plasma levels (primary outcome); patients and providers' acceptance and satisfaction; and cardiovascular morbidity- mortality (exploratory outcome). The study will also evaluate the cost effectiveness of the intervention. Patients will be followed for 36 months. Analyses will control for cluster randomization effects. The introduction of sustainable medication adherence monitoring in clinical practice holds great potential to improve health outcomes among patients with diabetes.

Principal Investigator: Williams, Keoki, M.D.
The EVE Asthma Genetics Consortium: Building Upon GWAS Gene Discovery

EVE is a consortium comprised of all U.S. investigators who have conducted genome-wide association studies (GWAS) of **Asthma** and whose main objective is to combine results of individual studies to increase the overall power to identify **Asthma**-susceptibility loci. The consortium includes investigators at 10 U.S. institutions with GWAS results for >30,000 individuals representing European American, African American, U.S. Hispanic, and Mexican populations. As part of the initial goals of **EVE**, investigators aim to d**EVE**lop a common set of >1 million genotyped and imputed SNPs to be tested for association with **Asthma** in this primary sample followed by association statistics to be combined in a grand meta-analysis for **Asthma** gene discovery. In this GO application, we propose four specific aims: 1) to replicate the most significant meta-analysis results in >15,000 **Asthma** cases and controls of European American, African American, and U.S. Hispanic ethnicities; 2) to resequence 5-10 genes associated with **Asthma** in European Americans but not in African Americans or Hispanic cases and controls (>1,500 individuals) to identify rare and common variants that are not well-tagged by SNPs on the genotyping platforms; 3) to conduct additional meta-analyses in the primary sample for **Asthma** associated phenotypes (e.g., measures of lung function, total serum IgE), and to examine interactions with sex, tobacco smoke exposure in infancy, and between genes; and 4) to d**EVE**lop methods that combine data from different types of study samples (case-control, trios, cohorts) for the meta-analyses described in Aim 3, and integrate network and pathway analyses into our approaches for gene discovery. Discovery of risk alleles for **Asthma** and its associated phenotypes could significantly impact public health and health care delivery by allowing for population screening to identify at-risk individuals who could be candidates for early intervention (disease pr**EVE**ntion) or for personalized therapeutics based on molecular pathology rather than on symptomology (disease treatment). PUBLIC HEALTH RELEVANCE: **EVE** is a consortium comprised of all U.S. investigators who have conducted genome-wide association studies (GWAS) of **Asthma** and whose main objective is to combine results of individual studies to increase the overall power to identify **Asthma**-susceptibility loci. The consortium includes investigators at 10 U.S. institutions with GWAS results for >30,000 individuals representing European American, African American, U.S. Hispanic, and Mexican populations. In this application, we propose to replicate the most significant GWAS results in >15,000 **Asthma** cases and controls of European American, African American, and U.S. Hispanic ethnicities, resequence 5-10 genes associated with **Asthma** in European Americans but not in African Americans or Hispanic cases and controls, to study additional **Asthma**-associated phenotypes and examine interactions, and d**EVE**lop methods to facilitate gene discovery. Discovery of risk alleles for **Asthma** and its associated phenotypes could significantly impact public health and health care delivery.

Hematology, Medical Oncology, Josephine Ford Cancer Center

Senior Research Staff

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Frederick Valeriote, Ph.D.

Research Summaries

Principal Investigator: Valeriote, Frederick, Ph.D.
Cynaophytes Anticancer Drug Discovery (NIH R01 CA100851-07)

The overall goal of this project is the discovery and development of new anticancer agents with solid tumor selectivity from leads obtained from marine cyanobacteria. The need for new anticancer drugs is significant given the paucity of agents active against the major solid tumors of man. An underlying hypothesis of our screening strategy is that it will generate drugs active against the major solid tumors (such as lung and colon), which are not effectively treated at present. Marine cyanobacteria are abundant as both free-living and symbiotic tropical organisms, and have a correspondingly rich and diverse secondary metabolism. We propose to produce between 1000 and 1500 extracts per year from field collected and cultured tropical marine microalgae, mainly cyanobacteria, with a focus on those of low natural biomass or found in symbiosis with marine invertebrates, such as sponges and tunicates and to characterize "super-producing" marine cyanobacterial strains. Extracts will also be obtained from collections of tuft-forming marine cyanobacteria and planktonic/thin slime forming marine cyanobacteria for culture as well as cultured cyanobacteria isolated from invertebrate hosts under natural product-eliciting conditions. We will use a unique in vitro disk diffusion assay to both identify solid tumor selectivity in the extracts and to direct the isolation of putative anticancer agent. Drug structure will be determined by using and developing innovative NMR pulse sequences and integrating this with MS and other spectroscopic information. If necessary; we will scale-up the culture or recollect selective species to provide sufficient drug to advance to preclinical studies. The first step requires about 20 mg of drug and incorporates information from in vitro concentration-survival clonogenic studies on a solid tumor with pharmacokinetic information (serum and tumor drug levels). The drug is first formulated for intravenous administration and an HPLC assay is developed to monitor serum and tissue levels. The clonogenic/pharmacokinetic information is analyzed to determine whether the more expensive in vivo therapeutic trial should be undertaken. If positive, then an efficacy trial in tumor-bearing mice will be carried out in at least one xenograft model. Therapeutically active drugs will be pursued outside of this application.

Principal Investigator: Valeriote, Frederick, Ph.D.
Novel Cytotoxic Products from Marine Sponges (NIH R01 CA047135-20)

The overall goal of this project is the discovery and development of new anticancer drugs with solid tumor selectivity from leads obtained from collected and cultured marine cyanobacteria and marine microalgae. The need for new and effective anticancer drugs is critical given the paucity of ones active against the major solid tumors in people. Over the course of this grant, 450 taxonomically diverse samples are proposed to be obtained as a source of novel natural products. Micro-elicitation culture methods will be employed on a

set of these samples to thoroughly query their secondary metabolomes. Nine fractions plus crude extract are produced from each organism for the anticancer screen (over 900 test samples per year). We employ a unique and novel disk diffusion assay to both identify solid tumor selectivity in the initial extracts and also to direct the isolation of the putative anticancer agent. The assay has been expanded to examine the 7 major solid tumor types in vitro and then in vivo. We expect to both functionally and structurally identify about 6 solid tumor selective compounds per year. While many of the leads will be novel structures, some of the leads may be known compounds or analogues of known compounds; however, very few of these latter compounds will have been evaluated for anticancer activity either in vitro or in vivo. We expect to take all of our lead compounds through a drug development paradigm so as to determine whether they have clinical potential. The first step of drug development requires 15 mg of pure compound to produce in vitro IC50 values and concentration-survival clonogenic studies; and, in vivo maximum tolerated dose and pharmacokinetic information (plasma and tumor levels). The drug is formulated for intravenous administration and an HPLC assay is developed to monitor serum and tissue levels. We expect that all 6 of the yearly discovered in vitro lead compounds will be examined in this pharmacologic phase. These data will be analyzed to determine whether the more expensive efficacy trials in tumor-bearing mice should be undertaken. We expect 3 drugs per year will go to therapeutic efficacy trial in at least one xenograft model. Such a trial will likely require a further collection, culturing or synthetic efforts to gain sufficient material, estimated at 50 - 200 mg. We expect to find one compound per year that has efficacy in the xenograft models, and this lead structure will be chemically explored through synthesis of simple analogs and synthetic modification of the natural product. Therapeutically active drugs will be pursued further in preclinical and clinical development outside of this application. PUBLIC HEALTH RELEVANCE: Anticancer drug leads will be discovered, their structure determined and developed both in tissue culture and animal models to a stage where they should be attractive to either Biotech or Pharmaceutical companies to continue with their development towards the clinic. Given the lack of effective anticancer drugs for the major solid tumors, especially for metastatic disease, our leads can have a significant positive impact on the cancer patient.

Hypertension and Vascular Research

Senior Research Staff

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Research Summaries

Principal Investigator: Carretero, Oscar A., M.D.
Regulation of Renal Micro-circulation by the Connecting Tubule (NIH 1R01 HL088036-01A1)

In hypertension the pressure natriuresis set point is shifted to a higher pressure, due to an increase in both renal vascular resistance and Na+ reabsorption. The afferent arterioles (Af-Art) and efferent arterioles account for most renal vascular resistance; they control glomerular filtration rate (GFR) and peritubular pressure, and consequently renal function. Af-Art resistance is regulated by factors similar to those that control other arterioles; in addition, the Af-Art is also controlled by tubuloglomerular feedback (TGF). TGF operates via the macula densa, which senses increases in NaCl and sends a signal that constricts the Af-Art. We have evidence that increasing NaCl delivery to the connecting tubule (CNT) dilates the Af-Art, and that this dilatation can be blocked by inhibitors of Na+ transport. We refer to the cross-talk between the CNT and Af-Art as connecting tubule glomerular feedback (CTGF). Here we propose to study CTGF both in vitro and in vivo to determine its physiological role and the mechanisms by which Na+ causes CTGF. We will also study the regulation of CTGF by nitric oxide (NO) and the tubular renin-angiotensin system (RAS), since both NO synthase and renin and angiotensinogen are expressed in the nephron. In vitro and in vivo we propose to test the general hypothesis that Na+ reabsorption by the connecting tubule induces the release of arachidonic acid metabolites that diffuse to and promote dilatation of the Af-Art (CTGF response). Thus CTGF antagonizes vasoconstrictor stimuli such as TGF. The tubular RAS potentiates CTGF by stimulating Na+ transport by the CNT, while NO blunts CTGF by inhibiting this process. We will test this general hypothesis in four Aims. Aim I will test whether an increase in Na+ reabsorption in the CNT causes an increase in intracellular Ca++ via the Na+/ Ca++ exchanger, which results in Ca++-mediated activation of phospholipases, release of arachidonic acid, and formation of eicosanoids which diffuse to the Af-Art and cause dilatation. Aim II will test whether in vivo, CTGF opposes the vasoconstrictor effect of TGF and whether in the absence of TGF, CTGF causes Af-Art dilatation. Aim III will test whether NO produced by NOS 3 in the CNT decreases CTGF by blocking Na+ transport by ENaC via activation of guanylyl cyclase, increasing cGMP, activating cGMP-dependent protein kinase, and reducing cAMP. Aim IV will test whether the tubular RAS via Ang II and the AT1 receptor enhances CTGF directly by acting on ENaC and indirectly by stimulating the release of O2- via NADPH oxidase. This will be the first study to determine the role of the renal connecting tubule in the regulation of afferent arteriole resistance and glomerular filtration rate. This is a novel mechanism that will provide new insights on the regulation of renal function.

Principal Investigator: Carretero, Oscar A., M.D.
PPG: Vasoactive Autocoids in Blood Pressure Regulation (NIH P01 HL028982)

This PPG was started in September, 1982. The central theme is "the study of the role of vasoactive systems (autocrine, juxtacrine, paracrine and endocrine) in the regulation of renal function and blood pressure (BP) and mediation of target organ damage". The general hypothesis to be tested is that there is a balance between systems that promote water and sodium retention, hypertension and target organ damage (Ang II, COX-2 products and free radicals), and systems that antagonize these effects (kinins, NO, Ac-SDKP and activation of the Ang II type 2 receptor). Alterations of this balance in favor of the former are responsible for the development of hypertension and target organ damage, while alterations of this balance in favor of the latter have therapeutic effects. We will use molecular, physiological, and pharmacological approaches to study vasoactive systems at the subcellular, cellular, and isolated organ levels and in intact animals in both acute and chronic models, including transgenic mice. In project 1 we will study whether a novel peptide (Ac-SDKP) alters the balance between systems that promote and oppose target organ damage in favor of the latter, thus preventing and regressing this process. In project 2 we will study whether the local effects of Ang II in the heart are antagonized by activation of the AT2 receptor, kinins and NO. In project 3 we will study whether COX-2 via EP1 and EP3 receptors promotes the development of cardiovascular disease and whether this effect is antagonized by the PPAR receptor. In project 4 we will study the regulation of renal microcirculation by the juxtaglomerular apparatus to see whether there is an interplay between vasodepressor autacoids (NO, kinins and vasodilator eicosanoids) and vasopressor systems (Ang II, reactive oxygen species and cP450 vasoconstrictor metabolites). In project 5 we will study whether NO produced by eNOS in the renal tubules alters the water and sodium balance in favor of natriuresis and diuresis, thus opposing hypertensive stimuli. Four core units (Administrative, Analytical and Morphology, Mutant Mouse, Biostatistics) will support and facilitate the scientific efforts of the investigators. Special expertise is centralized in the cores so that resources can be used more efficiently. The Program Project provides integration of our efforts, continuing collaboration and sharing of ideas and expertise; thus it accelerates acquisition of knowledge on the pathogenesis of hypertension and target organ damage.

Principal Investigator: Garvin, Jeffrey L., Ph.D.
Blood Pressure Regulation: Novel Roles for the Kidney (NIH 1P01HL090550-01A1)

This is a revised Program Project Grant, the central theme is that "endocrine, paracrine and autoerine factors produced by the epithelial, vascular smooth muscle, endothelial and interstitial cells play an important role in regulating salt and water excretion by the kidney, and thus blood pressure, by altering renal hempdynamics, changing NaCI reabsorption and mediating cross-talk between cells." The central hypothesis to be tested is that blood pressure regulation by the kidney occurs via integration of the actions of prch and anti-hypertensive agents on nephron transport, renal vascular resistance, release of renal hormones and cross-talk between epithelial and vascular cells. Defects in the integration process and/or actions of pro- and anti-hypertensive agents lead to renal dysfunction, salt retention and hypertension. This hypothesis will be tested in four projects that break new ground in our understanding of how the kidney regulates blood pressure. Project 1 will study whether increasing luminal flow in the thick ascending limb stimulates nitric oxide (NO) production by NO synthase 3, the signaling cascades

involved, the effects of flow-induced NO on NaCI reabsorption, and whether a defective response to flow-stimulated NO production enhances sait retention and promotes salt-sensitive hypertension. Project 2 will test whether NO inhibits thick ascending limb NaCI reabsorption by activating cGMP-stimulated phosphodiesterase 2 (PDE2), reducing cAMP, and thus decreasing Na/K/2CI cotransport. It will also test in Dahl salt-sensitive rats whether a reduction in NOinduced inhibition of NaCI reabsorption and hypertension is caused by diminished PDE2 activity and enhanced cGMP degradation by phosphodiesterase 5. Project 3 will test whether heme oxygenases in the macula densa produce carbon monoxide (CO) and biliverdin, which act synergistically and in an autocrine manner to inhibit tubuloglomeailar feedback. It will also test whether CO acts by stimulating cGMP which inhibits Na/K/2CI cotransport, and blocks ATP release and biliverdin acts by decreasing superoxide, thereby increasing NO. Project 4 will test whether increased extracellular Ca inhibits renin release by activating Ca sensing receptors on juxtaglomerular cells which increases intracellular Ca and reduces cAMP production by inhibiting adenylyl cyclase-V and stimulating phosphodiesterase 1. These studies will be performed in vitro at the subcellular, cellular, and isolated tissue levels and in vivo using both acute and chronic models, and genetically manipulated mice. The four projects will be supported by three core units (Administrative, Molecular Biology and Analytical, and Imaging) that will facilitate the scientific effort. The Program Project Grant will provide integration of our efforts, continued collaboration and shared ideas and expertise. Thus it will accelerate acquisition of knowledge of the novel mechanisms by which the kidney regulates blood pressure, and may provide new targets for anti-hypertensive drugs.

Principal Investigator: Herrera, Maria Marcella, Ph.D.
Role of the Kidneys in Hypertension: Paracrine Actions of NO in the Renal Medulla (NIH 5F32DK081333-02)

Hypertension afflicts approximately 1/3 of the U.S. population. The kidney plays an important role in the regulation of blood pressure through the regulation of extracellular volume. Renal nitric oxide (NO) plays an important role in the regulation of extracellular volume and thus blood pressure. Inhibition of renal NO production in general and in the renal medulla specifically causes hypertension. The latter is due to changes in medullary blood flow and nephron transport. In the renal medulla, NO dilates the vasa recta pericytes to increase medullary blood flow. At least some of this NO comes from the adjacent thick ascending limb of the loop of Henle (THAL). Free diffusion is assumed to be the primary mechanism whereby NO leaves the THAL and enters the pericyte. However we have recently shown that aquaporin-1 (AQP-1) transports NO across cell membranes 4 times faster than free diffusion and that AQP-1-dependent NO transport is required for endothelium-induced relaxation of thoracic aortas. Although THALs reabsorb no water, their basolateral membranes are water permeable. Our preliminary data show that this is in part due to AQP-1, which is also expressed in the vasa recta. We hypothesize that AQP-1 transports NO out of the THAL and into the vasa recta pericytes. First, we will investigate whether AQP-1 transports NO out of the THAL by measuring NO efflux from single, microperfused THALs isolated from wild-type and AQP-1 knockout (-/-) mice using a NO-selective electrode. Second, we will investigate whether

AQP-1 transports NO into vasa recta pericytes by measuring NO influx into single, microperfused vasa recta isolated from wild-type and AQP-1 -/- mice using fluorescent dye and fluorescent confocal microscopy. Third, we will investigate whether AQP-1-dependent NO transport is involved in tubular vascular crosstalk between the THAL and vasa recta pericytes by measuring the effect of stimulating NO production by the THAL on NO influx into descending vasa recta from wild-type and AQP-1 -/- mice using a single, isolated THAL with an adjacent descending vasa recta attached. Finally, we will measure the effect of restoring AQP-1 expression by gene transfer technology specifically in the THAL, vasa recta pericytes, or both on: 1. Efflux of NO out of the THAL, 2. Influx of NO into the Vasa recta and 3) THAL-derived NO-dependent relaxation of vasa recta. Data from this proposal will contribute to our understanding of regulation of renal blood flow. Defects in AQP-1 - dependent NO transport from the THAL to the DVR may play a role in the development of hypertension. Results from this proposal may offer new targets for the development of pharmacological tools for the treatment of hypertension.

Principal Investigator: Mendez, Mariela, Ph.D.
Molecular Mechanism of Renin Release, Role of Snares (NIH 5F32HL096346-02)

Renin is a rate-limiting enzyme in the formation of Angiotensin-ll and plays a dominant role in the control of blood pressure. Abnormally enhanced circulating renin induces a pathological increase in blood pressure, ultimately leading to cardiovascular dysfunction and kidney disease. The kidney secretes most circulating renin. Renin is stored in granules in kidney pre-glomerular juxtaglomerular (JG) cells and it secreted mainly after stimulation of intracellular cAMP. Renin release from JG cells occurs by exocytosis, however the mechanism and proteins involved in cAMP-stimulated renin release are not known. In most cells, exocytosis is mediated by "soluble NSF attachment protein receptors" (SNAREs).There are 3 essential SNARE proteins required to form a complex that mediate exocytosis: one vesicle associated membrane protein (VAMP), one SNAP and one syntaxin. The expression and function of SNAREs in juxtaglomerular cells have not been studied. Our preliminary data suggest that VAMP-2, VAMP-3, syntaxin-4 and SNAP-23 are expressed in primary cultures of mouse JG cells. Our main hypothesis is that VAMP-2, syntaxin-4 and SNAP-23 form the essential SNARE complex that mediates cAMP-stimulated renin release from juxtaglomerular cells. First, we will study the localization of VAMP-2, syntaxin-4 and SNAP-23 in primary cultures of mouse JG cells. Second, we will study their individual involvement on cAMP-stimulated renin release by using a) clostridial toxins that specifically cleave and inactivate VAMP-2 and SNAP-23; b) adenoviral-mediated short interfering RNA (siRNA) c) adenoviral expression of dominant negative truncated syntaxin-4 and SNAP-23. We will also determine whether VAMP-2 physically interacts with syntaxin-4and SNAP-23 in JG cells before and after stimulation of endogenous cAMP. PUBLIC HEALTH RELEVANCE: Hypertension affects 29% of the adult population in the U.S. and is a major risk factor for kidney and cardiovascular disease. In a large percentage of hypertensive patients plasma renin is elevated. The proteins involved in renin exocytosis are not known. Identifying the specific proteins required for renin exocytosis will increase our understanding of the basic mechanism of renin release and will provide new targets for pharmacological

intervention aimed at inhibiting the renin-angiotensin system. This would provide more effective alternatives to current therapies for the treatment of High Blood Pressure, making this area of basic research critical for future advances.

Principal Investigator: Rhaleb, Nour-Eddine, Ph.D.
Hypertension and Collagen: Effect of Ac-SDKP (NIH 2R01HL071806-05A1)

Hypertension is a major risk factor for .cardiovascular and renal diseases. Inflammation and components of the extracellular matrix (EM) have a negative impact on the physiology and function of end target organs such as the arteries, heart and kidneys in hypertension. Blocking angiotensin-converting enzyme (ACE) decreases angiotensin II (Ang II) and increases kinins, leading to decreased cardiovascular inflammation, hypertrophy and collagen. ACE inhibitors (ACEi) increase plasma Ac-SDKP, a negative regulator of cell proliferation present in plasma and tissue. In hypertension and heart failure, Ac-SDKP prevents monocyte/macrophage infiltration and fibrosis in the aorta, kidneys and left ventricle (LV). By virtue of its anti- fibrotic and anti-inflammatory effects, Ac-SDKP was able to improve renal function in hypertension, diabetes and other experimental models of renal diseases. However, the mechanism(s) or receptor(s) involved in Ac- SDKP's cardiovascular and renal effects are not fully understood. We hypothesize that Ac-SDKP exerts its anti-inflammatory and anti-fibrotic effects on the cardiovascular and renal systems in hypertension via specific receptor(s) located on the plasma membrane, contributing to end organ protection. In aim I we will identify and characterize Ac-SDKP receptors using pharmacological tools [l]Hpp-Aca-SDKP, 5(6)FAM-SDKP and new analogues of Ac-SDKP), proteomic technology, and cloning techniques. In aim II we will 1) perform a more extensive examination of the structural activity of Ac-SDKP in order to a) develop potent antagonists that lack partial agonistic activity and b) improve the affinity of the radio-iodinated peptide; and 2) characterize the Ac-SDKP receptor in fibroblasts and macrophages (rat and human), using [l]-Hpp- Aca-SDKP and newly developed antagonists; and 3) compare rat cardiac fibroblasts and human cardiac fibroblasts for the inhibitory effect of Ac-SDKP or analogues on collagen synthesis and proliferation. In aim we will study whether Ac-SDKP receptor activity depends on mechanisms closely linked to the regulation of receptor internalization. In aim IV We will determine 1) the effect of Ac-SDKP on the non-receptor tyrosine kinase Src and HB-EGF on Ang II and ET-1-stimulated transactivation of the EGFR; 2) whether Ac-SDKP inhibits the effects of calcium ionophores or EGF on p42/44 MAPK and collagen synthesis; 3) whether PLC, EGFR, cSrc, calmodulin kinase or IP3 inhibitors attenuate MAPK activity and collagen synthesis to the same extent as Ac-SDKP in response to Ang II or ET-1; and 4) whether inhibition of MAP kinase activation by Ac-SDKP is mediated by MAP kinase phosphatase-1, using selective inhibitors of phosphatases and specific SiRNAs. This project will provide important new information on the d the mechanism of action of Ac-SDKP. Consequently, it will identify another component (Ac-SDKP) as part of the multiple mediators participating in the cardioprotective effects of ACEi in hypertension.

Infectious Disease

Senior Research Staff

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Jose Vazquez, M.D.
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Research Summaries

Principal Investigator: Markowitz, Norman, M.D.
CPCRA Clinical Trial Unit ACTG (U01AI069503-01)

The Division of Infectious Diseases at Henry Ford Hospital (HFH) was an original CPCRA unit in 1989 and was refunded as a CPCRA Unit in 1994. The HFH unit has extensive experience in conducting community-based clinical trials with excellent long-term follow-up. As of 11/30/98, the HFH unit has enrolled 1,506 subjects in CPCRA studies, with 7,392 clinic visits. In 25 percent of studies, the unit accrual exceeded 10 percent of total CPCRA enrollments. HFH ranks third in overall study accrual, fifth in cost effectiveness, and in the top third for overall data quality among active CPCRA units. In protocols that require long-term follow-up, there are no patients whose vital status is unknown and only one patient with unknown diagnostic status. The Henry Ford Health System (HFHS) serves a diverse population of HIV-infected persons in Detroit and Southeastern Michigan. The HFH CPCRA unit serves an HIV-infected population that is 86 percent male, 14 percent female, 55 percent black, 42 percent white, 2 percent Hispanic and 24 percent injection drug users. Extensive efforts are being made to increase outreach and protocol participation by under-served populations such as minority women and injection drug users. All HIV positive persons in the HFHS receive care under the auspices of the Division of Infectious Diseases (and CPCRA primary care providers). This centralized structure with research protocols offered to all patients has led to high levels of participation in clinical trials. The HFH Community Advisory Board is integrated into all aspects of the HIV clinical care and research. HFH investigators support the CPCRA serving on numerous committees and study teams. The local physicians, nurses, CAB and patients all actively support the proposed scientific agenda to evaluate the long-term virologic, immunologic and clinical impact of antiretroviral therapies in diverse patient populations across the full spectrum of HIV disease. The HFH unit is committed to enroll 42 patients into CPCRA 057 (PIP), 80 patients into CPCRA 058 (FIRST) and has aggressively enrolled patients into CPCRA 059 (IL-2). The HFH CPCRA unit expects to enroll a minimum of 250 HIV-infected patients on study at any given time throughout the course of this grant.

Principal Investigator: Markowitz, Norman, M.D.
Strategic Timing of Antiretroviral Therapy (START OR INSIGHT I01)

Recent data from epidemiological studies indicate that the risk of AIDS is graded and persists even at levels of relatively preserved immune function. Moreover rates of serious

non-AIDS diseases - cardiovascular, renal and hepatic disease and non-AIDS malignancies - are lower at higher levels of immune function. Antiretroviral treatment appears to reduce both AIDS-related and non-classically AIDS-related complications. INSIGHT START 001 (Strategic Timing of AntiRetroviral Treatment) is an international NIH-funded randomized trial to determine whether starting antiretroviral therapy earlier than currently recommended in DHHS guidelines reduces HIV-associated morbidity and mortality. Individuals are enrolled from over 22 countries in the Americas, Europe, Middle East, and Australasia. Over 4000 individuals will be enrolled in START. The entire study is expected o last about 6 years.

Principal Investigator: Zervos, Marcus, M.D.
Annual Estimates of Influenza Vaccine Effectiveness for Preventing Laboratory-Confirmed Medically Attended Outcomes (Centers for Disease Control and Prevention/DHHS)

Influenza vaccination is the most effective means of preventing influenza virus infection and its more severe complications, such as pneumonia. Due to the changing nature of the influenza viruses, regular updating of vaccine components and annual vaccination are necessary for continuing vaccine protection. Similarly, annual evaluation of vaccine effectiveness is desirable to inform public health policy and advise vaccine manufacturers. The "Annual Estimates of Influenza Vaccine Effectiveness for Preventing Laboratory-confirmed Medically-attended Outcomes" (MFIVE) study provides useful information regarding both the use and effectiveness of vaccine. This observational study uses defined surveillance periods and laboratory-confirmation of medically attended influenza-like illnesses to assess annual effectiveness of licensed influenza vaccines in preventing medically-attended influenza, including influenza-related complications. This following are the study objectives: (1) identification of patient cohorts that are followed for outpatient health care contacts for acute respiratory illness (ICD-9-CM 460-466) or pneumonia and influenza (ICD-9-CM 480-487), and hospitalization for pneumonia and influenza (ICD-9-CM codes 480-487); (2) collection of specimens from a subset of patients with ILI and laboratory processing of specimens using viral culture and real-time PCR methods to confirm illnesses as influenza; (3) determination and validation of influenza vaccination status of cohort members; and (4) assessment of vaccine effectiveness through analyses are health care encounter data. Study objectives will be carried out each year, over three years of influenza seasons beginning in Fall 2008 with surveillance activities conducted within five HFHS primary care ambulatory sites and at Henry Ford Hospital.

Pulmonary and Critical Care Medicine

Senior Research Staff

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Michael Simoff, M.D.

Research Summaries

Principal Investigator: Kvale, Paul, M.D.
National Lung Screening Trial (NLST) (NIH/NCI NO1 CN25512)

Approximately 75 per cent of lung cancer patients present with advanced disease, for which there is no effective cure. The best hope of lung cancer survival comes with early stage diagnosis, which generally responds favorably to surgical resection. The National Cancer Institute-sponsored NLST is investigating whether annual screening with low-dose helical computed tomography (*spiral* CT) can reduce lung cancer mortality, compared to annual chest x-ray, by leading to earlier stage detection. NLST was launched in September 2002 and by February 2004 had completed its nationwide recruitment goal of 50,000 high-risk study subjects. More than 30 study sites nation-wide are participating in this study. With a recruitment goal of 3500, HFHS is one of the largest study centers in the country. Study subjects receive an annual screening, half with spiral CT and half with chest x-ray, for three consecutive years and will be followed up with annual monitoring until 2009.
In 2003, Dr. Paul Kvale took over leadership as principal investigator of NLST at HFHS from Dr. Raymond Demers. In 2003 at HFHS, 2675 individuals were recruited and 2534 individuals received their screening intervention. By the end of 2003, a total of 3395 subjects had been recruited into NLST at HFHS.
Large cohort studies such as NLST frequently generate secondary studies that contribute consequential scientific information far beyond that intended by the primary study hypothesis. In 2003, NLST was at a nascent stage, and not enough data had been generated to initiate many ancillary studies. However, HFHS researchers were developing ideas for a NIH RO1 proposal to investigate the application of artificial intelligence to digital computed tomography images and improve accurate detection of lung cancers. HFHS is making valuable contributions to NLST, which is expected to produce definitive answers to important public health questions within the next 5 years.

Principal Investigator: Kvale, Paul, M.D.
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (NIH N01-CN2-5512)

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a large scale, randomized controlled trial to determine whether certain screening tests will reduce the number of deaths from these cancers. PLCO is a multi-institutional clinical trial being conducted at ten sites, geographically and demographically disparate, around the U.S. This controlled trial is a Phase III trial conducting human subjects research. PLCO enrolled 154,942 male and female participants. The PLCO participants are comparable to the general United States population. Life style, dietary and risk factor information was collected from participants. The intervention arm received for lung cancer, posterior-anterior (PA) chest x-ray annually for four screens (except never smokers who received three annual screens), flexible sigmoidoscopy (FSG) at enrollment and again at the fourth or sixth annual screening interval depending on time of enrollment to screen for

colorectal cancer. For prostate cancer, men received six annual prostate screens with prostate-specific antigen (PSA) and four digital rectal exams (DRE). Women were screened for ovarian cancer with CA-125 antigen for six annual screens and with transvaginal ultrasound (TVU) for four annual screens. The usual care (control) arm received regular health care from their primary care provider. Whole blood, sequential serum samples and one plasma sample were collected from the intervention arm. Aliquots from these samples are stored in the PLCO Biorepository through collaboration with the Division of Cancer Epidemiology and Genetics (DCEG). The usual care arm provided buccal cell DNA samples which are also stored in the PLCO Biorepository. The PLCO Biorepository currently has over 2.9 million specimens that can be used for etiologic and early marker studies. PLCO is collecting colo-rectal, ovarian, prostate and lung tumor tissue from those participants who have developed cancer. Tissue microarrays are then constructed. STUDY DESIGN The PLCO is a two-armed, randomized trial in which more than 38,000 men were screened for lung, colorectal, and prostate cancers and approximately 39,000 women were screened for lung, colorectal, and ovarian cancers. Equal numbers of men and women participating as controls continue their usual medical care practices. The eligible age range at entry was 55-74 years. Both screened and control participants are to be followed for at least 13 years from randomization for cancer and death ascertainment to determine if the screening regimen results in reduced disease-specific mortality. Baseline information including demographic characteristics, known risk factors for the cancers under study, and screening history were collected from all participants. In addition, participants completed dietary, food frequency questionnaires and subsequently a risk factor questionnaire that supplements the baseline data provided at the time they enrolled. Blood samples collected at each screening visit were processed into separate components and stored for future molecular analyses. Control participants provided Buccal cell DNA. Participants in both the intervention and control arms completed a dietary questionnaire. All participants also provide annual health status information. Special efforts made to enhance the recruitment of minorities occurred at several screening locations. One site in Detroit, MI focused efforts on increasing the participation of African Americans. A site in Denver, CO hired Spanish speaking staff to enhance the number of Hispanic Americans enrolled in PLCO. BIOREPOSITORY The PLCO Biorepository contains approximately 2.9 million biologic specimens collected during the six screening years. These samples include serum, plasma and buffy coat and DNA samples. These specimens are an invaluable resource for cancer research. Some of the characteristics that make the PLCO biospecimens uniquely valuable include: - Large sample size allows statistical power - Specimens are collected prospectively, before cancer diagnosis - Serial specimens are collected at each of the 6 annual screenings - Detailed background and clinical data are available The PLCO Etiology and Early Marker Studies (EEMS) component is an integral part of the PLCO Trial. The PLCO EEMS has two main focuses: etiologic studies that investigate the environmental, biochemical and genetic risk factors for cancer; and early detection studies that aim to develop reproducible, diagnostics-ready biomarkers of early disease. The PLCO EEMS directly addresses the following strategic priorities of the National Cancer Institute: - Understand the causes and mechanisms of cancer - Improve early detection and diagnosis.

Sleep Medicine

Senior Research Staff

Christopher Drake, Ph.D.
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Timothy Roehrs, Ph.D.
Thomas Roth, Ph.D.

Research Summaries

Principal Investigator: Drake, Christopher, Ph.D.
Longitudinal Study of Predisposition and Life Events in Triggering Insomnia (NIH R01 MH082785)

Most models of insomnia hypothesize an individual predisposition to the disorder along with precipitating factors. Converging evidence suggests exposure to stressful life events can precipitate insomnia. However, research has yet to identify a trait predisposition to insomnia, or investigated the interaction of stress exposure with that predisposition. The purpose of this study is to prospectively determine the importance of sleep reactivity (i.e., non-insomniac individuals who reliably exhibit sleep disruption in response to stress) for the development of chronic insomnia following naturalistic exposure to stressful life events. We have developed and validated a measure of sleep reactivity that in normal individuals is predictive of 1) polysomnographic sleep disturbance in response to laboratory stressors and 2) the prospective development of insomnia over a 13-month follow-up period. It is hypothesized that normal sleeping individuals without a history of insomnia who have a high premorbid sleep reactivity will be at greater risk (i.e., predisposed) to developing chronic insomnia following exposure to stressful life events when compared to individuals with low sleep reactivity. Prospective data will be collected from 2,200 individuals without insomnia regarding their experiences of stressful life events and insomnia incidence during a 2-year assessment period. It is hypothesized that these two factors will have a greater than additive effect in predicting insomnia incidence (i.e., exposure X predisposition interaction). The predictive value of laboratory measured sleep reactivity in predicting insomnia incidence will also be determined in a randomly selected subset of individuals over a 4 year follow up period. Identifying and following individuals who are likely to develop insomnia will allow the study of phenotypic traits characteristic of insomnia prior to the development of the disorder, improve our limited understanding of its temporal course and its association with morbidity, help identify specific triggers and their impact in at-risk populations, and permit efforts to be directed toward prevention rather than treatment. PUBLIC HEALTH RELEVANCE: Insomnia is a sleep disorder hypothesized to be triggered by stress in vulnerable individuals. The current proposal is a 2 year prospective study testing the hypothesis that elevated "sleep reactivity" is a predisposing risk factor for the development of chronic insomnia following exposure to stressful life events. Specifically, we hypothesize an interaction between stress and the predisposition to insomnia whereby

individuals with a predisposition will have a higher incidence of the disorder given stress exposure compared to non-predisposed individuals.

Abstracts – Medical & Surgical – Part II (Other Departments)

- **Dermatology**
- **Neurology**
- **Neurosurgery**
- **Orthopedics (Bone & Joint Center)**
- **Surgery**
- **Urology**

Dermatology

Senior Research Staff

Henry Lim, M.D., Chairman
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Li Zhou, Ph.D.

Research Summaries

Principal Investigator: Mi, Qing-Sheng, M.D., Ph.D.
miRNAs and Epidermal Langerhans Cell Development and Function
(1R21AR059976-01)

Dendritic cells (DCs), a heterogeneous population originating from hematopoietic stem cells (HSCs) in the bone marrow (BM), are professional antigen-presenting cells that play key roles in determining the balance between immunity and tolerance induction. Langerhans cells (LCs) are skin-resident DCs that express the C-type lectin Langerin and have a life cycle distinct from many other types of DCs. Even though LCs were first described more than 100 years ago, their development and immunological functions still remain enigmatic. MicroRNAs (miRNAs), a class of 21-25 nt single-stranded non-coding small RNAs, are increasingly being recognized as important regulators of gene expression through the inhibition of effective mRNA translation. The ribonuclease III enzyme Dicer is required for the processing of mature and functional miRNAs. Using Cre-loxP tissue-specific Dicer deletion, our laboratory and others have reported that deletion of miRNAs in HSCs significantly affects the development and function of different immune cells. However, the role of miRNAs in the development of LCs is still currently unknown. To test the roles of miRNAs in the development of LCs, we generated a new mouse strain with tissue- specific disruption of Dicer in LCs using Langerin-Cre. Surprisingly, mice with miRNAs-deficiency in LCs had significantly reduced number of epidermal LCs and the expression of Langerin was significantly reduced in miRNA-deficient LCs. Furthermore, LCs have a specific miRNA gene expression profile compared to other immune cells. Thus, our central hypothesis is that miRNAs are very important components of the molecular circuitry that controls LC development and function. We will test our hypothesis by pursuing the following three

Specific Aims: 1) To determine the expression patterns of miRNAs during LC maturation; 2) To investigate the role of miRNAs in LC development and function; 3) To identify the target genes of miRNAs involved in LC development. Our study will dramatically advance our knowledge on the molecular mechanisms underlying LC development and function, and may also facilitate the development of new intervention strategies for cancer, infectious and autoimmune diseases. PUBLIC HEALTH RELEVANCE: Langerhans cells (LCs) are skin-resident DCs that maintain skin homeostasis, but the detailed molecular pathways regulating LC development and function remain largely unknown. MicroRNAs (miRNAs) are a recently discovered class of evolutionarily conserved small non-coding RNAs that negatively regulate the expression of protein-coding genes. The overall goal of this proposal is to identify the LC-specific miRNA expression profile during development and define their function and direct targets. The results from the above pioneering studies may not only illuminate the new immunological and molecular mechanisms underlying LC development, but may also facilitate the development of new intervention strategies for related autoimmune diseases, infection, and cancer based on the LC cell therapy.

Neurology

Senior Research Staff

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Research Summaries

Principal Investigator: Chen, Jieli, Ph.D.
Neurorestorative Therapy of Stroke with Agents that Increase HDL (NIH R01 AG03181101A1)

High-density lipoprotein cholesterol (HDL-C) has a positive effect on endothelial cell and vascular wall function. To our knowledge, there are no studies investigating the use of increasing HDL-C as a neurorestorative therapy to promote brain plasticity and recovery of neurological function after stroke. Based on robust preliminary data that agents which increase HDL-C when administered starting one day after stroke, promote vascular remodeling and significantly reduce functional deficits after ischemic stroke, we seek to develop a novel neurorestorative treatment of ischemic stroke. The following specific aims and associated hypotheses are designed to develop this restorative therapy and to investigate their molecular mechanisms in a pre-clinical rodent model of middle cerebral artery occlusion (MCAo). Aim 1 will investigate safety, toxicity and neurorestorative effects of select agents which increase HDL-C after stroke in adult mice. We hypothesize that treatment of stroke in mice with agents that increase HDL-C {Niaspan (N) and TO901317 (T)} initiated at one day after stroke onset improves neurological functional recovery, and is safe and well tolerated. The minimally toxic and more effective agent (Niaspan or TO901317, N-or-T) that promotes functional outcome after stroke will be identified and will be employed in the following Aims 2 & 3. Aim 2 will elucidate the effect of N-or-T treatment of stroke on the regulation of angiogenic factors and vascular remodeling, i.e. cerebral blood flow (CBF), angiogenesis, and arteriogenesis. The contribution of vascular remodeling induced by N-or-T in functional outcome after stroke will be tested. We hypothesize that N-or-T treatment of stroke induces endothelial nitric oxide synthase (eNOS) and Angiopoietin-1(Ang1)/Tie2 signaling activity, which increase CBF, angiogenesis and arteriogenesis after stroke in mice. Inhibition of vascular remodeling by an anti-angiogenic factor, Angiostatin (K1-5), impairs functional outcome after stroke and attenuates the N-or-T induced restorative effect after stroke in mice. Aim 3 will identify the molecular signaling pathways by which N- or-T induces vascular remodeling and functional recovery after stroke. The contribution of eNOS and Ang1/Tie2 to N-or-T induced restorative effect and vascular remodeling will be examined by using eNOS knockout mice and a specific antibody to Tie2 in mice subjected to stroke and treated with N-or- T, respectively. The underlying hypotheses are that: Increasing HDL-C agent (N-or-T) fosters functional recovery after stroke by increasing the expression and activation of eNOS and Ang1/Tie2 signaling in cerebral tissue; these factors promote vascular remodeling via the induction of angiogenesis and arteriogenesis, which augment functional recovery. This study provides a new and highly effective way to treat stroke and may permit translation of our findings of the restorative therapeutic benefit of agents which increase HDL-C in experimental stroke to the patient. PUBLIC HEALTH RELEVANCE: Stroke is the third leading cause of morbidity and long-term disability. High-density lipoprotein cholesterol (HDL-C) has a positive effect on endothelial cell and vascular wall function. Based on robust preliminary data that agents which increase HDL-C when administered starting one day after stroke, promote vascular remodeling and significantly reduce functional deficits after ischemic stroke, we seek to develop a novel neurorestorative treatment of ischemic stroke. Niaspan and TO901317 are effective medications for increasing HDL-C. Thus, we propose to develop neurorestorative therapy for stroke using agents that increase HDL-C and to investigate their molecular mechanisms in a pre-clinical rodent model of middle cerebral artery occlusion (MCAo). This study provides a new and highly effective way to treat stroke and may permit translation of our findings to the patient.

Principal Investigator: Chopp, Michael, Ph.D.
Center for Stroke Research (NIH P01 NS23393-17)

The applicants propose a highly integrated application focused on preclinical and clinical studies to investigate and develop treatment of stroke with an anti-platelet aggregation agent alone, and in combination with thrombolysis using recombinant tissue plasminogen activator (rtPA). Permeating this Program is the development and application of MRI to enhance the management of the stroke patient. Three interdependent Projects and two Cores constitute this grant application. Project 1, Anti-Platelet Aggregation Therapy for Embolic Stroke, will investigate the mechanisms promoting secondary thrombosis after embolic stroke and treatment with rtPA in rat, and will test, in a controlled experimental model, treatment of embolic stroke with an antibody against the GPIIb/IIIa receptor. This receptor binds the platelet to fibrin and is responsible for platelet aggregation and therefore, platelet mediated thrombosis. This project leads into Project 2, MR Assessment of Transient Cerebral Ischemia, which develops and applies a multi-parameter MRI model to experimental embolic stroke in rats. The goals of this Project are to develop and test the application of the multi-parameter MRI model to identify candidates for therapy and to exclude candidates from therapy after embolic stroke. In addition, the MRI response to thrombolysis with rtPA and rtPA in combination with an antagonist to platelet aggregation will be tested. Projects 1 and 2 form the preclinical support for a Phase II Pilot Clinical Trial of treatment of stroke with an anti-platelet aggregation agent, abciximab. This Project will test activity of treatment of the stroke patient with abciximab and will identify an MRI based surrogate marker for activity and accrue MR data to select patients for anti-platelet aggregation therapy. Core A is an Administrative and Biostatistical Core. Core B, the MRI core, services all three Projects. The Program Project provides an integrated highly coherent effort to enhance management and therapeutic intervention in the treatment of acute stroke.

Principal Investigator: Ewing, James, Ph.D.
MRI Biomarkers of Response in Cerebral Tumors (NIH R01 CA135329-01A1)

Malignant gliomas present great difficulties in treatment, with little change over the past 25 years in the median survival time of 12 months. Current treatment options include surgery, radiotherapy (RT), and chemotherapy. New therapies aimed at suppressing the formation of new vasculature (antiangiogenic treatments), or destroying formed tumor vasculature (vascular disrupting agents) show promise. This application will use magnetic resonance (MR) contrast agents (CAs) and MR detection to measure blood volume, the blood-to-brain transvascular transfer constant, the extravascular extracellular space, and the total extracellular space in cerebral tumors, and also to measure tumor blood flow using MR arterial spin tagging. These parameters present an important summary of the physiology of vasculature, both normal and tumorous. It is proposed to use these vascular parameters as MR biomarkers in animal models of cerebral gliomas. In a series of experiments, we will examine the change in MR-measured vascular parameters after antiangiogenic therapy, after vascular disrupting agent, and after RT, with all MR measures correlated with histopathological assessments of vascular and

cellular density in the model tumors. After single-agent therapies are studied, combination therapies will be studied, and MRI vascular biomarkers will be examined as predictors of response as judged both by histopathological assessments and long-term survival. At the completion of these studies, the relation of MR-measured vascular parameters to cellular responses to single and combination therapies will be established, and the utility of MR-measured vascular parameters as predictors of long-term survival assessed. The MR-measured parameters can be translated to clinical use and evaluated as predictors of human tumor response to therapies. These studies represent a first step in a paradigm shift in cancer treatment delivery from a heuristic and formulaic approach to an individualized plan of image guided treatment and response monitoring. PUBLIC HEALTH RELEVANCE: The utility of quantitative MR-measured vascular parameters for predicting brain tumor response to promising anti-angiogenic agents and vascular disrupting agents applied singly or in combination with or without radiation therapy will be shown. The studies presented represent a first step in a paradigm shift in cancer treatment delivery from a one-solution-fits-all approach to an individualized plan of image guided treatment and response monitoring.

Prinicpal Investigator: Jiang, Feng, PharmD.
ADAM 17 and Glioma-tumor Progression and Treatment (NIH R01 CA129446-01A2)

There are no treatments of glioma multiforme that substantially extend life. The reasons behind the inability to effectively treat glioma remain obscure. In this proposal, based on robust preliminary data, we develop a novel hypothesis, that the enzyme, a disintegrin and metalloproteinase-17, also known as, tumor necrosis factor converting enzyme (ADAM17, TACE) fosters glioma invasion, proliferation and survival. Thereby inhibition of ADAM17 will be effective in reducing tumor growth. We propose three specific aims and corresponding hypotheses, directed at fully investigating the potential of ADAM17 as a pro tumorgenic agent and inhibition of ADAM17 as an anti-tumor treatment. Aim 1: Characterize the function of ADAM17 in glioma invasion, proliferation and survival in vitro, and in tumor progression in vivo. Hypothesis 1a: Increased ADAM17 activity induces invasion and promotes cell proliferation and survival of glioma cells in vitro and promotes tumor progression in vivo. Hypothesis 1b: ADAM17 activation of the epidermal growth factor (EGF) signaling pathway promotes glioma invasion, cell proliferation and survival, by stimulating the PI3K/Akt pathway. Aim 2: Investigate the role of ADAM17 in glioma progression in the context of hypoxic stress. Hypothesis 2: ADAM17 transcription and proteolytic activity are up-regulated by hypoxia-induced cellular stress, and this increase leads to enhanced glioma proliferation, invasiveness and survival. Aim 3: Investigate the therapeutic effectiveness of ADAM17-targeting RNAi gene therapy to treat U87 and HF66 human glioma xenographs in nude mouse models. Hypothesis 3: ADAM17-targeting RNAi gene therapy decreases ADAM17 expression and proteolytic activity within glioma cells, and thus reduces tumor progression and prolongs survival of nude mice bearing intracranial glioma xenographs. Both in vitro and in vivo models of glioma are employed in the proposed studies. Methods used range from siRNA to laser capture confocal microscopy and magnetic resonance imaging in an effort to dissect the contribution of ADAM17 to tumor

progression and to elucidate the molecular bases for tumor progression and effective treatment. Our long term goal is to develop an effective treatment for this devastating brain tumor and to translate our findings from the experimental system to the human.

Principal Investigator: Knight, Robert, Ph.D.
MRI of Acute Vascular Injury and Hemorrhagic Transformation in Ischemic Stroke (NIH 1R01 NS058630-01A2)

The entry of most plasma-borne materials into the brain is normally blocked by a blood-brain barrier (BBB) that protects the brain cells from the untoward effects of such substances. Injury to the BBB in ischemic stroke often leads to the leakage of ions, water, amino acids, and plasma proteins into the brain and as a result in large strokes significant brain swelling may occur before treatment is initiated. Over time this decay in barrier function can worsen such that red blood cells extravasate and form hemorrhages, a process referred to as hemorrhagic transformation (HT). Thrombolytic therapy with tissue plasminogen activator (tPA) acts to increase blood flow to the ischemic tissue and is the only approved treatment for acute ischemic stroke. But its usage increases the risk of symptomatic HT ten-fold. At present, the only criterion for tPA treatment of ischemic stroke is time (3 hr post-ictus and CT exam negative for bleeding, as no diagnostic imaging indicators are available for excluding high-risk stroke patients. Our previous stroke studies indicate that regions with acute BBB injury that show leakage of magnetic resonance contrast agents (MRCAs) and elevated T1sat, a magnetization transfer parameter, often develop HT at later times. From this work, two quantitative magnetic resonance imaging (MRI) methods have been identified as possible predictors of BBB injury and HT: 1) magnetization transfer MRI (MT-MRI), particularly the T1sat parameter; and 2) MRCA enhanced MRI of the blood-to-brain distribution of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA), with the influx rate assayed by Patlak plots. Neither the degree of acute BBB opening, predictive of severe vasogenic edema and HT, nor the physiological changes in the BBB components that contribute to these altered MRI signals are known. This proposal aims to test if the size of the MT- and/or MRCA-MRI parameter changes at an early stage of stroke can be used to establish a threshold of BBB damage that portends subsequent HT and if changes of this magnitude or larger can be used to identify subjects that are likely to develop HT after thrombolytic therapy. Two rat middle cerebral artery (MCA) occlusion models, intraluminal filament and embolic, will be used. Aim 1 is a translational aim; its purpose is to develop a predictive model that links the degree of abnormality of the MT- and/or MRCA-MRI parameters during the first several hours of ischemia and reperfusion to the probability of developing subsequent HT following tPA treatment. If successful, this predictive model would lay the groundwork for clinical trials and might be useful for selecting or rejecting patients for tPA treatment. Aim 2 is mechanistic in the sense that we will investigate physiological factors that may contribute to these changes in the MT and MRCA-MRI parameters and to acute BBB injury. The long-term goals of this proposal are to develop MRI signatures that can identify tissue at risk for HT, provide criteria for selecting patients for tPA treatment and to investigate the basic mechanisms of BBB opening and edema formation in stroke. Modified Specific Section Specific Aim 1: To quantify: 1) MT-MRI parameters at approximately 2, 5 and 48 hr after ischemia

onset; 2) the influx of Gd-DTPA across the BBB (a measure of permeability) at approximately 5 and 48 hr after ischemia onset; and 3) ischemic injury at 48 hr as determined by histological assessment and tissue hemoglobin content (a quantitative assay of HT) in both intraluminal suture and embolic stroke model in the rat with half of the animals receiving tPA and the other half placebo 3 hr after MCA occlusion (i.e. shortly after the acute imaging studies and reperfusion; n=20 per group). These data will be used to develop a predictive model that links the degree of MRI abnormality after several hours of ischemia to the incidence of HT at 48 hr and the probability of tPA treatment inducing HT. Hypothesis: This aim tests the hypothesis that the probability of tPA inducing HT can be accessed from MRI measures of T1sat and MRCA influx during the first few hours of cerebral ischemia and reperfusion. Specific Aim 2: To quantify the same set of MRI and histological parameters as in Aim 1, plus estimates of brain swelling by MRI and histology and the expression of various BBB-associated proteins by immunohistochemistry (IHC), in selected regions of interest (ROIs) in animals subjected to 3 hrs of MCA occlusion with half of the animals treated with tPA and half without. MRI studies will be performed at time points during ischemia (~ 2 hr post MCA occlusion) and at approximately 7, 11 and 24 hrs post-occlusion after which the brains will be taken for histological and IHC analysis (n=10 per time and treatment group). Hypothesis: This aim will test the hypothesis that: 1) changes in the MT parameters will be proportional to Gd-DTPA influx (i.e., BBB opening) and both will be functions of the variations in BBB associated proteins and/or brain swelling; and 2) the size of these changes are correlated over time, ROI, and treatment.

Principal Investigator: Li, Yi, M.D.
tPA, white matter and cell therapy for stroke (NIH R01NS066041-01A1)

Cell transplantation has shown promise in reducing neurological deficits associated with stroke. One of the most effective of these therapies is marrow stromal cells (MSCs), that has been demonstrated to be highly neurorestorative. In this application, we will investigate the mechanisms by which MSCs produce this neurorestorative effect. Our preliminary data strongly indicate that there is extensive axonal remodeling in both brain and spinal cord in response to MSC treatment which highly correlates with improvement of neurological function. Given these robust preliminary data, and the fact that the field of white matter changes after stroke is understudied, and that there are no investigations on the effect of cell-based therapies for stroke on spinal cord remodeling, we propose the following two specific aims: In Aim 1, we will test the effects of MSC treatment of stroke on axonal outgrowth in the brain and the spinal cord. We hypothesize that recovery of limb motor function after stroke depends on axonal remodeling of the corticospinal tract (CST). CST axons emanating from the ischemic boundary in the ipsilateral hemisphere and from the intact contralateral hemisphere sprout and extend to the denervated spinal neurons. MSCs enhance such axonal restructuring to promote functional recovery. In Aim 2, we will investigate the cellular and molecular mechanisms by which MSC treatment promotes neuronal remodeling after stroke. We hypothesize that neuronal remodeling in the central nervous system (CNS) after stroke with MSC treatment is mediated by astrocytes, the most numerous cells and the major endogenous repair mediators in the adult CNS. Neurite outgrowth after stroke is enhanced by MSC

treatment via astrocytic increase in the net activity of tissue plasminogen activator (tPA) via modifying the balance of tPA/plasminogen activator inhibitor-1(PAI-1) level. In this application, we employ genetically modified CST-YFP mice in which the CST is specifically and completely labeled with yellow fluorescent protein (YFP) and tPA knockout (tPA-/-)mice, as well as an array of novel and well-established experimental techniques in our laboratory. To our knowledge, our work is the first to investigate tPA as amplifying neurite remodeling and thereby mediating the beneficial actions of exogenous cells in the CNS. This project elucidates the interaction between MSCs and parenchymal cells that lead to white matter changes in the brain and spinal cord by which the injured CNS can be remodeled. Our ultimate goal is to delineate the mechanistic underpinnings of cell-based therapy in the restorative treatment of stroke. The proposed studies have high translational significance and will advance the field of stroke recovery. PUBLIC HEALTH RELEVANCE: This proposal will investigate the mechanism by which MSCs interact with parenchymal cells to promote neurite remodeling and functional benefit after stroke. Elucidating these cellular and molecular mechanisms will lead to improved restorative treatments for stroke and other forms of neural injury.

Principal Investigator: Mitsias, Panayiotis, M.D.
Magnetic Resonance Imaging and Laboratory Assessment of Stroke Recovery (NIH R01NS070922-01)

Stroke is the leading cause of serious long-term disability in the United States. Approximately 40% of patients are left with moderate functional impairments and 15-30% with severe disability. Some degree of spontaneous recovery occurs after an ischemic stroke, but very often this is incomplete. Various neurorestorative therapies, aiming at reducing disability by restoring and reorganizing the surviving brain elements are being tested but none has yet been approved and their optimal prescription remains unknown. At present, the brain changes occurring in the process of spontaneous, or treatment-induced, recovery remain undetermined and there are no available biological markers of recovery. The substrate of clinical recovery is very incompletely understood. It likely includes several different sub-processes, of which vascular and axonal remodeling and the brain's intrinsic ability to repair, are rather prominent. Defining these processes by using non-invasive MRI, laboratory and genetic methods and measurements, if proven valid and reliable, will have the tremendous potential to provide clinicians with tools to rationally guide future medical treatments for stroke recovery. The mains aims of the proposed study are three fold: 1) to define whether specific multiparametric MRI measures, namely cerebral blood volume and blood-to-brain transfer constant values in conjunction with qualitative assessment with susceptibility-weighted imaging, as well as fractional anisotropy, apparent kurtosis coefficient and T1 and T2 values in conjunction with qualitative assessment with q-ball imaging, are capable of characterizing ongoing vascular and axonal remodeling, respectively, in the brain of patients recovering from ischemic stroke, and that these measures and their dynamic temporal evolution correlate with the degree of functional recovery from ischemic stroke at 90 days after stroke onset, 2) to define the levels of vascular endothelial growth factor or stromal derived factor 1 and the numbers or circulating endothelial progenitor cells and whether these levels/numbers and their dynamic temporal evolution correlate with

the degree of functional recovery from ischemic stroke at 90 days after stroke onset and with the MRI markers of vascular remodeling, and, 3) to explore whether the presence of specific genotypes, mainly the brain-derived neurotrophic factor Val66Met polymorphism and ApoE subtypes, influence the degree of spontaneous recovery from ischemic stroke and result in attenuated and slower post-stroke vascular and axonal remodeling. Sixty patients will be studied. We expect that the proposed study will produce novel data that will provide new and important information on the morphological brain changes that accompany spontaneous stroke recovery, and will result in the development of an optimal model for rational, image-guided future neurorestorative treatment protocols. PUBLIC HEALTH RELEVANCE: In this study we will study stroke patients for the first three months after their symptom onset using serial, novel non-invasive magnetic resonance imaging techniques, laboratory and clinical assessments. Our aim is to define the evolving changes in brain structure and laboratory findings that correlate with clinical recovery after stroke. We expect that the novel data produced by this study will form the basis for the optimal design of treatment protocols aiming at enhancing post-stroke recovery.

Principal Investigator: Silver, Brian, M.D.
Secondary Prevention of Small Subcortical Strokes (SPS3) (Subcontract) (NIH U01NS038529)

The aim of the Secondary Prevention of Small Subcortical Strokes (SPS3) project is to define efficacious therapies for prevention of recurrent stroke and cognitive decline in patients with small subcortical strokes (S3) (a.k.a. lacunar infarcts). Nearly two million survivors of S3 in U.S. are at high risk for recurrent stroke and for developing vascular dementia. Additionally, "asymptomatic" (more accurately termed "subclinical") S3 are present in about 20% of people over age 65. While S3 can be caused by many types of cerebrovascular disorders, most are due to intracranial cerebral small artery disease. Optimal antiplatelet therapy and antihypertensive management of S3 patients to reduce stroke recurrence and cognitive decline has not been defined and is likely to yield important health benefits. Although MRI-defined symptomatic S3 in the absence of surgically amenable cervical carotid stenosis and major-risk cardioembolic sources is the index event for participation in SPS3 and recurrent stroke is the primary outcome, the goals of SPS3 are broader in scope and include assessment and prevention of vascular dementia. No previous clinical trials have addressed these important issues specifically in S3 patients. SPS3 will define optimal treatment to prevent recurrent stroke and cognitive decline for S3 patients without an indication for endarterectomy or anticoagulation. S3s are particularly frequent in Hispanics, in whom they are one of the most common stroke subtypes. Whether the prognosis of S3 and the benefits of aggressive blood pressure control and of enhanced antiplatelet therapy are importantly different in Hispanic are also not known, and these issues will be addressed by SPS3. SPS3 seeks to efficiently address several important clinical and scientific questions through two simultaneous clinical trials coupled with careful, prospective analysis of features potentially influencing prognosis and response to interventions. Since hypertension is the most prevalent and powerful risk factor for S3, and antiplatelet therapy is the standard of care for secondary prevention, definition of the efficacy and safety of blood pressure control and antiplatelet therapy

should optimally be tested together. SPECIFIC AIM: To define efficacious therapies for prevention of stroke recurrence and cognitive de-cline in patients with symptomatic S3. The core of SPS3 consists of two randomized clinical trials involving 2500 participants with symptomatic S3 randomized to two interventions in a factorial design. Primary Aims: A) To determine whether combination antiplatelet therapy consisting of aspirin (325 mg/d) plus clopidogrel (75 mg/d) is superior to aspirin (325 mg/d) for reducing stroke recurrence (the primary endpoint), cognitive decline and major vascular events. B) To determine whether "intensive" blood pressure lowering to a specific target range is superior to "usual" hypertension management for reducing recurrent stroke, cognitive decline and major vascular events. Secondary Aim: To compare the differences in absolute benefit of combination antiplatelet therapy vs. aspirin and of "intensive" blood pressure lowering vs. "usual control" between Hispanic participants vs. non-Hispanic white participants. Rationale'. Hispanics will have larger benefits (absolute risk reductions) from combination antiplatelet therapy and from "intensive" blood pressure control for prevention of stroke recurrence than non-Hispanic whites, based on their higher rate of recurrent stroke. In addition, the inclusion of 20% of Hispanic participants will serve to characterize S3 in this population, including stroke recurrence rate and risk factors, rate and risk factors for cognitive decline, response to antiplatelet intervention, and response to blood pressure control intervention. IMPORTANCE/RELEVANCE OF SPS3. At least 200,000 S3s occur annually in the U.S., with nearly two million S3 survivors at high risk for recurrent stroke and vascular dementia. It remains unclear how to optimally prevent stroke recurrence and cognitive impairment in S3 survivors. No clinical trials have specifically focused on this important, common stroke subtype. No secondary stroke prevention study has tested different target levels of blood pressure control in stroke survivors, despite the importance of hypertension as the most common independent risk factor for stroke, and particularly for S3. No previous stroke study has focused on Hispanics; S3 is one the most frequent stroke subtype among this fastest growing U.S. minority. Additional millions of Americans have "subclinical" S3 and cognitive impairment associated with cerebral small artery disease; the results of SPS3 will likely impact their management as well.

Principal Investigator: Tepley, Norman, Ph.D.
Development of Hardware and Software for Clinical MEG (NIH 5R01 NS030914-11)

The overarching goal of this proposal is to use evidence-based methodology to evaluate Magnetoencephalography (MEG) as a clinical tool for evaluation and planning of surgical treatment for patients with epilepsy. In patients where interictal spikes or ictal activity are not detectable, we will evaluate protocols for localizing epileptic cortex during brief MEG exams, by 1) localizing abnormal high frequency oscillations and slow waves using advanced analysis methods (LCMV beamformer and MR-FOCUSS); and 2) withdrawal of a short-acting barbiturate or 3) withdrawal of vagus nerve stimulation. We will validate these advanced MEG analysis techniques and the existing single equivalent current dipole (ECD) method against electrocorticography (ECoG), and determine their sensitivities and specificities. To benefit patients with complex patterns of partial epilepsy, we will use MEG to study the timing and propagation of spikes, and use

diffusion tensor imaging (DTI) tractography to identify the underlying network to distinguish multifocal epilepsy from unifocal epilepsy with consistent patterns of propagation. We will determine if MEG, alone, is sufficient to replace invasive intraoperative mapping for intractable epilepsy by comparison of simultaneous MEG and ECoG localizations of interictal spikes. Similarity and distribution of spike waveforms observed at the locations of the ECoG electrodes will be compared to MEG signals after a spatial filter (LCMV beamformer) has been applied. We will also validate the sensitivity and specificity of functional MEG language and memory imaging as a noninvasive alternative to the intracarotid amobarbital procedure (IAP, Wada test) by demonstrating that the spatial and temporal resolution provided by MEG is necessary to image the sequence and evolution of cortical source activity involved in language and memory; specifically 1) that MEG language and memory laterality indices agree with those from the Wada test; 2) that MEG language and memory imaging agrees with direct electro-cortical stimulation mapping (DECS); and 3) that MEG language imaging protocols are reliable (testing intrasubject reproducibility). We will determine the sensitivity and specificity of advanced analytical methods by comparison with the established ECD fit (when feasible) and semiology to electrocorticography. We will accomplish these goals by means of examining a set of readily testable hypotheses. Thus the completion of the proposed studies will establish MEG as a useful and reliable diagnostic tool. PUBLIC HEALTH RELEVANCE: The overall goal of this proposal is to extend MEG as a clinical tool for evaluating and planning treatment for patients with epilepsy. The objective of this study is to establish MEG as a reliable clinical diagnostic tool.

Principal Investigator: Zhang, Li, M.D.
Treatment of Stroke with a Clinically Approved Proteasome Inhibitor (NIH RO1NS062832-01)

Occlusion of the middle cerebral artery elicits a progressive vascular dysfunction, which contributes to the evolution of brain injury. Thrombolysis with tissue plasminogen activator (tPA) promotes adverse vascular events that limit the therapeutic window of stroke to three hours. Advanced age exacerbates vascular dysfunction after stroke which limits the utilization of tPA. Proteasome inhibitors enhance endothelial nitric oxide synthase (eNOS) expression and improve endothelial function. Our preliminary studies demonstrate that treatment with a proteasome inhibitor, VELCADE, an agent in clinical use for the treatment of cancer, effectively reduces cerebral infarction, and concomitantly reduces secondary thrombosis and microvascular permeability in young rats. In addition, treatment with VELCADE in combination with tPA extends the therapeutic window to at least 6 hours after stroke without increasing hemorrhagic transformation. However, stroke is a major cause of death and disability in the elderly. To mimic clinical situation, we propose to investigate the effect of VECLADE on aged rats. In Aim 1, we hypothesize that treatment with VELCADE dose dependently reduces infarct volume and neurological functional deficit in aged rats after stroke. Optimal doses of VELCADE extend the therapeutic window for stroke. In Aim 2, we will investigate the effects of combination treatment with VELCADE and tPA on cerebral infarction, neurological function, thrombolysis, microvascular thrombus formation, vascular patency and integrity

in aged rats after embolic stroke. By reducing the adverse vascular events, VELCADE amplifies the thrombolytic effect of tPA, and permits a reduction in the effective therapeutic dose of tPA. In Aim 3, using eNOS knockout mice and NOS inhibitors, we will examine the mechanisms that underlie the beneficial effects of VELCADE alone or in combination with tPA in the treatment of stroke. We propose that eNOS mediates the neuroprotective effect of VELCADE by down-regulation of pro- coagulation genes and matrix metalloproteinases (MMPs), which provoke thrombosis, and BBB damage. VELCADE counteracts the detrimental effects of delayed administration of tPA on vascular function and consequently improves microcirculation and vascular integrity. Our study may provide fundamental insights into the mechanisms underlying beneficial effects of VELCADE and combination of VELCADE and tPA in embolic stroke, and may lead to a novel treatment strategy for stroke. PUBLIC HEALTH RELEVANCE: Stroke elicits a progressive vascular dysfunction, which contributes to the evolution of brain injury. As the only FDA approved drug for the treatment of acute stroke, tissue plasminogen activator (tPA) potentiates adverse vascular events that limit the therapeutic window of stroke to three hours. Advanced age exacerbates vascular dysfunction after stroke which limits the utilization of tPA. Proteasome inhibitors enhance endothelial nitric oxide synthase (eNOS, an important regulator of vascular homeostasis) expression. Treatment with a potent proteasome inhibitor, VELCADE, an agent in clinical use for the treatment of cancer, effectively reduces the development of adverse vascular events, and concomitantly reduces cerebral infarction. Therefore, in the current application, we propose to investigate the neuroprotective effects of VELCADE alone and incombination with tPA and the mechanisms underlying the beneficial effects in aged rats after embolic stroke.

Neurosurgery

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Research Summaries

Principal Investigator: Seyfried, Donald, M.D.
Simvastatin Treatment of Experimental Intracerebral Hemorrhage (NIH 1R01NS058581-01A1)

Spontaneous intracerebral hemorrhage (ICH) affects approximately 75,000 people in the U.S. every year, yet current treatment modalities are limited and most of the patients either die or are left with significant neurological morbidity. Our study is designed to investigate the use of a statin drugs, simvastatin and atorvastatin, after experimental ICH in the rat. Preliminary work in the ICH model as well as in animal models of ischemic stroke and traumatic brain injury has suggested significant improvement in neurological outcome with statin medication, with postulated mechanisms of neurogenesis, angiogenesis, improved blood flow, decreased cerebral ischemia, and growth factor regulation in the region of brain injury. The goals of this revised study are to provide preclinical evidence of the benefit of statin drugs after ICH and to delineate the underlying mechanisms of action so that this type of medication, which is already in widespread clinical use for lowering cholesterol, can have application to patients suffering from ICH. We will compare the effects of simvastatin and atorvastatin on neurological recovery in rats after the autologous blood injection method of ICH using established behavioral measurements after various times of survival. Dose response testing and therapeutic response testing will be obtained to determine the dose and time window of greatest benefit from simvastatin after ICH. The mechanisms by which simvastatin and atorvastatin have their beneficial effects will be studied by measuring neurogenesis and changes in the cellular environment, including markers of new neuronal connections, secretion of growth factors, proliferation of endothelial cells and neovascularization in the perihematoma region. Local effects from the hematoma such as cerebral edema and altered cerebral blood flow will be measured by MR imaging, and the results of statin treatment on these parameters will be calculated. Since there normally is significant loss of cerebral tissue around the ICH in humans and in the animal model, preservation or restoration of the cerebral tissue in the region of the ICH by administration of simvastatin will be measured using both histological and MR imaging techniques. This study will demonstrate the efficacy of statin treatment of ICH and provide insight into the multifaceted restorative effects initiated by statins, with the ultimate objective of translating our pre-clinical studies to the ICH patient.

Principal Investigator: Xiong, Ye, M.D., Ph.D.
Treatment of Traumatic Brain Injury with Erythropoietin (NIH 1R01NS062002-01A1)

Traumatic brain injury (TBI) is a significant health concern, affecting 1.4 million people in the United States each year at a cost of $56 billion. The most common cognitive impairment among severely head-injured patients is memory loss. Although a number of therapeutic trials for TBI have been undertaken, there are no pharmacological therapies identified for TBI. Recently, attention has focused on potential therapeutic agents that enhance endogenous neuroplasticity including neurogenesis after brain injury, with a final goal of improving functional outcome. It is our objective to develop a restorative treatment for TBI by using recombinant human erythropoietin (rhEPO). Erythropoietin (EPO) is produced by the fetal liver and adult kidney and is the major cytokine that regulates erythropoiesis. In recent years, EPO has been demonstrated to have important nonhematopoietic functions in the nervous system. Our recent studies have shown that rhEPO enhances neurogenesis and improves cognitive function in TBI induced by

controlled cortical impact (CCI). CCI causes selective neuronal death in the hippocampal CA3 region and the dentate gyrus (DG) both in rats and mice, leading to spatial learning and memory deficits. Although TBI evokes neurogenesis, a large proportion of the cells newly generated in the DG during the early phase after TBI die, during the late phase after TBI. The central hypothesis behind the proposed research is that the spatial learning impairment can be improved by manipulating the brain microenvironment (angiogenesis and molecular targets) by rhEPO. However, dose-response and therapeutic window studies using rhEPO have not been performed, nor have the mechanisms underlying therapeutic benefit for the treatment of TBI been established. In light of the potential of rhEPO to improve neurological outcome after TBI, three specific aims are proposed. Specific Aim 1: To measure the dose-response of rhEPO treatment on spatial learning function in rats after TBI. In addition, the therapeutic time window for rhEPO of TBI will be determined. Specific Aim 2: To study the effect of rhEPO treatment on the temporal and spatial profiles of neurogenesis and angiogenesis in the dentate gyrus after TBI. Specific Aim 3: To identify the molecular targets of rhEPO-induced neurogenesis and angiogenesis after TBI, the contribution of growth factors (vascular endothelial growth factor, brain-derived neurotrophic factor, and fibroblast growth factor) and the phosphoinositide 3-kinase/threonine protein kinase (PI3K/Akt) signal transduction pathway will be investigated. We expect to demonstrate that this therapy has promise for the improvement of spatial learning associated with TBI through upregulation of growth factors and PI3K/Akt signal pathway and the subsequent induction of angiogenesis and neurogenesis. The long-term goal of this application is to translate our finding of therapeutic benefit after treatment of TBI with rhEPO to the patient. PUBLIC HEALTH RELEVANCE: Although a number of therapeutic trials for traumatic brain injury (TBI) have been undertaken, there are no pharmacological therapies identified for TBI. Given the enormity of the clinical problem of TBI, affecting 1.4 million people in the United States each year at a cost of $56 billion, it is imperative that therapeutic approaches designed to improve functional recovery after TBI be developed. In this proposal, based on the newly discovered neuroprotective/neurorestorative properties of recombinant human erythropoietin (rhEPO), we seek to investigate its effect on neurogenesis and functional outcome in the rat after TBI and the mechanisms underlying therapeutic benefit of rhEPO for treatment of TBI.

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Research Summaries

Principal Investigator: Bey, Michael, Ph.D.
Shoulder Function After Rotator Cuff Repair (NIH R01 AR051912-01A1)

Rotator cuff tears are a common shoulder injury, affecting 30-40% of individuals over age 60 and significantly impacting function and quality of life. Treatment strategies vary widely in invasiveness and cost, and there is significant controversy regarding the optimal treatment strategy. Consequently, shoulder function after rotator cuff surgery varies tremendously, with at least 30% of patients experiencing long-term shoulder disability and worker's compensation claims exceeding $2 billion per year in the U.S. alone.

It is believed that the rotator cuff contributes to shoulder strength and provides dynamic glenohumeral joint stability, but accurate measures of in-vivo glenohumeral joint stability do not exist. This study will use a unique, accurate biplane x-ray system to non-invasively measure dynamic glenohumeral joint stability in the repaired and contralateral shoulders of patients having rotator cuff repair surgery. These measurements, along with measures of shoulder strength, will be recorded at 3, 12, and 24 months post-surgery. In addition, dynamic glenohumeral joint stability and shoulder strength will be measured in a control population with no history of shoulder injury or shoulder surgery.

The *long-term goal* of this research program is to develop treatment techniques that restore and maintain shoulder function for patients with rotator cuff tears. The following *specific aims* will be investigated: 1) determine if rotator cuff surgery restores and maintains dynamic joint stability, 2) determine the relationship between shoulder strength and dynamic joint stability, and 3) determine if dynamic joint stability is predictive of clinical outcome. The *central hypothesis* is that dynamic joint stability is not completely restored by rotator cuff surgery, thus compromising shoulder function and potentially leading to long-term shoulder disability.

This study will provide data that are fundamental to our understanding of rotator cuff function and the effect of rotator cuff surgery on shoulder function. This study and subsequent studies will provide data necessary to form a basis for evaluating surgical procedures and rehabilitation protocols for patients with rotator cuff tears. As the population ages and stays active in later years, normal shoulder function will be critical to maintaining a healthy, active lifestyle. Improving the efficacy of rotator cuff surgery and rehabilitation will also reduce both direct healthcare costs and secondary costs resulting from diminished productivity.

Surgery

Senior Research Staff

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Research Summaries

Principal Investigator: Dulchavsky, Scott, M.D., Ph.D.
Bracelet Investigation Grant

Research to determine the effect of long duration exploration class space missions on the cardiovascular system of humans is currently being investigated by many space agencies. Regardless, currently manifested countermeasures are being performed by crewmembers to ameliorate these incompletely understood effects. This proposal teams U.S. space and terrestrial medical experts to evaluate the effects of currently used elastic thigh compression devices (Bracelet-M) on the cardiovascular system in terrestrial and microgravity conditions.

Principal Investigator: Dulchavsky, Scott, M.D., Ph.D.
Sonographic Astronaut Vertebral Examination

This proposal responds to NRA NNJ09ZSA002N and teams world experts in musculoskeletal (MSK) ultrasound at Henry Ford Health System (HFHS) and space medical experts at Wyle Integrated Science and Engineering to evaluate the ability of ultrasound to characterize acute microgravity associated changes in lumbar and cervical spine to provide operationally relevant data to optimize crew health and guide countermeasure development.
An increased height of astronauts is seen during microgravity; the exact mechanism is unclear. Relaxation of the postural muscles, combined with elongation of inter-vertebral disc spaces may be involved. Back pain is a frequent during adaption to spaceflight; however, this has not resulted in changes to mission requirements or objectives. Neurologic sequelae have been seen with terrestrial spinal elongation; fortunately this has not occurred in astronaut crews.
This proposal will determine the accuracy of MSK ultrasound in characterizing the anatomy of the vertebral unit (disc, musculature, facets, ligaments) and develop just-in-time training methodologies to provide essential information to answer operationally relevant mandates with a team of experts to conduct ground, simulated microgravity, and in-flight experiments to answer the aims:
1. Determine the accuracy of MSK ultrasound in characterizing the normal and microgravity associated changes in the vertebral unit.
2. Investigate the human factors, level of experience, and training necessary to perform focused cervical and lumbar vertebral MSK ultrasound in microgravity with inexperienced ultrasound operators in parallel with expert operators.
3. Determine the anatomic changes in the vertebral unit during long duration spaceflight with astronaut performed vertebral ultrasound.

Design and Methods
I. GROUND BASED INVESTIGATIONS
Baseline evaluation of vertebral unit with MSK ultrasound: Expert sonologists at HFHS will perform MRI and vertebral unit MSK examinations on normal volunteers to assess anatomic accuracy, develop normalization tables, and optimize methodology.
Just in time training methodologies for non-expert users
A multi-media, just in time training program with reference cue cards will be developed for non-expert operators. The ability of non-expert operators to perform vertebral MSK

examinations autonomously or with remote-expert guidance will be evaluated.
II. SIMULATED MICROGRAVITY INVESTIGATIONS
Human factors analysis of vertebral MSK ultrasound in a microgravity environment will be completed during parabolic flight to optimize subject and operator positioning and restraint.
III. FLIGHT INVESTIGATIONS
Pre-flight and Post-flight The flight procedures will consist of a comprehensive vertebral MSK ultrasound and MRI evaluation of long duration crew-members. In-flight procedures will be conducted on the ISS using the HRF ultrasound at early, mid and late mission time periods: a post-flight MSK ultrasound and MRI also be done to assess microgravity anatomic effects and gravitational return to baseline.

Significance To NASA This proposal will provide longitudinal, real time data regarding adaptation of the vertebral unit during long duration spaceflight to enhance mission completion, countermeasure development, and astronaut health. The ability to assess the crewmember musculoskeletal system is critical to guide countermeasures, provide functional data for high risk or impact activities, and assess acute injuries which may occur during exploration class spaceflight. Astronaut performed ultrasound examinations on the ISS have demonstrated that diagnostic quality images can be obtained with targeted training: the procedures developed and verified during this proposal will provide novel data and capabilities to enhance crew health for long duration space missions.

Principal Investigator: Gautam, Subhash C., Ph.D.
Mechanisms of Triterpenoids in Prevention of Prostate Cancer (NIH R01CA130948-01A1)

Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) including selective COX-2 inhibitors reduces the risk of prostate cancer. However, significant gastro-intestinal and renal toxicity, and increased risk of cardiovascular events associated with long-term use of COX-2 inhibitors undermine the use of these drugs as chemopreventive agents. Herbal remedies with anti-inflammatory and antioxidant activity without serious side effects provide an attractive alternative to these pharmaceuticals for prevention of prostate cancer. Oleanolic acid and ursolic acid are naturally occurring triterpenoids that have been used in traditional medicine as antibacterial, anti-inflammatory, and anti-cancer agents. Recent studies have shown that synthetic oleanane triterpenoids: 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and its C-28 methyl ester (CDDO-Me) and C-28 imidazole (CDDO-Im) are potent anti-inflammatory agents. Our preliminary data demonstrate that synthetic triterpenoids strongly inhibit cell proliferation and induce apoptosis in prostate cancer cell lines in potency order of CDDO-Me>CDDO-Im>CDDO. Furthermore, CDDO-Me inhibits the expression of antiapoptotic Akt and Akt-regulated NF-:B and p-mTOR pro-survival signaling molecules and growth of tumor xenografts in vivo. We hypothesize that early intervention with CDDO-Me will prevent or delay the development of prostate cancer in transgenic adenocarcinoma of the mouse prostate (TRAMP) model and growth of orthotopic tumor xenografts in nude mice by inhibiting Akt, NF-:B and mTOR, and cellular processes regulated by these molecules

(e.g., cell proliferation, apoptosis, inflammation, angiogenesis and metastasis). We will test this hypothesis by performing four specific aims. Specific Aim 1 will test the hypothesis that early intervention with CDDO-Me will prevent the development and/or retard the progression of prostate cancer in TRAMP mice. Specific Aim 2 will test that prevention of prostate tumorigenesis by CDDO-Me is linked to the inhibition of Akt/NF-:B and Akt/mTOR signaling pathways and cellular processes (cell proliferation, apoptosis, inflammation, metastasis, and angiogenesis) regulated by these molecular targets. Specific Aim 3 will determine the mechanism by which CDDO-Me inhibits Akt, and Specific Aim 4 will determine the efficacy and the mechanism by which CDDO-Me inhibits the growth of prostate tumor in an orthotopic xenograft model. This study will provide critical preclinical information on the efficacy and mechanism of action of CDDO-Me as a safe chemopreventive/therapeutic agent for prostate cancer in man. PUBLIC HELATH RELEVANCE Because the development of prostate cancer progresses slowly over a long period of time, early intervention with non-toxic herbal compounds to prevent or slow down the progression of prostate cancer is a promising approach to conquer this disease. Our proposal to investigate the efficacy and the mechanism of action of CDDO-Me, a synthetic triterpenoid derived from naturally occurring oleanolic acid, in prevention of prostate cancer in TRAMP mouse and tumor xenograft models will provide critical information for clinical trials of CDDO-Me to prevent prostate cancer in man.

Urology

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Research Summaries

Principal Investigator: Barrack, Evelyn, Ph.D.
MicroRNA Predictors of Prostate Cancer Outcome in African American Men

Despite improvements in diagnosis and treatment, prostate cancer remains the second leading cause of cancer deaths in the US. Prostate cancer disproportionately affects African American (AA) men, who have the highest incidence and mortality rates of any racial or ethnic group, yet who are rarely represented in studies to identify markers of disease; our study focuses on this group. Prostate specific antigen (PSA) screening has facilitated the diagnosis of early stage prostate cancer, and has led to an increase in the proportion of patients who undergo radical prostatectomy (RP), expecting to be cured. However, RP is not curative if patients have clinically undetected metastatic prostate

cancer, which will recur after RP. About 35% of men with clinically localized prostate cancer develop a biochemical recurrence (PSA rise) after RP. However, PSA recurrence may be due to local residual disease or to systemic (metastatic) disease. Therefore, the real challenge is to identify markers of metastatic disease. Our objective is to identify markers that indicate the presence of metastatic disease; such patients may benefit from systemic adjuvant therapy following RP. Our approach is to identify patients with organ-confined disease vs. metastatic disease at the time of RP, based on long-term follow-up after RP, and then to analyze the primary tumors to identify molecular changes that distinguish between these outcome groups. microRNAs (miRNAs or miRs), small noncoding RNAs that regulate the expression of protein-coding mRNAs, are revolutionizing our understanding of disease. miRNAs are preserved and readily extracted from formalin-fixed paraffin-embedded tissues; this makes it possible to take advantage of archived radical prostatectomy prostate cancer tissue, for which long-term follow-up of patients post-surgery is also available. Our goal is to identify miRNA expression changes that distinguish between organ-confined vs. metastatic prostate cancer. Patients predicted to develop disease recurrence could be followed closely and offered aggressive treatment. In addition, markers of disease reflect biochemical and molecular pathways that are dysregulated, and thus may represent potential therapeutic targets. Also, if these miRNAs are detectable in blood, they may be useful for early detection of aggressive prostate cancer.

Principal Investigator: Kim, Sahn-ho, Ph.D.
Androgen Receptor Interaction with Telomeric Complexes in Prostate Cancer Cells

The telomeric complex, shelterin, plays a critical role in protecting chromosome ends from erosion, and disruption of these complexes can lead to chromosomal instability culminating in cell death or malignant transformation. We reported previously that dominant-negative mutants of one of the telomeric proteins called TIN2 causes death of androgen receptor (AR)-negative, but not AR-positive prostate cancer cells, raising the question of a possible role of AR in the structural stability of telomeric complexes. Consistent with this possibility, in the present study we observed that the AR-antagonist Casodex (bicalutamide) disrupted telomeric complexes in AR-positive LNCaP cells, but not in AR-negative PC-3 cells. Immunofluorescent studies revealed colocalization of TIN2 and AR. Reciprocal immunoprecipitation studies showed association of AR with telomeric proteins. Furthermore, telomeric proteins were overexpressed in prostate cancer cells compared to normal prostate epithelial cells, and sucrose-density gradient analysis showed co-sedimentation of AR with telomeric proteins in a shelterin-like mega complex. Together, these observations suggest an allosteric role of AR in telomere complex stability in prostate cancer cells, and suggest that AR-antagonist Casodex-mediated cell death may be due to telomere complex disruption.

Abstracts – Hospital Based Departments

- **Diagnostic Radiology**
- **Emergency Medicine**
- **Radiation Oncology**

Diagnostic Radiology

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Research Summaries

Principal Investigator Ali, Messer Ph.D.
MR Imaging of pHe and Chemotherapeutic Response in a Rat Glioma (NIH R21NS066143-01)

Malignant glioma accounts for approximately one-third of all primary brain tumors in adults or 18400 new cases in the United States annually. Despite advances in recent conventional therapeutic regimen of surgery, radiation and anticancer chemotherapies, the clinical outcome in treating malignant brain tumors remains disappointing. The resistance of glioma to the conventional therapeutic regimen of surgery, radiation therapy, and chemotherapy is still not well understood. Successful malignant glioma treatment is highly dependent on the ability to diagnose patients at early stages of disease and to identify which therapy might respond. One approach that is beginning to succeed clinically is to exploit the dependence of most tumors on increased angiogenesis through neovascularization. Targeting the endothelial cells lining the tumor neovascularization has been found to impact cancers in a broad manner, with growing clinical success of this approach. Cilengitide is a highly selective integrin inhibitor targeting the tumor and its vasculature. We will apply Cilengitide therapy to rat models of U87MG brain tumors, and apply our MRI methods to measure longitudinal changes in extracellular pHe, v3 integrin expression and tumor vascular permeability before and after therapy. To achieve these goals, we are proposing to develop multifunctional denritic MRI contrast agents that will target multiple cancer biomarkers which are specific to tumor microenvironment. We will incorporate pH-responsive GdDOTA-4Amp, T1 relaxation agents and pH-unresponsive NdDOTA-4AmC, PARACEST agents in the same dendrimer molecule in order to measure extracellular pHe of malignant glioma accurately with high resolution and high sensitivity. We will use same nano-sized dendrimer-based pH-responsive contrast agent to measure tumor vascular permeability. In order to target v3 integrin, we will conjugate cyclic-RGD peptides to the PARACEST dendrimers. Finally, we will use these dendrimeric MRI contrast agents to measure extracellular pHe, v3 integrin expression and tumor vascular permeability in single MRI scan session before

and after therapy. Therefore, our multifunctional nano-sized dendrimeric MRI nanoprobes have great potential for future clinical applications in measuring in vivo pH non-invasively as well as to assess multiple biomarkers of malignant brain tumor during a single MRI session. PUBLIC HEALTH RELEVANCE: The results of this project will provide a direct method to measure in vivo pH non-invasively. Thus, the extracellular pH (pHe) within tumor tissues will be used as a diagnostic biomarker to determine the prognosis of pathology, to evaluate the efficacy of pHe-altering therapies and to predict the efficacy of pHe-dependent chemotherapies. Besides, multifunctional nano-sized MRI probes will be used to assess multiple, tumor specific, biomarkers in a single MRI scan session and this novel technology will significantly enhance in the early diagnosis and treatment of brain cancer.

Emergency Medicine

Senior Research Staff

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Research Summaries

Principal Investigator: Lewandowski, Christopher, M.D
The Henry Ford Health System: A Hub for the NETT Network (NIH 1U10NS058974-01)

The National Institute of Neurological Disorders and Stroke (NINDS) is seeking to develop a Neurological Emergencies Treatment Trials (NETT) Network of Clinical Site Hubs. The Hubs will work with the NETT Clinical Coordinating Center to improve outcomes for patients with neurological emergencies through research. The clinical site Hubs will be regional consortia of emergency departments (ED) that will recruit patients and carry out phase III clinical trials. The Henry Ford Health System (HFHS) has a long commitment to both basic science and clinical research in neurological disorders and is a NINDS designated Stroke Center with 18 years of continuous funding. This proposal is a natural extension of our current work. The objective of this proposal is to demonstrate that the HFHS is an ideal Hub for the NETT Network. The specific aims are to create a flexible Hub with seven "spokes" at HFHS, to participate in research that improves patient care, to help create an enduring research network, to allow multi-specialty collaboration, and to foster research skills in young investigators that will allow them to pursue a career in clinical research. The Hub will be designed around the HFHS because it is a regional, integrated system of 6 area hospitals, 9 emergency departments, including 4 JCAHO certified stroke centers, and 36 clinics. It also includes a closed medical group of over 800 physicians with over 2.5 million outpatient visits and over 350,000 emergency department visits annually. The HFHS serves a wide variety of minorities, women, and children. The system is integrated through a central IRB, shared electronic medical record, standardized patient care and referral protocols, communication systems, and an integrated governance and leadership structure. A dedicated ambulance service (Superior Ambulance) interconnects the system. This proposal will use three hospitals and seven EDs. The method of implementation will be the Ford Neurological

Emergencies Cross- disciplinary Team (Ford NEXT). This 28 member multi-specialty team with expertise in Emergency Medicine, Prehospital Care, the Neurosciences, Neuro- Intensive Care, Neuro-interventional Radiology, Trauma, Pediatrics, and Rehabilitation will implement and completely manage the clinical trials. The importance of this proposal is that the HFHS hub will build on a well established neuroscience foundation, rapidly complete studies in neurological emergencies, and improve patient care and outcomes.

Principal Investigator: Lewandowski, Christopher, M.D
ProTECT III: Progesterone for Traumatic Brain Injury: Experimental Clinical Treatment Multicenter Clinical Trial

Traumatic brain injury (TBI) is a major cause of premature death and disability worldwide. No therapy has been effective in reducing mortality and improving functional outcomes. We recently completed an NINDS-funded, Phase I/IIa double-blinded, randomized placebo-controlled pilot clinical trial examining the pharmacokinetics, safety, and activity of progesterone, a steroid found to have powerful neuroProTECTive properties in multiple different animal models of brain injury. Based on the extensive preclinical evidence of activity and the promising findings of our pilot study we propose to conduct a phase III clinical trial to definitively assess the efficacy of this treatment for adults with moderate to severe acute TBI. Our primary objective is to determine the effect of administering intravenous progesterone (initiated within 4 hours of injury and administered for 72 hours, followed by an additional 24 hour taper) versus placebo for treating victims of moderate to severe (GCS 12-4) TBI. Our secondary objectives are to examine the effects of progesterone vs. placebo in patients with moderate to severe TBI on 6 month mortality, Disability Rating Scale score, cognitive, neurological and functional outcome using a select battery of tests, and the rates of adverse and severe adverse events. If the therapeutic benefits observed in animals and from our pilot study are replicated, administration of intravenous progesterone should decrease mortality and improve neurological function. Positive results would represent a major advance in the treatment of TBI.

Radiation Oncology

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Research Summaries

Principal Investigator: Freytag, Svend, Ph.D.
Molecular Gene and Radiation Therapies for Cancer (NIH P01CA09701201A)

The NCI-sponsored Program Project entitled "Molecular Gene and Radiation Therapies for Cancer" builds on the past preclinical and clinical accomplishments of the Department of Radiation Oncology's Gene Therapy Program. Their program has developed a novel gene therapy approach designed to improve the effectiveness of radiation therapy. They recently sponsored and completed two successful prostate cancer clinical trials at the HFHS that were a direct result of their research efforts.
The newly awarded Program Project is comprised of three projects and four cores that function as a highly integrated and comprehensive unit that will advance gene therapy technology on three fronts: 1) by developing better gene therapy products (Project 1), 2) by developing better means of product delivery and monitoring (Project 2), and 3) by evaluating the merit of these preclinical advancements in the clinic (Project 3). An important aspect of the two preclinical projects (Projects 1 & 2) is that all of the studies were designed to be translatable into the clinic. Project 3 describes three Phase I/II clinical trials that will examine the safety and efficacy of their novel gene therapy approach in combination with radiation therapy in patients with newly diagnosed prostate cancer using a "new and improved" gene therapy product.

Principal Investigator: Kim, Jae Ho, M.D., Ph.D.
Mitigating Cutaneous Radiation Injury with CXCR4 Antagonist (1R21ES019251-01)

The goal of the proposed research is to develop an effective pharmacological strategy to mitigate and treat radiation-induced skin injury in humans. Skin injury following a sub- lethal dose of ionizing radiation has important implications both for the treatment of malignant disease and for radiological protection. Significant injuries to the skin decrease the LD50/60 and amplify the risk for death at any radiation exposure dose. Available countermeasures are suboptimal especially with respect to acute and sub-acute phases of the skin injury. The proposal is based on the hypothesis that progressive damage to the skin after sub-lethal dose of radiation is in part due to reduced functioning of the tissue stem cells that can no longer replace differentiated functional cells, resulting in loss of homeostasis. We propose to replace the loss of radiation-sterilized stem cells with endogenous bone marrow derived endothelial and stromal (mesenchymal) stem cells. Specifically, we will determine the potential of the CXCR4 antagonist, plerixafor with vascular endothelial growth factor (VEGF) to mitigate radiation-induced skin injury. The rationale of the combined use of plerixafor and VEGF is to mobilize differentially subsets of progenitor cells from the bone marrow. Primary endpoints for evaluation will be functional using a semi-quantitative scoring system, skin strength and leg contraction in C57BL/6 mice. Secondary endpoints will include histopathology and pro-inflammatory cytokines (TGF-?, TNF-?). We recently obtained encouraging data showing that radiation skin injury could be significantly reduced by plerixafor, CXCR4 antagonist when the drug was applied days after the exposure. We expect that our proposed pharmacological approach has the potential to effectively restore tissue homeostasis after radiation. PUBLIC HEALTH RELEVANCE: The broad, long-term goal of the proposed research is to develop an effective mitigator for radiation-induced normal tissue and organ damage. If successful, our proposed strategy would be clinically more attractive than the existing approach; the endogenous bone marrow derived stem cells strategy should provide a safer approach than allogeneic and even allogeneic stem cell therapy.

Principal Investigator: Zhong, Hualiang, Ph.D.
To Quantify Deformable Image Registration Errors in IGRT (1R01CA140341-01A2)

The purpose of this study is to develop a novel and systematic method to identify deformable image registration (DIR) errors and related dosimetric consequences in image-guided radiotherapy. The accuracy of the DIR and dose reconstruction process is central to determining whether or not the dose delivered to the patient is in agreement with the planned dose distribution. As we begin to reduce planning margins, based on the assurance afforded by daily imaging, and the introduction of real-time targeting devices (e.g. electromagnetic beacons), the impact of tumor (and surrounding organ) deformation may become a limiting factor in accurate targeting of the tumor. Under such circumstances, and regardless of whether on-line or off- line, adaptive corrections are applied, the accuracy of the image registration and dose reconstruction process becomes critical in evaluating the actual dose delivered to the tumor and surrounding healthy tissues. The long-term objective of this application is to ensure that each patient's treatment plan is properly adapted to account for DIR displacement and dose-related errors, to improve targeting accuracy and provide optimal sparing of healthy tissues. To accomplish the goals of this proposal, we will: (1a) Develop a novel elasticity-based model, founded on the concepts of unbalanced forces and energies, to quantify displacement vector field (DVF) errors in deformable image registration, and verify the results against measurements in a deformable phantom; (1b) Apply the method to a large number image datasets of prostate and lung cancer patients previously treated using daily CBCT imaging; (2) Perform dose reconstruction using tri-linear dose interpolation and Monte Carlo-based energy mapping and quantify the resulting dosimetric errors on the patient image datasets; (3) Develop methods to compensate for dose errors from DVF-based displacement errors; (3a) Develop a dose reconstruction system using an optimization process to minimize errors in the dose by incorporating feedback based on the quantified DVF-based dose errors; (3b) Quantify the dosimetric errors as a function of planning margin and develop a margin recipe to account for DVF-related dose errors based on registrations of daily cone-beam CT (CBCT) images with simulation CT images for a large group of prostate and lung cancer patients treated retrospectively. PUBLIC HEALTH RELEVANCE: We will investigate methods for quantifying deformable image registration (DIR) errors and related dosimetric consequences. DIR and dose reconstruction are principle processes in adaptive radiotherapy and are essential requirements for computation of the actual dose delivered to the patient. A feedback system will be developed to minimize the quantified errors and we will formulate margin recipes to account for them in treatment planning.

Abstracts – Health and Health Care Research

- **Department of Public Health Sciences**
- **Center for Health Services Research**

Department of Public Health Sciences

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Research Summaries

Principal Investigator: Alexander, Gwen, Ph.D.
CRN Comparative Effectiveness Research in Genomic and Personalized Medicine (Subcontract) (NIH RC2CA148471-01)

In recent years, genomic or other molecular tests have been recommended for clinical practice in the area of cancer treatment. They are used to identify individuals at high risk, screen and perform early detection, identify prognostic markers, and guide course of therapy. We propose a focused program of research that will investigate the Comparative effectiveness of several tests related to colorectal cancer. The proposed study is a collaboration of several of the member sites of the NCI-funded Cancer Research Network (CRN) and academic partners. Our comprehensive research program in GPM for colorectal cancer will have two main components: 1) secondary data collection through evidence synthesis and cost-effectiveness analysis, and 2) primary data collection through a proof-of-principle study to examine questions about personalized medicine for colorectal cancer. In the proof-of-principle study, we will evaluate the utilization of KRAS and Lynch Syndrome genetic tests within our health systems, and measure the effectiveness of

KRAS testing compared with a patient population that does not receive testing. We will also conduct patient and physician interviews to measure psychosocial issues related to KRAS testing, and to help us understand how the genetic test results are used to inform decisions. Our research program in colorectal cancer will build the experience, data systems, and methods that can apply to other cancer-related genetic or molecular tests in the future, such as UGT1A1 testing, or Oncotype DX and CYP2D6 testing for breast cancer. The interwoven research program that we propose will provide opportunities for synergy between teams of researchers conducting primary and secondary data collection. PUBLIC HEALTH RELEVANCE: We will study several genetic tests related to colon cancer that may help doctors understand who will get colon cancer and what therapies some patients should receive. We will study who gets tested, how the genetic test result helps people decide what to do, and whether patients have different health outcomes when they get tested. We will also summarize research that has already been published and analyze cost information about the use of these tests.

Principal Investigator: Cassidy-Bushrow, Andrea, Ph.D.
Race, Treatment and Cardiovascular Health: A Study of Men with Prostate Cancer

Few studies have examined racial differences in cardiovascular disease (CVD) in men with prostate cancer, although CVD is a leading cause of morbidity and mortality among men with prostate cancer. Androgen Deprivation Therapy (ADT) for prostate cancer is associated with CVD events in men with prostate cancer. Little is known, however, about the relationship between ADT, changes in CVD risk factor profiles and development of CVD events in minority populations, despite CVD risk being disproportionally distributed among racial minorities in the general population. We will establish a retrospective cohort of 2,000 Caucasian and African-American prostate cancer cases. We hypothesize that among these cases (1) African Americans compared to Caucasians will have more deleterious changes in their CVD risk profile and will experience more CVD events and (2) CVD risk factor changes and events will be most profound in men treated with ADT. This study may identify modifiable factors that could improve the health of prostate cancer survivors and reduce disparities in the survivorship of African-American men with prostate cancer relative to Caucasian men.

Principal Investigator: Cassidy-Bushrow, Andrea, Ph.D.
Development of a Cardiovascular Surveillance System in the CRVN (Subcontract) (NIH RC2HL101666)

This project will establish a surveillance system for cardiovascular disease in approximately 11 million health maintenance organization (HMO) members. The surveillance system will be initially established for coronary heart disease (CHD), heart failure (HF), and stroke. The broad goals of this project are to: 1. Establish a surveillance system for coronary heart disease (CHD), heart failure (HF) and stroke in the 15 centers of the National Heart Lung and Blood Institute (NHLBI) funded Cardiovascular Disease Research Network including therapeutic interventions, post-event outcomes and important risk factors and confounders. 2. Work collaboratively to establish and implement an aggregate database incorporating coronary heart disease CHD, HF, and stroke data from all 15 CVRN sites that can be used by CVRN investigators and other qualified research scientists to conduct studies related to comparative effectiveness and health disparities. 3. Identify standard criteria for coronary heart disease, heart failure and stroke

clinical outcomes, as well as all components noted in goal #1 to enable data aggregation 4. Determine the most recent 10-year trends in the rates of acute myocardial infarction and stroke hospitalization and their relationship to trends in risk factors, co-morbidities, therapeutic interventions, medications, and diagnostic modalities. 5. Demonstrate that the data can be used to address research questions regarding comparative effectiveness and novel methods of monitoring health disparities, areas that have been identified as RC2 topics by NHLBI. This project will result in a surveillance system in a consortium of 15 geographically diverse health plans that provide health care to about 11 million people, nearly 4% of the U.S. population. This surveillance system will be significantly larger than other existing cardiovascular surveillance efforts in the U.S. and includes a population that is diverse in race/ethnicity and sociodemographic characteristics. The surveillance system will include for CHD, HF, and stroke electronically available data on risk factors, co-morbidities, prescription medications, therapeutic interventions, and laboratory testing, and physician and patient characteristics. These data can be utilized to provide timely surveillance reports for CHD, CF, and stroke; a comprehensive description of a patient's longitudinal course both prior to and subsequent to development of CHD, CF, and stroke; and enable research questions to be addressed that assess the relationship of these variables to the course of disease as well as to address research questions relating to comparative effectiveness and to disparities in medical treatment and outcomes. PUBLIC HEALTH RELEVANCE: This project will establish a large database of information about heart disease and stroke in about 11 million members of 15 HMO providers of comprehensive medical care. This information will be used to examine patterns over time in the rates of heart disease and stroke, the first and third leading causes of death in the U.S. These data will enable the medical and public health community to assess progress over time in reducing the rate of these deadly and expensive diseases, to help identify interventions that are effective in preventing heart disease and stroke as well as interventions that favorably impact the lives of those who live with these conditions.

Principal Investigator: Cassidy-Bushrow, Andrea, Ph.D.
Cost-Effectiveness of Hormonal Therapy for Clinically Localized Prostate Cancer (Subcontract) (NIH RC1CA146238-01)

This application addresses broad Challenge Area (05) entitled "Comparative Effectiveness Research (CER)". Within that area, we are addressing the specific high priority challenge topic 05-CA-104* Comparative Effectiveness Research on Cancer Treatment. Our application also responds to the specific challenge topic 04-CA-110 Treatment of Prostate Cancer. Androgen Deprivation Therapy (ADT) has become increasingly used as primary monotherapy for older men with newly diagnosed localized disease not receiving other curative treatments (surgery or radiotherapy), despite the fact that there is no proven mortality benefit from clinical trials. Given the increasing number of elderly men, the high incidence and survival rates from prostate cancer, and the use of ADT in one-third of 2 million men newly diagnosed or surviving with prostate cancer, there is a growing need for information on effectiveness and costs to inform policy and treatment decisions. Clinical trials are not ongoing or likely to be conducted to address these issues. To address the limitations of prior observational database studies, we propose a new comparative effectiveness study to provide information on the risks and potential benefits of immediate ADT in men diagnosed with localized prostate cancer. Our three aims include estimating the comparative effectiveness of immediate ADT versus observation in terms of all

cause and prostate-cancer specific mortality and progression-free survival, estimating the longitudinal direct medical care costs to capture the impact of ADT, and calculating the cost-effectiveness (cost per life years saved) and cost-utility (quality-adjusted life years) using published patient utilities for multiple prostate cancer health states. We will assess all outcomes according to prognostic risk groups defined by age, stage, serum biomarker values (PSA), and other pathological markers of tumor aggressiveness. We will account for variations in baseline comorbidity and sociodemographic factors, and use state-of-the-art comparative effectiveness techniques to address selection bias. The retrospective observational study will be conducted using a large, diverse population of nearly 10,000 men with localized disease diagnosed from 1995-2007 with a mean follow up of 6 years. There are comprehensive computerized clinical utilization data for this population from 2 large integrated health care plans, including longitudinal information on tumor characteristics, risk factors and outcomes. Key variables will be derived from inpatient, outpatient, pharmacy and radiology data and lab test values. In contrast to prior observational studies, ours will have the combination of size, follow up, and detailed clinical information over the entire disease trajectory needed to significantly improve the precision of estimates of mortality and progression-free survival following ADT in sub-groups of men at varying levels of baseline risk. These strengths, and our multi-disciplinary team experienced in prostate cancer research using large databases, ensure that our results will be useful to improve practice, policy, and health outcomes. This is a multisite study to investigate the Challenge Area of Comparative Effectiveness Research on Cancer Treatment and specifically the Treatment of Prostate Cancer. We propose a new comparative effectiveness study to provide information on the risks and potential benefits of immediate ADT in men diagnosed with localized prostate cancer using data from two integrated health delivery systems with access to comprehensive health, utilization, cost, and socioeconomic data.

Principal Investigator: Cole-Johnson, Christine, Ph.D.
Statins & Lymphoid Malignancy Risk in a Large Multi-Site Population Based Cohort (NIH 5R01CA140754-02)

In vivo and in vitro studies suggest that HMGCoA reductase inhibitors, or statins, may have a number of antitumor activities. They have been found to arrest cell cycle progression, induce apoptosis, and suppress angiogenesis and inflammation. The relation between chronic use of statins and the risk of lymphoid malignancies in humans has not been well characterized and the limited epidemiologic evidence to date is conflicting. The overall objective of this application is to examine the association between use of statins and risk of a lymphoma and whether this association is modified by the presence of conditions related to a higher risk of lymphoma. We will achieve our objective by pursuing two specific aims: 1) To quantify the association between statin use and risk of lymphoma, overall and by lymphoma subtypes; and 2) To assess the association of lymphoma risk with statin use among persons at high risk for lymphoma. The study will be a nested case-control study conducted within 6 health systems in the Cancer Research Network (CRN), with a total population of over 8 million members. Incident diagnoses of lymphoid malignancies (n~ 18,000) will be identified from population-based health system cancer registries. Five controls will be matched to each case on, age, sex, health system, and duration of membership. Statin and other medication use will be obtained from comprehensive electronic pharmacy records. The proposed study will include the largest study population and have the most detailed pharmacy data to address this research question to date. Conditional

logistic regression analysis will be used to address aim 1; statin users will be compared both to non-users and to users of other antilipemics (i.e., anion exchange resins, fibrates, nicotinic acid, and ezetimibe). The working hypothesis is that use of statins overall will be associated with a reduced risk of lymphoma while use of other antilipemics will not, and that the association will be stronger for lipophilic statins (i.e., lovastatin, simvastatin, and atorvastatin) and for lymphoma subtypes most strongly related to chronic inflammation (i.e., diffuse large B cell lymphoma). Under the second aim, the working hypothesis is that statins will show a stronger protective effect against lymphoma among subjects affected by autoimmune conditions related to higher risk of lymphoma (i.e., rheumatoid arthritis, systemic lupus erythematosus, and Sjvgren's syndrome). The proposed research is significant given the high and expanding prevalence of statin use in the US and the need to identify and quantify any secondary risks and benefits of these widely used drugs. Significance. Lymphomas are a group of malignancies whose etiology remains poorly understood and for which few risk factors have been identified. Therefore, limited preventive measures are available. The confirmation that statins protect against the development of lymphoma will provide enormous scientific and public health impact and significance in the general population. An additional examination that will be included in this study (Aim 2) could lead to effective chemoprevention strategies for persons at high risk for lymphoma. Like most systemic agents, statins are not risk-free. However, statins are widely used, and the risk of serious adverse events is relatively low given the exposure prevalence. To provide thorough evaluation, the risks related to statin exposure will be evaluated in this study in addition to the benefits. Investigators. This study includes experienced investigators as well as early stage investigators. In collaboration with experienced investigators, an early stage investigator (Dr. Chun Chao) will lead evaluation of statins and lymphoma in a high-risk population (Aim 2). Novelty/Approach/Environment. This study will build upon existing resources to evaluate the benefit (and risk) of statins on risk for lymphoma. Therefore, this study will provide cost- and time-efficient results that will address this important public health issue. PUBLIC HEALTH RELEVANCE: Lymphomas are a group of malignancies whose etiology remains poorly understood and for which few risk factors have been identified. Therefore, limited preventive measures are available. The confirmation that statins protect against the development of lymphoma will provide enormous scientific and public health impact and significance in the general population, and will provide chemoprevention strategies for persons at high risk for lymphoma.

Principal Investigator: Cole-Johnson, Christine, Ph.D.
Michigan Alliance for the National Children's Health Study (NIH-NICHD-NCS-07-11)

The National Children's Study (NCS) was established by an Act of Congress in 2000. Its development has been overseen by a consortium of federal agencies including the NIH, EPA, and CDC. The NCS is distinguished from all previous studies of child health by its size (N = 100,000) and its depth of investigation into risk factors for health and disease (biological, social, environmental and clinical) from pre-conception throughout childhood. To achieve the NCS aim of obtaining a sample of US births that is representative of the nation's population, the study will identify, in randomly selected regions of the US including 5 counties (Wayne, Macomb, Genesee, Lenawee, Grand Traverse) in Michigan (sampled segments within sampled counties), women of child-bearing age. These women will be followed from prior to conception through pregnancy to birth and thereafter until the child turns 21 years of age. The initial hypotheses are

focused on risk factors for birth defects, neuro-developmental conditions, asthma, obesity and injury. A coalition of the major Michigan research institutions, MSU, UM, WSU and HFHS, along with the Michigan Dept of Community Health, successfully competed to obtain the contracts for all five counties.

Principal Investigator: Hensley Alford, Sharon, Ph.D.
Long-Term Survivorship in Older Women with Early Stage Breast Cancer (Subcontract) (NIH R01CA093772-06)

Earlier diagnosis, improved treatment, and the overall increase in longevity in later life continue to expand the number of breast cancer survivors who are 65+ years of age, already estimated to be one million (43%) of the total 2.3 million breast cancer survivors. This group of older breast cancer survivors represents 17% of all older cancer survivors, yet the impact of breast cancer and its treatment on survivorship is poorly understood. The parent study (Breast Cancer Treatment Effectiveness in Older Women - BOW I) studied 1859 women 65+ years of age with early stage breast cancer and provided strong evidence that variations in care have substantial consequences for older women: less-than-standard treatment is associated with increased rates of recurrence and breast cancer-specific mortality,while mammography surveillance during the first 5 years after diagnosis is associated with a reduced rate of breast cancer mortality. However, little is known about the effectiveness of mammography surveillance for recurrence and second primaries beyond five years; the cost implications associated with short-term and long-term survivorship care; and the risk of late treatment effects. Responding to the survivorship research priorities of the National Cancer Institute (NCI) and the Institute of Medicine (IOM) to understand and reduce the adverse effects of cancer treatment in older adults, this renewal project (BOW II) will collect additional information about the BOW I breast cancer cohort through 15 years after diagnosis. A comparison cohort of women without breast cancer will be enrolled and matched on age, study site, and breast cancer diagnosis year that will be followed for the same period of time. We will characterize the survivorship of older breast cancer patients and in relation to a comparison cohort cared for in integrated health care systems through the efficient collection of data from medical records and electronic sources. This uniquely detailed dataset, collected by an experienced interdisciplinary team of investigators, will provide new knowledge in three domains of survivorship research: follow-up care, health care costs, late effects of treatment. Both BOW I and II take advantage of the resources of the recently renewed Cancer Research Network (CRN). BOW specific aims will be: (1) To determine whether surveillance mammography beyond 5 years following diagnosis reduces breast cancer-specific mortality, and explore whether surveillance mammography is cost-effective. (2) To determine the cost-effectiveness of standard primary tumor therapy (breast conserving surgery [BCS] followed by radiation therapy or mastectomy) and adjuvant (tamoxifen) therapy, compared with less-than- standard therapy, for older women with breast cancer. (3) To identify late effects of breast cancer and its treatment by comparing incident comorbidity in 5-year breast cancer survivors to a matched comparison cohort without breast cancer. PUBLIC HEALTH RELEVANCE: The average age of all cancer patients is 70 years, and this is projected to increase to 75 years by 2030. BOW II will characterize the survivorship of older breast cancer patients cared for in integrated health care systems

where complete data collection through 15 years of follow-up can be accomplished efficiently. It will provide much needed evidence about the effectiveness of surveillance mammography and the occurrence of late effects which, together with cost analyses, will inform the design of systems changes to promote evidence- based survivorship care for older breast cancer survivors.

Principal Investigator: Joseph, Christine, Ph.D.
Racial variation in Food Allergy: Mechanisms and Risk (NIH 5R21AI080066-02)

Research on risk factors for IgE-mediated food allergy is limited. Given that food allergy is often the first manifestation of atopy, it is not only important to increase our knowledge of food allergy etiology and progression, but to identify risk factors for transient vs. persistent IgE-mediated food allergy, and ultimately use this information to develop interventions to prevent what amounts to an onset of the allergic march. The overall goal of this project is to use an existing birth cohort to explore potential risk factors for milk, egg, or peanut allergy, by age 24 months. Central to this proposal is the risk of food allergy associated with infant feeding practices, including age at introduction of solid or complementary foods and factors related to breastfeeding and duration of breastfeeding. We propose using data from the Wayne County Health, Environment & Atopy Longitudinal Study, or WHEALS birth cohort, established with NIAID funding in 2002. To this data, the proposed study will add (1) a panel of allergists who will make a determination of IgE-mediated food allergy by review of data from interviews with caregivers of infants in the cohort as well as available clinical data, including serum total and specific IgE measured from birth - 2 years and skin prick tests conducted at 2 years; (2) a medical chart review of the infant record, which will also be available to the panel of allergists for determination of IgE-FA; and (3) measurement of concentrations of transforming growth factor beta (TGF¿) and interleukin 10 (IL10) in mature breast milk. These activities are not included under funding of the current WHEALS grant, and neither food allergy nor food sensitization is an outcome for the aims of the previously funded WHEALS grant. Aim 1 of the proposed application is to estimate the prevalence of IgE-mediated food allergy at age 2 years. Aim 2 is to examine the relationship of infant feeding practices to prevalence of food allergy, adjusting for family history of allergy, exposure to tobacco smoke, indoor allergens and endotoxin measured in house dust. An exploratory Aim 3 is to use a case-control study to examine the relationship between prevalence of IgE-mediated food allergy and concentrations of transforming growth factor beta (TGF¿) and interleukin 10 (IL10) in mature breast milk. We will take advantage of the diversity in the WHEALS cohort to describe these relationships by race. The identification of modifiable risk factors for food allergy may lead to development of interventions that can delay progression of the allergic march, thereby reducing risk of asthma or other atopic diseases. This exploratory proposal should result in new paradigms of disease risk that can be applied to an increasingly diverse population, and represents a unique opportunity to gain a more comprehensive picture of how inherited and environmental factors can interact with behavior to influence risk of IgE-mediated allergy to milk, egg, and peanut. Research on risk factors for IgE-mediated food allergy is limited. It is important to increase our knowledge of the causes of food allergy and how it progresses. In this study, we will use an existing birth cohort to explore how infant feeding practices can influence development of IgE-mediated food allergy to egg, milk, or peanut. We will take advantage of the racial diversity in this study population to explore these relationships by race.

Principal Investigator: Joseph, Christine, Ph.D.
Promoting Asthma Wellness in Rural Communities (NIH R01HL092412-01A2)

Asthma is a common disease of both children and adults that disproportionately affects African-Americans with both greater asthma morbidity and mortality. This is especially true fo African American male youth where the rate of death from asthma is more than four times greater than for white male youth of the same age. The literature is relatively consistent showing that cigarette smoking, both active and passive, increases the morbidity from asthma. It is therefore concerning that surveys in both the United States and other countries have shown that youth with asthma are approximately 1.5 to 2.0 times more likely to actively smoke than are their peers. Therefore, targeting youth with asthma who smoke for smoking cessation is likely to significantly improve health both by reducing the health risks of smoking and by reducing the morbidity of asthma. Puff city was the name given to an NHLBI funded study (PI C. Joseph; Col D. Ownby) that targeted three key asthma management issues: 1) reducing or stopping smoking in those who smoke; 2) improving adherence to asthma controller medication use; and 3) improving compliance of carrying a rescue inhaler at all times so that they could be used at the first sign of asthma symptoms. The study was implemented in high schools in inner city Detroit, MI. The randomized trial showed favorable outcomes in the treatment group to include: short-term behavior changes, fewer Emergency Department (ED) visits, fewer hospitalizations, improved quality of life morbidity. Given the success of Puff City among mid-western, inner city, youth, an important question is whether such a program can be transplanted and effective for youth living in a different environment, the rural south. Our pilot data with the rural youth and their parents showed that rural, Georgia youth are at equal or greater risk from asthma symptoms as inner city, Detroit youth. Additionally, in our pilot work, the Puff City computer intervention was well received by the Georgia youth. Our team has established an outstanding collaborative relationship with school systems and jointly developed a feasible plan resolving any logistical concerns for successful implementation of the study. The specific aims of this proposal are to evaluate the effectiveness of the Puff City computer based asthma and smoking management tool among African American youth attending public high schools in two rural counties of Georgia. Approximately 220 students will be individually randomized to either intervention or control conditions. We propose that youth receiving the tailored computerized educational intervention will have greater improvement in the level of asthma management and control and a decrease in cigarette smoking and passive exposure as measured by subjective (self-report) and objective (physiological markers) outcomes of the dependent measures than youth in the control group. Specific dependent variables include: 1) asthma symptoms: wheezing, school attendance [missed school days], emergency department visits, quality of life – measured by self report and exhaled nitric oxide (eNO) concentrations; and 2) cigarette smoking and passive smoke exposure – measured by self-report and salivary cotinine. Control group subjects with receive matched time and attention of web-based computer, self-guided asthma and smoking education. Self-report and biomechanical measures will be obtained at baseline and short term (immediately post intervention) and long-term (6 and 12 month post-intervention).

Principal Investigator: Lamerato, Lois, Ph.D.
Racial Disparities in the Initiation and Intensity of Adjuvant Therapy for Breast Cancer

The purpose of this Department of Defense-funded Breast Cancer Center of Excellence Study is to address a key issue in the quality of cancer care – the use of optimal systemic therapy and implications of its non-use for disparities in outcome between black women and women of other races. A population of newly diagnosed breast cancer patients recruited from three health systems has been recruited for this prospective observational descriptive study. The specific aims are: 1) to identify barriers to receipt of optimal treatment (chemotherapy/hormonal therapy), focusing on both clinical and psychosocial factors; 2) to identify racial differences in the distribution of these barriers; and 3) to model the effects of these barriers on racial disparities in survival by estimating the benefits and costs of mortality reductions that could be achieved if all women received the most intensive treatment regimens. The current status of this project is that nearly 1,200 women have been recruited, providing survey data and biological specimens (saliva for genotyping for polymorphisms), and administrative data from clinical care. We are currently conducting data analysis, as well as long-term follow-up.

Principal Investigator: Levin, Albert, Ph.D.
Validation Study of a Multi-Gene Test for Lung Cancer Risk

Lung cancer is the leading cause of cancer mortality in both men and women in the United States with cigarette smoking being the primary known risk factor and has a low survival rate in part because it typically is at an advanced stage when first detected and treated. Studies to improve post-diagnosis outcome of lung cancer through early detection by means of low-dose spiral coaxial tomography (CT) screening and surgical intervention are promising. However, because more than 90 million active or ex-smokers in the United States alone are candidates for screening the potential cost is very high and may be prohibitive. Additionally, CT screening studies completed thus far are associated with a high incidence of false positive findings which may lead to unnecessary follow-up diagnostic testing. Based on demographic criteria it is possible to identify a group of individuals for whom the 10 year risk for lung cancer is more than 20%. Even in a group as selected as this, subjecting all individuals to close monitoring is costly and is associated with risk of false positive results. In previous studies we reported that key antioxidant and DNA repair genes are regulated differently in normal bronchial epithelial cells (NBEC) of lung cancer cases compared to non-lung cancer controls. A Lung Cancer Risk Test (LCRT) was identified comprising transcript abundance measurement of 14 key antioxidant, DNA repair and transcription factor genes measured in NBEC sampled at the time of bronchoscopy. The test was discovered in a case control study comprising 49 subjects (25 cancer and 24 controls) and validated in a second case-control study comprising 40 subjects (20 cases and 20 controls). In these studies the test had ROC AUC of better than 0.84 and odds ratio of more than 20 for identifying individuals over the age of 50 with more than 20 pack years smoking history who have lung cancer. The Specific Aims of this GO grant are: Aim 1. Establish a prospective cohort nested case control study to test the validity of a lung cancer risk test (LCRT) comprising 14 genes measured in normal airway epithelial cells obtained at bronchoscopy. Enroll at least 1050 subjects over the age of 50 and with more than 20 pack year smoking history but without prevalence lung cancer which will result in identification of 15 incident lung cancer cases with eight randomly selected controls for each case. This study will have sufficient power (>80%) to test an Odds Ratio of greater than 5.0. Establish a plan and resources for long-term (10-20 years) sample storage and analysis and subject follow-up. Aim 2. Establish a bank of NBEC and corresponding blood samples from the subjects enrolled in Aim 1.

RNA, protein, and cytology slides from NBEC and peripheral blood leukocyte RNA and DNA and frozen plasma from blood will be archived. A biomarker that identifies individuals within a demographically defined high risk group who will develop lung cancer will enable even more focused selection for closer monitoring and further reduction in risk of false positive findings. Further, if CT screening is validated, limiting screening to the individuals with the highest demographic and biological risk will markedly reduce cost of implementation.

Principal Investigator: Rybicki, Benjamin, Ph.D.
A Nested Case-Control Study of Prostate Carcinogenesis (NIH 2R01ES011126-06A2)

Prostate Cancer is a slow growing disease that likely involves a series of environmental insults resulting in accumulated DMA damage eventually leading to overt carcinogenesis. DNA adducts are one of the few biomarkers for exposures directly related to cancer that can be quantified in human cells and a reliable measure of biologically effective dose for known carcinogens such as polycyclic aromatic hydrocarbons (PAH) and 2-amino-1-methyl-6-phenylimidazo[4, 5-b]pyridine (PhIP). Epigenetic markers are emerging as important in determining the extent of prostate carcinogenesis. Recent studies suggest that DNA adduct formation and aberrant gene promoter hypermethylation may be related elements in environmentally-induced carcinogenesis. Most research done with respect to DNA adducts, promoter hypermethylation and prostate cancer has focused on cells harvested from patients with prostate cancer or pre-malignant lesions. While these studies have been instructive, a clearer picture of the interconnection and risk associated with DNA adduct formation and epigenetic changes in prostate can only be gained from studies of prostate tissue captured before the onset of disease. At the Henry Ford Health System, we have characterized and have access to a racially diverse cohort of over five thousand men without prostate cancer from whom benign prostate specimens were surgically removed between 1990 and 2002. We plan to expand this cohort through 2006, and will follow-up cohort members for incident prostate cancer diagnoses through 2010 to achieve a desired study sample size of 800 matched case-control pairs. Building on findings from our initial funding period that characterized determinants of PAH- and PhlP-DNA adducts in the prostate cells of men with prostate cancer, in this competing continuation we seek to better understand the temporal relationship between DNA adducts and other epigenetic changes in the benign prostate and later prostate cancer development. To achieve this objective, we plan to conduct a nested case-control study of prostate cancer that will: 1) determine whether PAH- and PhlP-DNA adducts are predictive of later prostate cancer development after adjusting for other possible confounders; 2) determine in a multivariable model how aberrant gene promoter DNA methylation affects the association between PAH-and PhlP-DNA adducts and prostate cancer; and 3) determine whether DNA adducts in the benign prostate are associated with the level of expression of the p53 and p21waf/cip1 tumor suppressor genes in prostate tumors of men who develop prostate cancer.

Principal Investigator: Rybicki, Benjamin, Ph.D.
Admixture Mapping of Sarcoidosis Genes in African Americans (NIH 1 R01 HL092576-01A2)

Sarcoidosis, a multiorgan granulomatous inflammatory disease, likely results from an exaggerated T cell response to an airborne antigen. A genetic predisposition to sarcoidosis has

long been posited, and independent genome scans in German and African-American affected sib pair samples suggest that multiple genes are involved. African-Americans are more commonly and severely affected by sarcoidosis, which imply that genes of African ancestry play a significant role in the disease etiology and pathogenesis. Recent characterization of ancestry informative markers across the genome now makes it feasible to scan the genome for disease genes linked to ancestry in African-American populations. As a research group that has extensively studied the genetic susceptibility of sarcoidosis in African Americans, we have accumulated DMA samples for 1,302 African-American sarcoidosis cases. Many of these cases have participated in one of three previous NIH-funded studies, two family studies and one case-control, that provide a wealth of clinical and epidemiologic data in addition to a DNA sample. From these three studies, we also have DNA and epidemiologic data on 695 African Americans without sarcoidosis who will serve as a control sample. Using these samples, we propose a mapping by admixture linkage disequilibrium (MALD) study to identify sarcoidosis genes linked to African ancestry. The study will involve a multi-staged genome-wide scan targeting specifically those genes of African origin in African Americans that predispose to sarcoidosis susceptibility and radiographically persistent disease. We plan to first screen the genome using a set of 1,536 SNP markers evenly spaced approximately 1.9 cM throughout the genome that are highly informative European - African ancestry differences. In the second stage, we will triple density genotype ancestry informative markers to increase statistical confidence in the results and refine the positions. We will then move to a targeted haplotype-based association study in the most interesting regions. Once we have narrowed the associated genomic areas to specific genes or areas within specific genes, we will sequence the areas that have the highest probability of harboring causal variant(s). In addition, to better understand how putative candidate genes we identify act in sarcoidosis causal pathways involving environmental inciting agents, we will utilize comparable environmental data collected across the three study samples to test for gene-environment interaction. Our proposed study has the potential to uncover genes of modest effect not easily detectable by linkage and may in some instances actually be more statistically powerful than traditional case-control association methods.

Principal Investigator: Rybicki, Benjamin, Ph.D.
African American Sarcoidosis Genetics Resource (Subcontract) (NIH RC2HL101466-01)

Sarcoidosis is a multiorgan granulomatus inflammatory disorder likely resulting from an exaggerated T-dell response in genetically susceptible individuals. African-Americans are more frequently and severely affected by Sarcoidosis yet few collections of African American patients exist. We however, have amassed a large, well phenotyped cohort of close to 3,000 Sarcoidosis patients, family members and controls on which to perform an extensive search of the genome to identify potential susceptibility loci. Specifically, this "Grand Opportunity" proposal will, using a unique and easily-accessible cohort, perform the first, and much needed, genome-wide association (GWA) scan in African Americans using the first and only commercially available genotyping product that results in adequate coverage (>85%) of the African genome. Because of the size of our cohort, we are poised to replicate our findings in an independent sample and therefore propose candidate genes and regions for further characterization. We can further characterize the population origin of these effects based on ancestry data already obtained. Finally, we will develop a bioinformatics tool for the repository and investigation of genetic data (e.g. single nucleotide polymorphisms, copy number variants, etc), genomic data (e.g. physical location, genic location, function, degree of conservation, etc), and statistical data from prior

linkage, admixture and candidate gene association studies as well as this and other GWA studies. This project aligns with the goals of the GO mechanism in that we can begin immediately upon funding, the discoveries made herein will birth multiple follow-up studies, the database resource will allow our field to take the next step beyond association into pathway-based and bioinformatics-driven analyses and finally, we will stimulate the American research enterprise via the purchase of over $2M in domestically produced goods and services and the creation and retention of several biotech and administrative jobs. In sum, our extensive African American cohort and our genotyping, analysis and bioinformatics resources as well as the extensive experience of our team of experts in AA Sarcoidosis genetics make an experiment of this magnitude and scope very unlikely to be completed by any other group. PUBLIC HEALTH RELEVANCE: This project will fast-forward Sarcoidosis, and likely other granulomatus or inflammatory disorders, genetics research by 1) identifying and replicating association to genetic variants throughout the genome and 2) facilitating characterization of these effects using related statistical, genetics and genomics data. In addition, this project will generate extensive revenue for American biotech products and jobs.

Principal Investigator: Wegienka, Ganesa, Ph.D.
Regulatory T Cells in Gestation and Childhood Allergic Disease (NIH 1K01AI070606-01A2)

This Mentored Research Scientist Development Award in Epidemiology and Outcomes Research (K01) will allow me to transition from reproductive epidemiology to childhood allergic disease (CAD) epidemiology research under the guidance of a successful CAD epidemiology research group. Through this proposed research and training program, I will develop the skills needed to become an independent researcher in the field of CAD. CAD are a growing epidemic and are associated with mortality and considerable morbidity. Thirty percent of cases have been attributed to the children's birth order. But, the underlying mechanism cannot be explained by the hygiene hypothesis, because there is little evidence of covariation of infection rates with birth order. Allergic status has been characterized by the T-helper1/T-helper2 ratio (Th1/Th2 ratio) skewed toward a Th2 cell-cytokine predominance, with the role of Th1 in the allergic response not yet defined. Pregnancy is assumed to be a Th2 dominant process. Thus pregnancy is likely a critical component in the causal web of CAD. T regulatory cells (Tregs), which suppress allogenic responses against the fetus in mice and humans, increase in successful pregnancy and decrease, but remain above pre-pregnancy levels, during the postpartum. Research has indicated that Tregs can control both Th1 and Th2 responses. Although a mode of tolerance transference from mother to fetus has not yet been identified, this could explain the observed association between birth order and subsequent CAD risk. Hence the question: what is the role of maternal Tregs during pregnancy in the risk of CAD? As part of an ongoing NIH-funded study, a birth cohort is being recruited for longitudinal study in the Detroit area to study early life exposures in the development of CAD. Using a subset of 225 mother-child pairs from this cohort, we will study the following hypotheses (Tregs: CD4+CD25+FOXP3+ and CD4+CD25+CTLA4+). Our hypotheses are: 1) More prior live births and shorter pregnancy intervals will be predictive of: a. Higher maternal Tregs during pregnancy and at 1, 6 and 12 months postpartum; b. Lower maternal prenatal IgE; and 2) Higher maternal Tregs during pregnancy are predictive of: a. Higher Tregs in their child's blood at delivery (cord), 6 and 12 months and 2 years; b. Lower IgE in their child's blood at delivery (cord), 6 and 12 months and 2 years; c. Reduced risk of their

child having a positive skin prick test for common aeroallergens and food allergens at age 2 years.

Principal Investigator: Wegienka, Ganesa, Ph.D.
Study of Environment, Lifestyle and Fibroids (Subcontract) (NIH HHSN291200555546C)

More than 80% of African American women and almost 70% of White women will have had uterine fibroids by the time they reach menopause. These benign tumors cause menstrual gushing and debilitating pelvic pain. Fibroids are the leading cause of hysterectomy in the United States. The Study of Environment, Lifestyle & Fibroids (SELF) is a longitudinal cohort study from the National Institute of Environmental Health Sciences (NIEHS). On behalf of NIEHS and their clinical coordinators at Social and Scientific Systems, Inc., HFHS is serving as the sole clinical site for this landmark study. For this investigation of risk factors for fibroids, HFHS will recruit 1600 African American women who will undergo a series of uterine ultrasounds over five years. Participants will also provide biological samples and interview information for this investigation. The work at HFHS is a collaboration between members of the Department of Public Health Sciences and the ultrasonographers in the Department of Diagnostic Radiology. The project began in the fall of 2010 and is expected to span 9 years. The goal is to identify modifiable risk factors so that strategies can be developed to prevent fibroid incidence and growth.

Center for Health Services Research

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Research Summaries

Principal Investigator: Elston Lafata, Jennifer, Ph.D.
Michigan Center for Health Communications Research II (Subcontract) (NIH 5P50CA101451-08)

Research on tailoring for health-related behaviors and decision-making has increased dramatically since the early 1990's. Results from numerous randomized trials suggest that tailored communications for cancer prevention and control have a greater influence on behavioral and decision making outcomes than one-size-fits-all approaches. Until recently, however, we had little understanding of why tailored communications influenced behavior, or which components of these communications were effective. CECCR1 funding helped us to organize a concerted interdisciplinary effort to open the "black box" of health communications interventions, which led to identifying a broad array of psychosocial and communications

components relevant to health behavior change and decision making. We also identified important individual characteristics that moderate the impact of health communications messages. Results from several of these studies have already been published, and are leading to significant new research funding and a new generation of health communications investigators. Moreover, CECCR1 results are also being adopted in health care, employer, pharmaceutical, and government settings of the U.S. and other parts of the world. The overarching aims of CECCR2 are to: (1) Extend our tailoring research beyond the prevention area to the broader cancer care continuum, including early detection, treatment, and long-term survival; (2) Extend our tailoring research to new clinical and post-treatment settings; (3) Deepen our understanding of the key psychosocial and communications components identified in CECCR1, including motivation, ethnic identity, risk perception, and cognitive processing; (4) Explore methods of tailoring to patient preferences for shared decision making; (5) Develop new social and cognitive neuroscience strategies for identifying immediate impact and mechanisms of health communications messages; (6) Develop new interdisciplinary collaborations with scientists and research institutions; (7) Train a new generation of health communications scientists and practitioners; and (8) Disseminate both the scientific and practical results of our research efforts. Woven through CECCR2 research are crosscutting interests related to: tailoring and relevant communications channels; reaching underserved populations through more relevant and easier-to-process content; physiological mechanisms of communication effect; and methodological issues of design, data collection, and measurement. CECCR2 involves four primary research sites and networks, and collaborations with 34 research investigators from 13 institutions. Because of the ambitious scope of our proposed studies, we have obtained over $10 million in matched funding from other sources to help us carry out the proposed research.

Principal Investigator: Nerenz, David, Ph.D.
Back Pain Outcomes Using Longitudinal Data (BOLD) (Subcontract) (NIH R01HS019222-01)

Low back pain is one of the most important causes of functional limitation and disability, an Institute of Medicine priority condition, and it remains a particularly important problem for the elderly, an AHRQ priority population. While there are numerous guidelines regarding the use of diagnostic testing and treatments for the general low back pain population, there is a paucity of evidence-based guidelines for the elderly. This is more than a mere academic concern. The annual direct medical costs of low back pain were $86 billion in 2005 and by 2010 are likely to rise to over $100 billion. Despite the high prevalence and cost of low back pain, important questions remain unanswered regarding the comparative effectiveness of most commonly used diagnostic tests and treatments. Our primary goal is to establish a large, community-based registry of elderly patients with low back pain. This registry will provide a foundation for rigorous prospective studies including large, practical, randomized controlled trials (RCTs). Alongside the registry, we propose to enroll patients into two studies: 1) an RCT of elderly patients with spinal stenosis to evaluate the effectiveness, cost and safety of combined epidural steroid injections and local anesthetics compared with local anesthetic injections alone, and 2) a prospective observational cohort study of early advanced imaging (MRI and CT) compared to no advanced imaging in elderly patients with new episodes of low back pain. These studies will serve as demonstration projects for the value of the registry for comparative effectiveness research. The registry will provide the infrastructure for future studies to evaluate back pain care

at multiple stages of development, from the early market penetration of relatively immature technologies (e.g. artificial discs, genomics) to widely disseminated mature interventions (e.g. MRI, physical therapy, spinal fusion). The overall goal of this project is to establish a sustainable and rich registry to evaluate prospectively the effectiveness, safety, and cost-effectiveness of interventions for patients over age 65 with low back pain. PUBLIC HEALTH RELEVANCE: Low back pain is one of the most important causes of functional limitation and disability, an Institute of Medicine priority condition, and it remains a particularly important problem for the elderly, an AHRQ priority population. The overall goal of this project is to establish a sustainable and rich registry to evaluate prospectively the effectiveness, safety, and cost-effectiveness of interventions for patients over age 65 with low back pain. We propose 3 specific aims: 1) To establish the Back pain Outcomes using Longitudinal Data (BOLD) registry;2) To conduct a randomized controlled trial (RCT) in elderly patients (an AHRQ priority population) with spinal stenosis to test if the effectiveness of epidural steroid injections (ESI) plus local anesthetics (LA) is greater than LA alone;3) To conduct a prospective, observational cohort study to compare the effectiveness of early (within 6 weeks of presentation) advanced imaging (MRI and CT) to no advanced imaging in elderly patients with new episodes of low back pain without radiculopathy with respect to pain, function and subsequent resource utilization.

Publications – Medical & Surgical – Part I (Internal Medicine Department)

Internal Medicine

- **Allergy & Immunology**
- **Cardiology/Cardiovascular Research**
- **Endocrinology and Metabolism**
- **Gastroenterology**
- **General Internal Medicine**
- **Hematology, Medical Oncology and Josephine Ford Cancer Center**
- **Hypertension and Vascular Research**
- **Infectious Diseases**
- **Nephrology and Hypertension**
- **Pulmonary and Critical Care Medicine**
- **Rheumatology**
- **Sleep Medicine**

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- **Nursing**
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Publications – Health & Health Care Research

- **Department of Public Health Sciences**
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