

Abstracts – Medical & Surgical – Part I (Internal Medicine Dept.)

Internal Medicine

- **Cardiology/Cardiovascular Research**
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Cardiology/Cardiovascular Research

Senior Research Staff

Ramesh Gupta, Ph.D.

Steven Keteyian, Ph.D.

David Lanfear, M.D.

Hani N. Sabbah, Ph.D., Director, Cardiovascular Research

Victor G. Sharov, M.D., Ph.D.

Albertas I. Undrovinas, Ph.D.

Research Summaries

Principal Investigator: Lanfear, David, M.D.

Pharmacogenetics of the B-type Natriuretic Peptide Pathway (NIH 1K23HLO 85124)

The overall 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: Sabbah, Hani, Ph.D.

Cardiac Energy Metabolism in Heart Failure Core B: Animal and Histomorphometry Core (NIH 1P01HL074237-01)

The scope of work is; 1) to assess the effects of chronic partial inhibition of long chain fatty acid oxidation on the progression of heart failure. 2) To assess the effects of stimulation of myocardial fatty acid oxidation by feeding a high fat diet on the progression of heart failure. 3) To assess the effect of partial inhibition of myocardial fatty acid oxidation on cellular and molecular remodeling of the myocardium over the course of evolving heart failure. 4) To perform histological analysis on sample from Projects 1-3.

Principal Investigator: Sabbah, Hani, Ph.D.

Cardiac Energy Metabolism in Heart Failure - Project 2: Heart Rate Control, Myocardial Energetics and Progression of Heart Failure (NIH 1P01HL074237-01)

Heart failure (HF) is an enormous medical, social and economic burden. It is a leading cause of mortality and morbidity in the United States and rivals or exceeds that of many cancers. The search for better treatments for HF is one of the major challenges in cardiology. The high morbidity in HF is fueled by the progressive nature of the disease whereby the status of the affected patient worsens over time despite the absence of concurrent clinically adverse events. Therefore, any therapeutic approach that can retard this relentless progression or reverse it is bound to have a major impact on survival and on the quality of life of patients with HF. There are many reasons why a heart can fail. The concept that the failing heart is "energy starved" is a centerpiece of this project. A major reason why one should pay close attention to this topic is the underlying concept that any energy-sparing treatment for HF is likely to improve cardiac function and hence long-term outcome. Cardiac energy metabolism, while complex, can be reduced to essentially 3 components namely, 1) substrate utilization, 2) oxidative phosphorylation and 3) energy transfer and utilization. In HF, mitochondria, the source of ATP supply to cardiomyocytes is structurally and functionally abnormal leading to abnormal oxidative phosphorylation. In this project, modulation of energy utilization will be explored in the form of heart rate (HR) reduction and its impact on the progression of HF. Resting HR is increased in HF and is a determinant of poor long-term outcome. HR is a determinant of myocardial oxygen consumption and, hence, energy utilization. Our working hypothesis is that optimal HR reduction in the setting of HF prevents or reverses deterioration of mitochondrial function, maintains or restores normal cardiac substrate metabolism, and retards or reverses progressive LV dysfunction and remodeling. All studies will be conducted using the well established canine coronary microembolization model of chronic HF. Three distinctly differing approaches to chronic HR reduction will be implemented, namely, 1) chronic HR reduction with electrical Vagus nerve stimulation,

2) chronic HR reduction with pharmacological selective and specific inhibition of the pacemaker If current and 3) chronic HR reduction with traditional beta-adrenergic receptor blockers. All studies will be performed in dogs with moderate HF (LV ejection fraction ~35%) as well as in dogs with advanced HF (LV ejection fraction <20%).

Endocrinology & Metabolism

Senior Research Staff

Abraham Thomas, M.D., Division Head
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: Thomas, Abraham, M.D. Henry Ford High-Risk Diabetes Program for Diabetes Management of Diabetic Individuals with Limited or No Health Insurance (H75 DP002310)

Diabetes mellitus is one of the fastest growing diseases in the world and the state of Michigan, faces some of the highest rates of diabetes around the country. There are well-established guidelines by organizations, such as the American Diabetes Association, for the care of our diabetic patients, yet many, if not most of our patients do not achieve these guidelines.

The Henry Ford High-Risk Diabetes Program for Management of Diabetic Individuals with Limited or No Health Insurance seeks to use state of the art skills in management and education of diabetic patients to improve their glucose control along with their blood pressure and lipid control. Targeted patients include those with limited or no health insurance, and in particular those who have been hospitalized or been to the emergency

room for their diabetes or a complication related to their diabetes. The program will operate in conjunction with the Henry Ford Macomb Hospital Warren Campus, Warren, Michigan, in Macomb County.

The overall goal of this grant is to develop a model program for the delivery of diabetes care in a cost-effective manner to a population that does not have resources to access the usual medical care system. We expect the following two points will guide our program.

1. Based on the methods used to control diabetes from our past research studies , we anticipate that patients who have not been able to control their diabetes will be more likely to control their diabetes and even if they do not reach optimal control will be better off than their current state of diabetes control.
2. The case management can be accomplished with other strategies (telephone, email, etc.), disease management classes (nutrition, etc.) that may provide a reduced cost per patient and as a result allow more patients to be seen and taken care off.

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

John Popovich, M.D., Chair

Keoki Williams, M.D.

Scott Kaatz, M.D.

Research Summaries

Principal Investigator: Kaatz, Scott M.D.

Title: Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) Trial (HL0 87229)

Temporary interruption of warfarin therapy for an elective surgical or other invasive procedure is a common clinical problem, affecting ~400,000 patients in North America annually. Increasingly, clinicians employ a low molecular weight heparin (LMWH) as a 'bridge' before and after surgery or a procedure, when warfarin is withheld and anticoagulation is otherwise sub-therapeutic. This empiric strategy has several drawbacks, including lack of proven efficacy to prevent arterial thromboembolism, additional cost to the healthcare system, and the potential for increased peri-operative

bleeding. Unfortunately, there are no high-quality clinical trials to provide Level 1A evidence to guide patient care. We hypothesize that simply withholding warfarin in the perioperative setting for patients with atrial fibrillation will not meaningfully increase the risk for arterial thromboembolism, and will forestall hemorrhagic complications, compared to a strategy using LMWH before and after surgery. To address this important question, we propose a multi-center, prospective, double-blind, placebo-controlled randomized clinical trial that randomly allocates 3,282 patients with atrial fibrillation to either therapeutic dose LMWH or matching placebo before and after surgery (1641 patients per arm). Forty enrolling centers in North America will recruit over 44 months. Exclusion criteria include: mechanical heart valve; recent stroke or major bleed; severe renal insufficiency, thrombocytopenia; or planned surgery that precludes use of post-operative therapeutic-dose LMWH. Primary efficacy outcome is arterial thromboembolism (stroke, TIA, or systemic embolism), and primary safety outcome is major bleeding (symptomatic, clinically-overt, or fatal). We will conduct a non-inferiority efficacy analysis to demonstrate that "no bridging" has a risk for arterial thromboembolism equal to a bridging strategy. Clinical outcomes will be analyzed using the per protocol population for the efficacy outcome and the intention-to-treat population for the safety endpoint. Dissemination of trial results will target physicians and other providers who manage patients with atrial fibrillation on chronic warfarin therapy. This randomized trial comparing bridging therapy to a "no bridging" strategy will establish a clear standard-of-care for the management of these patients. This application is in companion application to the Statistical Data Coordinating Center submitted separately. Clinicians frequently use low-molecular weight heparin as a 'bridge' before and after an elective procedure for patients on chronic warfarin therapy. It is unknown if this practice is efficacious, however, and it may actually result in an increased risk for periprocedural hemorrhage. This prospective, randomized, double-blind study will definitively answer this question for patients with atrial fibrillation who are on warfarin therapy.

Principal Investigator: Kaatz, Scott, M.D.

Title: A Randomized Clinical Trial of Genotype-Guided Dosing of Warfarin Therapy (NIH HHSN26820080000)

Current dosing practices for warfarin are empiric and result in the need for frequent dose changes as the international normalized ratio (INR) gets too high or too low. As a result, patients are put at increased risk of thromboembolism, bleeding, and premature discontinuation of a highly efficacious therapy. Also, primarily because of difficulties using the drug, there is substantial underuse of warfarin in millions of patients who would benefit from anticoagulation (AC). There is clearly a need to improve warfarin management. Although clinical research has identified clinical and genetic factors that can alter warfarin dose requirements, limited prospective clinical research has examined the utility of using clinical and genetic information to improve outcomes among a large, diverse group of patients using warfarin. The objective of the Clarification of Optimal Anticoagulation through Genetics (COAG) trial is to conduct a 1,238 participant, multicenter, double-blind, randomized trial comparing two approaches to guiding warfarin therapy initiation: 1) initiation of warfarin therapy based on algorithms using

clinical information and an individual's genotype using genes known to influence warfarin response ("genotype-guided dosing"), and 2) initiation of warfarin therapy based on algorithms using only clinical information ("clinical-guided dosing"). The study hypothesis is that the use of genetic and clinical information for selecting the dose of warfarin during the initial dosing period will lead to improvement in stability of AC relative to a strategy that incorporates only clinical information (without genetics) for initial dosing. Each study arm will include a baseline dose initiation algorithm and a dose revision algorithm applied over the first 4 to 5 doses of warfarin therapy. By comparing the two strategies in this trial, the study will be able to determine if genetic information provides added benefit above and beyond what can be gleaned simply with clinical information.

Principal Investigator: Williams, Keoki, M.D.

Title: 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 dipropionate (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.

Hematology, Medical Oncology, Josephine Ford Cancer Center

Senior Research Staff

Robert Chapman, M.D., Division Head and Director, JFCC
Frederick Valeriote, Ph.D.

Research Summaries

Principal Investigator: Chapman, Robert, M.D.
Cancer Prevention and Treatment Demonstration for Ethnic and Racial Minorities (CPTD) (CMS/DHHS IAO 30006810)

This CMS sponsored demonstration project will show the racial disparity in cancer screening, diagnosis, and treatment between African American and Caucasian Medicare recipients in Southeast Michigan can be substantially and significantly reduced. We are located in a large geographic community with a large African American community (over 80% of the population of Detroit). The proportion of Detroit residents existing below the poverty line is more than double that in the nation or the state of Michigan. Corporate data stores indicate that roughly 13,000 African American Medicare recipients receive their care at the Henry Ford Health System (HFHS). Our Information Technology Systems allow us to readily create a database of those target individuals who elect to enroll in the project. This database will be enriched by the individuals referred from our partnering organizations (AARP, Adult Well-Being Services, and our Faith Based Initiative). The data on disparities in stage at diagnosis, along with other data from our Henry Ford linking disparities in stage at diagnosis to disparities in outcomes, strongly suggest the need for additional effort made on enhancing cancer screening rates. Although some screening tests may not be recorded in the administrative data systems at HFHS, we believe that the cancer screening rates are well below achievable levels in our over-65 population and that there is a clear opportunity for improvement. The HFHS patient data base indicates very poor utilization of our screening services and presentation of our African American patients with more advanced stages of cancer than their

Caucasian counterparts. Other published studies from HFHS have documented disparities in treatment patterns and outcomes for patients with lung cancer or breast cancer. These disparities have been shown to be related to clinical factors like comorbidities or obesity, pointing the way to identification of patients at higher risk for suboptimal treatment, and suggesting opportunities for provider-directed as well as patient-directed interventions.

Principal Investigator: Valeriote, Frederick, Ph.D.
Cynaophytes Anticancer Drug Discovery (NIH R01 CA10085)

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)

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

William Beierwaltes, Ph.D.

Oscar Carretero, M.D.

Marie Cavasin, M.S

Jeffrey L. Garvin, Ph.D., Division Head

Pamela Harding, Ph.D.

Margot C. LaPointe, Ph.D.

Pablo A. Ortiz, Ph.D.

Nour-Eddine Rhaleb, Ph.D.

Edward Sheseley, Ph.D.

Xiao-Ping Yang, M.D.
Jia Long Zhou, M.D.

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.

Salt-Sensitive Hypertension: Role of Renal Superoxide (NIH/NHLBI 2R01 HL70985-05)

In our second project we are studying the role of reactive oxygen species or oxidants in the regulation of salt absorption by the thick ascending limb. All cells produce oxidants, but when production is unchecked serious consequences occur. Oxidants have been implicated in many pathological states from atherosclerosis to hypertension. In the kidney, oxidants increase salt and water retention, promoting hypertension. In the thick ascending limb of the kidney, we are investigating how oxidants increase salt absorption. To date we have found that oxidants work in two ways. First, they reduce the amount of nitric oxide. Thus they reduce the levels of a chemical that inhibits salt absorption. Secondly, and perhaps more importantly, they stimulate the proteins involved in salt absorption. Oxidants do not act directly, but rather through a series of other small molecules and proteins that form so-called signaling cascades. In the thick ascending limb, oxidants activate the protein kinase C signaling cascade, named for the final

mediator of cellular events in this pathway, protein kinase C. Protein kinase C chemically alters the proteins that allow salt to enter the cell and thereby enhances their activity. Because oxidants increase salt retention by the thick ascending limb, we are now studying whether they also cause hypertension.

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 autocrine 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 hemodynamics, changing NaCl 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 pro- 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 NaCl reabsorption, and whether a defective response to flow-stimulated NO production enhances salt retention and promotes salt-sensitive hypertension. Project 2 will test whether NO inhibits thick ascending limb NaCl reabsorption by activating cGMP-stimulated phosphodiesterase 2 (PDE2), reducing cAMP, and thus decreasing Na/K/2Cl cotransport. It will also test in Dahl salt-sensitive rats whether a reduction in NO-induced inhibition of NaCl 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 tubuloglomerular feedback. It will also test whether CO acts by stimulating cGMP which inhibits Na/K/2Cl 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: Ortiz, Pablo, Ph.D.
Salt Absorption by the THAL: Role of NKCC2 Trafficking (NIH 5R01 HL080409-02)

The number of Na-transporters in the cell membrane is regulated by dynamic insertion, retrieval and recycling of transporters. Collectively these processes are known as trafficking. In some form of human and experimental hypertension, salt retention is caused by abnormally high levels of Na-transporters in the apical membrane of some

nephron segments. The thick ascending limb (THAL) absorbs NaCl and contributes to salt and water homeostasis, thereby influencing blood pressure. NaCl absorption by the THAL is primarily regulated by NKCC2, an apical Na/K/2Cl cotransporter that mediates Na and Cl entry into the cell. To date, it is not clear whether trafficking of NKCC2 regulates NaCl absorption. It is also not clear whether vasoactive hormones that stimulate and autoids that inhibit NaCl absorption by the THAL regulate NKCC2 levels in the apical membrane by affecting its trafficking. We hypothesize that NaCl absorption by the THAL is regulated in part by trafficking of NKCC2 into the apical membrane, in a process stimulated by cAMP and inhibited by nitric oxide. Enhances insertion of NKCC2 into the apical membrane contributes to salt retention in models of salt-sensitive hypertension. In Aim 1 we will examine whether NKCC2 levels in the apical membrane and NaCl absorption are regulated by insertion and retrieval of NKCC2. In Aim 2 we will study whether hormones that stimulate NKCC2-dependent NaCl entry into THALs via cAMP increase NKCC2 levels in the apical membrane. In Aim 3 we will study whether nitric oxide inhibits NKCC2-dependent NaCl entry by decreasing NKCC2 levels in the apical membrane. Finally we will examine whether basal and hormone-stimulated NKCC2 levels in the apical membrane are enhanced in THALs from salt-sensitive animals. We will use state-of-the-art techniques to measure NKCC2 trafficking and activity in isolated rat THALs. Data from this proposal will increase our understanding of how salt absorption by the THAL is regulated in normal and salt-sensitive animals, and will identify new targets for the development of diuretics.

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 [¹²⁵I]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 [¹²⁵I]-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 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.

Principal Investigator: Zhou, Jia Long, M.D.

Role of Intracrine Angiotensin II in Kidney Cells (NIH R01DK067299)

Angiotensin II (Ang II) plays an essential role in maintaining body sodium and fluid balance and normal blood pressure by regulating proximal tubular sodium reabsorption. Ang II exerts powerful effects on sodium transport and cell growth by activating cell surface receptors on brush borders and basolateral membranes of proximal tubule cells. However, we have new evidence that a) extracellular Ang II is taken up by proximal tubule cells in vivo and in vitro; b) microinjection of Ang II directly into the cells increases intracellular calcium; and c) Ang II induces RNA transcription and expression in isolated nuclei. Our results suggest that internalized Ang II may act as an intracellular hormone to play important physiological and pathological roles in these cells. In this project, we propose to test the general hypothesis that extracellular Ang II is taken up by proximal tubule cells through AT1A receptor-mediated internalization, and that internalized Ang II binds to cytoplasmic and nuclear receptors to induce intracellular responses. To test this hypothesis, we will conduct both in vitro and in vivo studies, using complementary biochemical, morphological, cellular and molecular biology approaches. In Aim I, we will study whether proximal tubular cells take up extracellular Ang II in vitro and in vivo and elucidate the mechanisms by which Ang II receptors and the endocytotic machinery regulate Ang II trafficking. In Aim II, we will use confocal microscopy, state-of-the-art EM autoradiography and immunohistochemistry to trace intracellular trafficking pathways of internalized Ang II to the endosomal compartments and its translocation to the nucleus in vitro and in vivo. In Aim III we will study whether microinjection of Ang II increases intracellular calcium through activation of cytoplasmic AT1 receptors and the cellular mechanisms involved. Finally, in Aim IV we will investigate whether internalized Ang II binds to intracellular Ang II receptors to activate transcription factor NF κ B and its translocation to the nucleus, and whether internalized Ang II stimulates nuclear receptors to increase transcription and expression of the Na⁺/H⁺ exchanger NHE3 and pro-inflammatory cytokines. These studies will

provide new insights into the important role of internalized Ang II in renal physiology and Ang II-induced hypertensive renal injury.

Infectious Disease

Senior Research Staff

Norman Markowitz, M.D.

Jose Vazquez, M.D.

Marcus Zervos, M.D., Division Head

Research Summaries

Principal Investigator: Markowitz, Norman, M.D.

Expanded and Integrated Human Immunodeficiency Virus Testing for Populations Disproportionately Affected by HIV, Primarily African Americans. (Michigan Department Community Health)

The overall goal of the study is to evaluate the performance of two rapid HIV tests not currently used by Michigan's publicly-supported HIV testing sites (i.e. Clearview and UniGold). The study will also seek to identify the features that influence use and acceptance of the test among providers (e.g., ease of use, readability, and cost). The findings from this study will guide decisions regarding utilization of HIV rapid tests in Michigan's publicly funded test sites. Specifically, the findings of this study will help to ensure the effectiveness and efficiency of HIV testing services supported by the Department.

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: 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

Paul Kvale, M.D.

Michael Simoff, M.D.

Michael Eichenhorn, M.D., Division Head

Research Summaries

Principal Investigator: Kvale, Paul, M.D.

Pathology Specimen Collection for the PLCO Project (NIH/NCI N01 CN25512)

The pathology collection for PLCO will collect and analyze pathology tissue samples from the existing cohort of PLCO participants. NCI is funding pathology specimen collection for a period of 12 months with a collection of approximately 300 samples from each of the 10 screening centers for the first year. NCI has developed a strategy to collect as few as 50 and as many as 300 samples per SC for up to an additional 4 years. Tumors of the following tissue types will be collected: colorectal (including adenomas), ovarian, lung, prostate and breast plus additional cancers as determined by NCI. First year collection will begin with colorectal cancer and adenomas.

Pathology tissue from cancer patients provides increasing opportunities for the study of biological questions relevant to tumor etiology. The material obtained from this study is expected to answer crucial questions about cancer etiology and cancer screening tests.

Pathology tissue samples will be collected from pathology labs and sent to a central NCI lab and used to generate tissue microarrays.

Based on participant selection criteria developed by NCI, screening centers will receive a list of potential participants for pathology specimen collection. The selection criteria will include participants in both the screening and control arms of PLCO, with a signed Etiologic Studies Consent. Confidentiality will be maintained and protected as stated in the Privacy Act System of Records Notice. Access to study data will be limited to staff working on the study and all staff will sign a confidentiality statement.

Screening centers are responsible for obtaining participant authorization, requesting tissue from pathology departments, shipping and tracking this effort. There will be contact with PLCO participants, medical records departments, pathology laboratories, shipping companies and UCLA all of which will be tracked by each screening center and monitored by the coordinating center.

UCLA is responsible for processing pathology specimens into tissue microarrays for future analysis and for storage of TMA's. In addition UCLA will store any tissue blocks sent for permanent retention. The coordinating center is responsible for coordination, data management, systems support and quality control. PLCO is led by the PLCO Steering Committee, consisting of lead investigators from each screening center, UCLA and the NCI project Officer.

Principal Investigator: Kvale, Paul, M.D.

National Lung Screening Trial (NLST) (NIH/NCI N01 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.
David Hudgel, M.D., Division Head
Gary Richardson, M.D.
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)

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

Neurology

Senior Research Staff

Susan Bowyer, Ph.D.
Jieli Chen, M.D.
Stanton B. Elias, M.D., Chair
James Ewing, Ph.D.
Michael Chopp, Ph.D., Vice Chair for Research
Feng Jiang, Pharm.D.
Hao Jiang, Ph.D.
Quan Jiang, Ph.D.
Robert Knight, Ph.D.
Yi Li, M.D.
Rhonna Shatz, D.O.
Norman Tepley, Ph.D.
Stephen Robinson, Ph.D.
Li Zhang, M.D.
Zheng Gang Zhang, M.D., Ph.D.

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 Angiotensin-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.

Prediction of Stroke Outcome from Early MRI Data Using an Adaptive Neural Network (NIH R03NS061170-02)

We have previously used combined MRI image sets and iterative self-organizing data analysis (ISODATA), to obtain a time-independent prediction of eventual lesion volume in animal models of stroke and in humans. Recently, we have refined and improved this approach by introducing an adaptive neural network (ANN) as a predictor of the T2-weighted image at 3 months, thus providing an essentially continuous descriptor of tissue outcome, rather than the much coarser classification scheme produced in ISODATA. In this R03 application, we propose to apply this methodology to the reanalysis of an existing data set of human studies obtained over a period of ten years by the human arm of a stroke program project grant, and thereby provide an early and robust predictor of outcome in stroke. An external stroke data base will be used as an independent validating set. Finally, an examination of MRI changes in an open-label trial, and in a blinded trial, of the anti-platelet drug abciximab will be conducted. This latter examination will allow the description of the operating characteristics of the ANN predictor (i.e., its connection to clinical measures) to be refined. If this effort is successful, we will produce a surrogate MRI outcome measure that will be quickly available (essentially in real time) to predict the final results of stroke in the parenchyma of the brain, at the acute and subacute stages of stroke. This will allow the real-time assessment of treatment effects in acute and subacute stroke patients. PUBLIC HEALTH RELEVANCE: Stroke is a leading cause of death and disability in the United States. Using MRI images taken in the early stages of stroke, we aim to produce a predictor of stroke outcome so that therapeutic interventions can be assessed in real-time.

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.

Principal Investigator: Jiang, Feng, Ph.D.

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 tumorigenic 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: Jiang, Quan, Ph.D.

In Vivo MR Evaluation of Cell Therapy for Stroke (NIH RO1 NS48349)

Treatment of stroke with bone marrow stromal cells (MSCs) significantly improves functional recovery in experimental stroke. However, little is known about temporal and spatial profiles of migration of transplanted MSCs and the effects of these cells on host cerebral tissue leading to functional recovery. We propose to develop noninvasive *in vivo* magnetic resonance (MR) methodology for tracking transplanted MSCs and investigating their effects on the host brain. In Specific Aim 1, we will first optimize methodology for magnetic contrast agent labeling and *in vivo* three dimensional magnetic resonance (MRI) monitoring of transplanted MSCs in the host brain. Using the optimized methodology, we will then examine the effects of different routes (intravenous vs intracisternal) of transplantation on survival, migration, and distribution patterns of transplanted cells in brain subjected to stroke. In Specific Aim 2, dynamic effects of transplanted MSCs on the host brain angiogenesis and functional recovery after stroke will be noninvasively measured by means of MR. Neurological outcome will be measured using a battery of behavioral tests. Correlation between changes in MR measurements and dynamic functional improvements will be analyzed in the same animal. In addition, changes in MR measurements of angiogenesis resulting from MSC transplantation will be verified using three dimensional laser scanning confocal microscopy in combination with immuno-histochemistry. With these novel approaches, we expect that noninvasive MR measurements will simultaneously detect the migration and distribution of transplanted cells and the effects of these cells on the host brain tissue, and that changes in MR measurements will correlate to neurological function. Therefore, MR could potentially provide important noninvasive measurements for developing a successful cell therapy for stroke. After completing our studies, we expect to demonstrate that MR tracking magnetic labeled cells is a valid new technique for studying cell therapy for stroke, which

will lead to optimization of cell transplantation protocols and improved management of stroke.

Principal Investigator: Knight, Robert

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: 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 in combination with tPA and the mechanisms underlying the beneficial effects in aged rats after embolic stroke.

Principal Investigator: Zhang, Zheng Gang, M.D.
Treatment of Acute Embolic Stroke with Statins and rt-PA (NIH 2R01HL064766-05A2)

Approximately 80-90% of human cerebral ischemic events are caused by thromboembolism. There is a compelling need to develop acute therapeutic interventions for the treatment of stroke. We present preliminary data indicating that atorvastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, extends the therapeutic window of thrombolysis in a rat model of embolic stroke by activation of the PI3- K/Akt signaling pathway. However, the atorvastatin mediated therapeutic effect is independent of eNOS and lipid levels. The goals of this application are to determine the efficacy of statins in combination with thrombolysis for treatment of acute ischemic stroke and to investigate mechanisms underlying the therapeutic effects of atorvastatin as an adjuvant agent to recombinant human tissue plasminogen activator (rht-PA). Our hypotheses are: 1) Treatment of stroke with atorvastatin in combination with rht-PA extends the therapeutic window for acute stroke; 2) Atorvastatin activates the PI3-K/Akt signaling transduction pathway in cerebral endothelial cells, which decreases cerebral microvascular thrombosis and blood brain barrier (BBB) leakage by negatively regulating endothelial cell genes that promote thrombogenicity, vascular permeability, and inflammation; 3) Activation of the PI3-K/Akt cell survival pathway in neurons by atorvastatin attenuates ischemic neuronal damage exacerbated by delayed treatment of rht-PA. The proposed experiments have been designed to test these hypotheses. Using Magnetic Resonance Imaging (MRI) and 3D laser scanning confocal microscopy (LSCM) techniques, we will first investigate the effects of short-term, high-dose atorvastatin on cerebral vascular patency and integrity including cerebral blood flow (CBF) and BBB leakage, and the neurotoxic effects of tPA. Using laser capture microdissection in combination with real time PCR, Western blot analysis and specific inhibitors which block PI3-K/Akt activation, we will then delve into the mechanisms by which the PI3K/Akt signaling pathway mediates expression of endothelial cell genes involved in thrombosis and BBB leakage, and expression of neuronal genes engaged in the neurotoxic effects of tPA. These studies will lead to a

comprehensive understanding of mechanisms underlying the therapeutic effects of statins on extending the window of thrombolysis for acute ischemic stroke and may provide a novel and useful treatment strategy for human ischemic stroke.

Neurosurgery

Senior Research Staff

Chaya Brodie, Ph.D.
Kost Elisevich, M.D.
Dunyue Lu, M.D.
Asim Mahmood, M.D.
Thomas Mikkelsen, M.D.
Sandra Rempel, Ph.D.
Mark Rosenblum, M.D., Chair
Donald Seyfried, M.D.
Ye Xiong, M.D., Ph.D.

Research Summaries

Principal Investigator: Brodie, Chaya, Ph.D. Regulation of Glioma Cell Apoptosis in PKCdelta (NIH-NCI R01CA109196)

PKCdelta is a key enzyme in the regulation of cell apoptosis in various cellular systems. PKCdelta acts as a pro or anti-apoptotic kinase depending on the specific cell type and apoptotic stimulus, however the mechanisms underlying its diverse effects are not understood. In this proposal we seek to understand the molecular mechanisms involved in the regulation of cell apoptosis by PKCdelta focusing on gliomas as a cellular system. Gliomas exhibit deregulated cell apoptosis due to altered apoptotic pathways that favor cell survival. In a recent study we demonstrated that PKCdelta expression is reciprocally correlated with the degree of malignancy in gliomas. Moreover, PKCdelta regulates the apoptosis of these cells in a stimulus-specific manner. The main hypothesis of this proposal is that PKCdelta is a major regulator of glioma cell apoptosis and that the pro and anti-apoptotic effects of PKCdelta in glioma cells are determined by its activation, phosphorylation on distinct tyrosine residues and by its subcellular localization. To test this hypothesis we will employ different apoptotic stimuli and will first examine the role of PKCdelta activity in its pro and anti-apoptotic effects by using a PKCdelta inhibitory peptide, a PKCdelta KD mutant and siRNAs directed against PKCdelta mRNA. Tyrosine phosphorylation of PKCdelta is often induced by apoptotic stimuli. Therefore, the tyrosine phosphorylation of PKCdelta will be studied in response to the various apoptotic stimuli employed in this study. The specific tyrosine residues and the tyrosine kinases involved in their phosphorylation will be identified and their role in the PKCdelta apoptotic effects will be determined. The translocation of PKCdelta in response to the different apoptotic stimuli will be examined using GFP-tagged PKCdelta and the role of PKCdelta tyrosine phosphorylation in the translocation of PKCdelta will be explored using PKCdelta tyrosine mutants. The role of PKCdelta localization in its apoptotic

effects will be studied using a PKCdelta mutant in which the NLS was mutated and by employing vectors targeting PKCdelta to the nucleus, ER, cytosol and mitochondria. Finally, the cleavage of PKCdelta and the roles of the cleaved regulatory and catalytic fragments will be studied for their effects on the apoptotic function of PKCdelta. To identify proteins and signaling pathways that mediate the pro and anti-apoptotic effects of PKCdelta the effect of PKCdelta on the levels, activation and phosphorylation of different apoptosis-related proteins and on the activation of signaling pathways associated with cell apoptosis and survival (members of the MAP kinase family and Akt) will be determined. The roles of tyrosine phosphorylation and subcellular localization of PKCdelta in the activation of these proteins will be then evaluated. Another important factor in delineating the function of PKCdelta in glioma cell apoptosis is identifying its binding partners. This will be done using GST-PKCdelta and GST-PKCdelta mutants fusion proteins to identify PKCdelta binding proteins in glioma cells stimulated with different apoptotic stimuli and by screening glioma cDNA libraries using the yeast two hybrid system. The results of this study will enhance our understanding of the factors contributing to the divergent effects of PKCdelta on cell apoptosis and of the role of PKCdelta in the regulation of glioma cell apoptosis. A better understanding of the molecular mechanisms underlying the diverse effects of PKCdelta in gliomas may enable us to predict the tumor response to therapy based on its molecular profile and may lead to novel approaches for altering the sensitivity of gliomas to specific therapeutic agents.

Principal Investigator: Mahmood, Asim, M.D.

Treatment of Traumatic Brain Injury with Simvastatin (NIH R01 NS052280-02)

The goal of this research project is to study the potential therapeutic role of statins in traumatic brain injury (TBI), particularly in ameliorating or preventing memory impairment. The investigators will study the effects of atorvastatin and simvastatin administered at different doses and time points after TBI. Effect on spatial memory will be tested using the Morris Water Maze. The investigators will also use histological techniques and other biochemical assays to study the temporal profile of neurogenesis, astroglialogenesis, and oligodendrocyteogenesis in the dentate gyrus after TBI. In addition, the effects of treatments on angiogenesis and growth factors will be investigated.

Principal Investigator: Mahmood, Asim, M.D.

Traumatic Brain Injury and Marrow Stromal Cells (NIH 5R01 NS042259)

This project is designed to investigate the efficacy of combination treatment of marrow stromal cells (MSCs) and statins (simvastatin) in improving functional outcome after traumatic brain injury (TBI). Our previous studies have shown that MSCs have a beneficial effect after TBI in rats. To augment the therapeutic benefit of MSCs a combination therapy of MSCs with simvastatin has been designed. Female Wistar rats will be injured using the controlled cortical impact model of head trauma. After injury, simvastatin will be administered orally, and MSCs harvested from male adult rats will be injected in the tail vein of the rats. To compare the efficacy of combination treatment (MSC + simvastatin) with MSC and simvastatin monotherapies, other group of rats will be administered either MSCs or simvastatin, solely. The functional outcome of rats will

be monitored with a battery of test, and animals will be sacrificed at different time points. Brain sections will be stained with immunohistochemistry and MSCs will be identified by localizing Y chromosomes within them. The induction of brain plasticity with treatment will be measured by studying neurogenesis, synaptogenesis and angiogenesis. In addition, growth factors which are mediators of this plasticity will be measured using enzyme-linked immunosorbent assay (ELISA). If the treatment combining MSCs with simvastatin is found to be more effective than monotheapy, this will increase the clinical relevance of MSC treatment by allowing us to use smaller and safer doses.

Principal Investigator: Mikkelsen, Tom, M.D.

Adult Brain Tumor Consortium (ABTC) (Formerly ABCC) (NIH U01CA137443-01)

Since 1993 and the inception of the NCI sponsored brain tumor consortia for early stage clinical trials, HFH has been among the leaders in accrual to innovative clinical trials and data quality. Over the years, we participated in the New Advances in Brain Tumor Therapy (NABTT) group, which has now merged in the most recent funding cycle with the North American Brain Tumor Consortium (NABTC) to form the NCI Adult Brain Tumor Consortium (ABTC). This permits us to work closely with all the major brain tumor centers in the country and allows our patients to access the latest agents and strategies for the management of malignant glioma brain tumors. Through close interaction with NCI and small, medium and big pharma, we currently have 8 ABTC trial active at our center. Many of our early stage trials have gone on to larger national and international drug development efforts, many of which we also participate in. The past 15 years of clinical trials activity has resulted in two dozen publications, 2 approved therapies for brain cancer and hundreds of patients treated

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., PhD.

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.

Orthopedics and Bone & Joint Center

Senior Research Staff

Michael Bey, Ph.D.
Gary Gibson, Ph.D., Division Head for Research
Clifford M. Les, D.V.M., Ph.D.
Len Lutter, Ph.D.
C. William Wu, Ph.D.
Yener Yeni, Ph.D.
Shi-jing Qiu, M.D.

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.

Principal Investigator: Gibson, Gary, Ph.D.

Serum MicroRNAs as Biomarkers of Post-Traumatic Osteoarthritis (NIH 1 RC1 AR058728-01)

This application addresses the broad Challenge Area (03) Biomarker Discovery and Validation, and the specific Challenge Topic, 03-AR-101: Biomarkers of Persistent Damage after Acute Joint Injury. Serum microRNAs as biomarkers of post-traumatic osteoarthritis. This study proposes to define a panel of serum miRNAs and validate their use as biomarkers of post-traumatic osteoarthritis (PTOA). Approximately 12% or 5.6 million patients suffering osteoarthritis (OA) in the United States can attribute their disease to prior joint injury. However; since not all joint injuries progress to joint degeneration there is a pressing need to develop biomarkers that would facilitate prediction of the progression from joint injury to joint degeneration and OA. Biomarkers would also provide an insight into disease pathogenesis and serve as a guide to the development of therapeutic interventions. MicroRNAs (miRNAs) are small (20-22 nucleotide) noncoding RNAs that have been shown to play an overarching regulatory role in normal cellular function and in many diseases. Quantification of miRNAs present in plasma and serum has been very recently shown to provide an excellent biomarker for cancer and other diseases. We have demonstrated miRNA expression by cartilage and chondrocytes and the presence of miRNAs in human and mouse serum. We have also shown that specific miRNAs have a markedly increased expression in OA cartilage suggesting a role in OA development. We propose to characterize miRNAs in the serum and joint tissues in a mouse model of OA and in the serum of patients developing OA after ACL injury to identify biomarkers of OA development. Validation of this panel of miRNA biomarkers will then be conducted in two distinct models of PTOA; a much

larger group of patients with ACL injury and a sheep model of PTOA, mimicking human PTOA resulting from impact trauma. MiRNAs offer a number of advantages over traditional biomarkers for PTOA. There are fewer known miRNA species than proteins or carbohydrates, so obtaining a complete profile is relatively easy. Serum miRNAs show consistent expression between individuals and are present in a remarkably stable form. Detecting and quantifying specific miRNAs is inherently a much easier task than detecting proteins due, in part, to their small size and very similar chemical properties. A modified RT PCR assay for miRNAs is specific and extremely sensitive. MiRNAs also show a restricted tissue expression profile that provides the capacity to trace plasma or serum miRNAs to a source tissue. Furthermore analysis of serum miRNAs makes no assumption about involvement of specific joint tissues and allows for the detection of contributions from tissues other than those currently known while permitting the examination of progressive changes in joint tissues already implicated in the disease. The course of PTOA progression after knee trauma is expected to have substantial overlap with disease progression in general OA. Thus the development of biomarkers for progression of PTOA will have benefits for prediction of progression of OA pathology, provide an indication of pathways of disease pathology and serve as a guide to therapeutic intervention in PTOA as well as OA generally. The recent demonstration of miRNA biomarkers in serum or plasma together with their unique characteristics provides a new dimension in the search for biomarkers for many pathologic conditions including PTOA. The studies proposed will thoroughly assess the potential of serum miRNAs as biomarkers of PTOA using unique animal models and patient serum from to an ongoing, well-defined, human study. Osteoarthritis is a debilitating widespread disease that involves the loss of function of articular cartilage; the smooth bearing surface of our joints. For many years the research community has been trying, largely unsuccessfully, to develop biomarkers that will provide clinical guidance and enable development and assessment of treatment strategies. We propose to develop osteoarthritis biomarkers by measuring a family of newly discovered small RNA molecules present in serum and shown in other diseases to provide exciting new disease biomarkers.

Principal Investigator: Les, Clifford M., Ph.D.

Degradation and Recovery of Bone: OVX and Treatment (NIH R01AR050562)

Age-related bone fracture is only partially explained by the reduction in bone mass that universally occurs with aging. The failure to predict fracture comes in part from a) the loss of geometrical information when projection x-ray methods are used to measure bone mass, b) ignorance of sufficiently detailed information about the failure properties of bone, and also c) ignorance of detailed in vivo loads on bones (Fracture risk is related to the ratio of load to strength, rather than to bone strength alone). A fourth barrier to accurately predicting fracture risk is that changes in bone tissue mechanical properties caused by age or disease related changes in the collagen, non-collagenous proteins or water content of bone are not detectable to xray methods. As a result of the invisibility of soft tissue changes to x-ray detection, there are age and menopause related changes in tissue material properties (in bone quality) that are invisible, not understood and that unpredictably increase bone fracture risk. Our data support the novel working hypotheses: 1) The viscoelastic properties of bone affect the fracture toughness and

apparent strength of bone tissue, 2) The viscoelastic properties of ovine bone degrade after ovariectomy, causing a decrease in the strength and fracture toughness of bone tissue for rates of loading associated with falls. The main goal of the proposed work is to determine the onset time of viscoelastic property degradation and whether cortical bone can recover normal viscoelastic and strength properties with estrogen replacement.

Otolaryngology

Senior Research Staff

Kathleen Yaremchuk, M.D., Chair
Maria Worsham, Ph.D.

Research Summaries

Principal Investigator: Worsham, Maria J., Ph.D.
Molecular Modeling of Diagnosis and Prognosis in HNSCC (NIH R01 1DE01599002)

Head and neck squamous cell carcinoma (HNSCC) carries a high mortality rate despite advances in chemotherapy and radiation therapies. This is due mainly to the highly heterogeneous nature of the disease, both morphologically and genetically. A current shortcoming in the diagnosis, prognosis, and treatment of HNSCC is a lack of methods that adequately address the complexity and diversity of the disease. A major objective of the proposed research is to develop a detailed molecular fingerprint of HNSCC tumor tissues that is linked to clinical information. Diagnostic and prognostic marker systems based on single parameters have generally proven inadequate. Thus, multiparametric methods, which rely on many pieces of information, are ideally suited to the grouping of tumor subtypes and the identification of specific patterns of disease progression and clinical outcomes. Our goal is to accomplish a multivariable comprehensive genome-wide molecular blueprint of HNSCC integrated with clinical risk factors in order to refine patient diagnosis and prognosis to aid in the clinical management of patients at the earliest disease stages. We will interrogate an evidence-based panel of gene loci implicated in head and neck cancer, many of which are distributed along critical pathways utilized by HNSCC cells. The molecular targets to be investigated using a novel assay will be done in an epidemiologically well-characterized cohort of 1000 primary HNSCC derived from a large, multi-ethnic, primary care patient population diagnosed by surgical biopsies in the Henry Ford Health System from 1986-2003, and followed from 5-22 years. This approach should yield a validated multivariable genetic blueprint for diagnosis and prognosis analogous to or even more powerful than TNM-staging, permitting more accurate grouping of tumor subtypes, more accurate distinction of prognostic groups, and better prediction of effective treatment strategies.

Surgery

Senior Research Staff

Scott Dulchavsky, M.D., Chairman
Subhash C. Gautam, Ph.D.
Daniel Reddy, M.D.

Research Summaries

Principal Investigator: Gautam, Subhash C. PhD.

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 gastrointestinal 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- κ 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- κ 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- κ 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 HEALTH 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.

Part III: Abstracts – Hospital Based Departments

- **Diagnostic Radiology**
- **Emergency Medicine**
- **Medical Genetics**
- **Pathology**
- **Pharmacy**
- **Radiation Oncology**

Diagnostic Radiology

Senior Research Staff

Arbab S. Ali, Ph.D.

Messer Ali, Ph.D.

Manuel Brown, M.D., Chair

Michael Flynn, Ph.D.

Hamid Soltanian-Zadeh, Ph.D

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 dendritic 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 nanoprobe has 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.

Principal Investigator Ali, Syed Arbah, Ph.D.
Cellular MRI in Glioma and Radiation Necrosis (NIH R01CA122031-01A2)

Recently, using two FDA-approved agents, we formed ferumoxides-protamine sulfate complex and labeled any kind of mammalian cells. To examine whether labeled cells can be used as probes to detect and differentiate physiological and/or pathological conditions, we have selected glioma and radiation necrosis models. It is hypothesized that in vivo MR tracking of magnetically labeled cells will enable us to identify different patterns of accumulation and incorporation of labeled injected cells, thus allowing for differentiation between recurrent glioma and radiation necrosis. Glioma is a central nervous system neoplasm that typically shows hypervascularity. Unlike the surrounding normal regions of cerebral vasculature, areas of hypervascularity are typically permeable to contrast agents, and can thus be detected by contrast-enhanced MRI or CT. However, areas of radiation necrosis can also show enhancement due to active inflammatory reactions and increasing vascular permeability. Thus, distinguishing recurrent glioma from radiation necrosis becomes problematic if only changes in vascular permeability and/or volume are considered. One distinguishing characteristic, however, is that there is little active angiogenesis at the site of radiation necrosis. By determining the differential migration and incorporation patterns of labeled endothelial progenitor cells (EPCs) at the site of glioma, it should be possible to differentiate between radiation necrosis and recurrent glioma. If this proves feasible, a translation into clinical trials can quickly follow, employing autologous labeled EPCs. These labeled cells, once incorporated into the tumors or areas of necrosis, can be detected as low signal intensity areas on in vivo and ex vivo MRI because of the susceptibility effects of iron oxides inside the cells. These objectives will be achieved by obtaining serial MRI of tumors and radiation necrotic areas after injecting labeled cells at different time points. The findings on MRI will be correlated with histology and different markers of endothelial cells. Angiogenic factors will also be assessed by immunohistochemistry at the site of accumulated EPCs in tumors or radiation necrosis. Early detection of recurrent or metastatic glioma as well as early differentiation of glioma from radiation necrosis will help clinician to tackle the devastating neurological disease.

Principal Investigator Ali, Syed Arbah, Ph.D.
Stem Cells as Delivery Vehicles and imaging Probes for Glioma Gene Therapy (NIH 1R21CA129801-01A1)

Malignant gliomas are among the most devastating tumors, with survival only one to three years after diagnosis even with the best of treatments. Surgery and radiation therapy (followed by adjuvant chemotherapy), which form the standard practice, very often fail because of uncertainty in delineating the margin of the tumor. Moreover due to infiltrative nature of glioblastomamultiforme (GBM), it is not possible to resect 100% of tumor mass during surgery. Gene therapy promises to improve the prognosis of GBM, however, several factors including the lack of an efficient vector limit the ability of gene therapy to produce the desired success. Moreover, the vehicles for successful delivery of desired gene at desired site is still lacking. In recent years, different stem cells have been successfully employed to carry a gene to target tumor sites. The combination of gene transfer techniques with cellular transplantation is an elegant and promising approach to the delivery of therapeutic molecules to normal or neoplastic cells in the CNS. We have reported the ability of endothelial progenitor cells (EPCs), a class of hematopoietic stem cells, to migrate and incorporate into the angiogenesis of implanted glioma. EPCs have migrated actively at the periphery of the tumors when administered intravenously or locally and incorporated into angiogenesis. Detection of migration and incorporation was possible due to magnetic labeling of EPCs. These EPCs can be used as carrier as well as delivery vehicles for gene into tumors. Moreover, by magnetic labeling (using FDA approved ferumoxides and protamine sulfate); these cells can be used as cellular probes for MRI to track the movement of the cells after administration. Accessibility, easy harvesting and established techniques for genetic manipulation renders EPCs as attractive cellular vehicles when systemic gene carrier is required. In this proposed research, we aim to investigate the ability of EPCs to carry a gene to the tumor sites and use these transgenic cells as cellular probes to track the migration and incorporation in the tumors by magnetic resonance imaging (MRI). The goals of this research will be achieved by making glioma model in nude rats and magnetically labeled or unlabeled transgenic (carrying human sodium iodide symporter, hNIS) EPCs will be administered either systemically or locally, and the migration, homing and incorporation of these cells into tumor neovasculatures will be detected by MRI and nuclear medicine imaging technique (SPECT). If these cells carry and express hNIS at tumor sites (which will be detected by SPECT), it will open a new area of investigation with clinical applicability, where EPCs can be used as gene carrier or delivery vehicles. The long-term goal of this proposal is to extend the findings into clinical use by collecting stem cells from patients' peripheral blood and manipulate them as gene delivery vehicles for both systemic and local administrations, which can also be used as imaging probes for MRI. The results of this proposed project will advance the methods of diagnosis and treatment in two ways. Magnetically labeled cells will help detect the tumors using in vivo MRI by targeting active site of angiogenesis and this may help clinician to plan anti-angiogenic treatment strategy. If we are able to efficiently transfect and track the homing of these transgenic cells at the site of glioma, it will open a new way of delivering gene (for different factors) to the site of tumors using EPCs. Mixing magnetically labeled cells (for example 10% of total administered cells) with transgenic cells, MRI can also be used to confirm the migration and homing of transgenic cells at the sites of interest. Moreover, magnetically

labeled transgenic cells can be delivered to a site of interest by applying external magnetic field during intra-arterial infusion.

Emergency Medicine

Senior Research Staff

Gerard Martin, M.D., Chair
Christopher Lewandowski, M.D.
Emanuel Rivers, M.D.

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.

Pathology

Senior Research Staff

Norman Lehman, M.D.
Richard Zarbo, M.D., Chair

Research Summaries

Principal Investigator: Lehman, Norman, M.D. Control of Genomic Stability by Emil and Securin (NIH 7K08NS045077-06)

Aneuploidy and chromosomal aberrations are common features of human neuroplasms. Genomic instability, or the tendency for mitotic errors to create chromosomal duplications, losses, and translocations has long been recognized as a major mechanism of tumorigenesis. The study of genomic instability promises new insights into cancer treatment. Recently, significant advances have been made in the understanding of the molecular details of the regulation of mitosis. Securin is a protein that functions to ensure accurate distribution of chromosomes to daughter cells by inhibiting anaphase progression until all chromosomes are properly aligned at metaphase. When cells are manipulated to over-or under-express securin they develop chromosomal abnormalities and micronuclei. Such micronuclei are frequently seen in neurological tumors, especially oligodendrogliomas. Another protein, Emi1, recently discovered by the Peter Jackson Laboratory, is involved in S phase activation and mitotic control. Emi1 blocks the degradation of securin by inhibiting its ubiquitination, but also directly binds to securin. Over-expression of Emi1 causes an abnormal prometaphase block and abnormal mitotic spindle formation. We hypothesize that the direct interaction of Emi1 and securin mediates this effect causing genomic instability. Hct116 colon carcinoma cells are a diploid cell line ideal for mitotic studies. I will use these cells as a tool to study the control of genomic stability by Emi1 and securin. I will also address the possible role of Emi1 and securin in the genesis of neurological tumors. The proposed research will specifically address the following questions. Do endogenous Emi1 and securin interact directly in cells, and if so, during which stage(s) of the cell cycle? Is the Emi1-securin interaction localized within the cell? Which functional domains of Emi1 and securin are important in determining their interaction? Does Emi1 misexpression cause spindle abnormalities or chromosomal missegregation, and is securin required for this effect? Does over- or under-expression of Emi1 produce chromosomal aberrations such as deletions or duplications? If so, do specific cytogenetic abnormalities occur? Does Emi1 over-expression induce cellular transformation, or cooperate with known oncogenes such as ras, myc, or securin, in inducing transformation? Does Emi1 misexpression occur in specific tumor types, including neurological tumors? Does Emi1 expression positively or negatively correlate with securin expression in tumors? Does Emi1 or securin expression correlate with activation of the cyclin D/Rb/E2F pathway in tumors? I will pursue an academic career in neuropathology and will apply the knowledge and experience gained from the proposed studies to translational neuro-oncology research.

Radiation Oncology

Senior Research Staff

Steve Brown, Ph.D.

Svend Freytag, Ph.D.

Jae Hoe Kim, M.D.

Benjamin Movsas, M.D., Chair

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.

Part IV: Abstracts – Health and Health Care Research

- **Biostatistics & Research Epidemiology/Cancer Epidemiology**
- **Center for Health Services Research**

Biostatistics & Research Epidemiology/Cancer Epidemiology

Senior Research Staff

Gwen Alexander, Ph.D.
Andrea Cassidy, Ph.D.
Christine Cole Johnson, Ph.D., Chair
George Divine, Ph.D.
Sharon Hensley-Alford, Ph.D.
Christine Joseph, Ph.D.
Lois Lamerato, Ph.D.
Mei Lu, Ph.D.
Edward Peterson, Ph.D.
Benjamin Rybicki, Ph.D.
Lonni Schultz, Ph.D.
Ganesa Wegienka, Ph.D.
Kimberly Woodcroft, Ph.D.
James Yang, Ph.D.

Research Summaries

Principal Investigator: Cole-Johnson, Christine, Ph.D.

Endotoxin Exposure Alers Anti-Tetanus IgE in Infants (NIH R21 AI059415, Subcontract)

Recent studies have suggested that high levels of endotoxin exposure during infancy are associated with a reduced risk of subsequent allergic sensitivity. Learning more about the relationship between environmental endotoxin exposure and subsequent allergic disease is potentially important given the increasing prevalence of allergic diseases in the United States. The goal of this proposal is to evaluate the hypothesis that high levels of environmental endotoxin exposure will be associated with reduced anti-tetanus IgE responses following routine immunizations with tetanus toxoid in infancy. This study will utilize the structure of the ongoing WHEALS Study (AI/ES 50681, a study to evaluate the hygiene hypothesis in a multi-racial birth cohort of 3000 children in and around Detroit, MI). In home endotoxin assessments will be increased from 1 to 5 locations (the floor beside the infant's crib, the infant's bed, the parent's bed, the floor beside the parent's bed, and the floor in the living/family room) during both the 1 and 6 month home visits. Endotoxin will be measured using a commercial kinetic Limulus assay. Relationships between endotoxin measurements by location, month of year, and household characteristics (e.g., animals in the home) will be examined. These analyses will provide a better understanding of variations in endotoxin exposure within homes and allow an assessment of whether measurements from certain locations are more closely related to altered IgE production.

All infants in this cohort are expected to receive routine immunizations with DTaP (diphtheria, tetanus and acellular pertussis) vaccine at 2,4, 6-7 and 15-18 months of age. In addition to measuring IgE specific for common allergens at 6 and 24 months of age, IgE specific for tetanus toxoid will be measured in the same blood samples using the commercial Pharmacia CAP assay. The anti-tetanus IgE measurements will be analyzed to learn whether IgE production is influenced by endotoxin exposure. Important advantages of measuring anti-tetanus IgE are the likelihood that most infants will receive all immunizations with identical doses at the same ages. The well standardized tetanus immunizations contrast with the highly variable and difficult to measure exposures to natural allergens. Anti-tetanus IgE responses are also likely to be measurable much earlier in infancy than are responses to other allergens. Finally, the designs of WHEALS and this application will allow us to compare the effects of endotoxin exposure on the expression of multiple cytokines related to the development of allergic disease.

Principal Investigator: Cole-Johnson, Christine, Ph.D.
CRN3-Infrastructure (NIH U19CA079689-09, Subcontract)

The CRN Infrastructure activities will work towards: 1) Further developing human and data resources and pursue projects related to our research theme of improving the effectiveness of cancer prevention and treatment through research that identifies system, provider, treatment, and patient factors affecting outcomes; 2) Providing more concerted training and mentoring to junior investigators at CRN sites and investigators at CRN sites and affiliated academic institutions; 3) Accelerating the development of the Virtual Data Warehouse, natural language processing and other standardized approaches to using the informatics resources of CRN delivery systems for research, and coordinate these efforts with the NCI's Biomedical Informatics Grid (caBIG™); 4) Increasing collaboration between CRN sites and investigators at the NCI as well as in cancer centers and other academic centers; 5) Building a productive research program studying the diffusion of innovations in cancer care; and, 6) Studying and implementing strategies for increasing accrual in clinical trials.

Principal Investigator: Cole-Johnson, Christine, Ph.D.
Early Environmental Hygiene and Pediatric Asthma (NIH R56AI050681-06A2)

The overall objective of this research project is to assess how differential environmental exposures to pets and endotoxin from birth through two years of age, hypothesized to be associated with immune stimulation, and biomarkers of immunologic response to that stimulation, relate to asthma phenotypes at 5-6 years of age. We will test these hypotheses in a population of study subjects that includes a majority of children whose heritage derives from sub-Saharan Africa versus other heritage since this minority group is at a higher risk for childhood asthma. Our intention is to utilize comprehensive measurements of these selected early exposure variables thought to be related to immune system provocation to test whether such factors help to explain the observed epidemiological patterns of pediatric allergy and asthma in U.S. cities over the last decades. The premise of recent thought from many investigators is that lack of such environmental stimuli during early infancy results in the maturing immune system's deviation from an optimal balance related to the Th2 response, which is associated with increased IgE, atopy and clinical atopic conditions; most importantly, asthma. The level of direct exposure of humans to animals have declined over most of the 20th century through urbanization and then suburbanization, although humans have evolved with close contact with animals. If a factor

related to animal contact is related to asthma risk, such a factor can likely be linked to a public health intervention.

Principal Investigator: Joseph, Christine, Ph.D.

A Tailored Asthma Education Program for Urban Teens II (NIH, R01HL068971-05A1)

Asthma death rates for teenagers 15-19 years of age are higher than that of younger children, despite a higher prevalence in the latter group. The small number of publications on urban adolescents suggests that inadequate asthma management plays a significant role in these grim statistics; however, this age group has been difficult to reach, in terms of both connecting and convincing. Consequently, there are few asthma management programs targeting urban, high school students with asthma. We have developed a unique, multi-media, web-based program (Puff City I) to motivate teens to change negative behaviors related to asthma management. Puff City I software uses "tailoring" in conjunction with theoretical models of behavior change, to personalize health messages according to the beliefs, attitudes, and barriers of students with asthma. A school-based approach ensures accessibility. An asthma counselor responds to referrals generated by the software, providing assistance in addressing barriers to effective asthma management. A randomized trial to evaluate Puff City I in Detroit high schools (98% African American) is in its final stages. Results of initial analyses demonstrate short-term behavior changes, in addition to fewer Emergency Department (ED) visits ($p=0.03$) and hospitalizations ($p=0.007$), and higher scores for quality of life ($p=0.02$) when compared to controls. As with any research trial, not all students improved, some relapsed, and a substantial number did not participate. To maximize effectiveness of the program, we propose to use Puff City I data, including teen sociodemographics, motivation, and reported barriers, to make refinements that would target program failures resulting in a new version or Puff City II. In addition, we will test new theory- and empirically-based approaches to recruiting urban high school students into this and other randomized trials. Not only would the latter be useful to research, in terms of generalizability, but will also yield valuable information about attracting this population to health-related interventions. We will evaluate Puff City II in another randomized trial in 9 Detroit high schools. Dissemination of this unique tool will also be explored as part of this proposal. Our collaborators include the University of Michigan Center for Health Communications Research, Detroit Public Schools, and the Detroit Department of Health and Wellness Promotion (formerly Detroit Health Department). The result of this proposal will be a powerful tool for changing negative behaviors related to asthma management in a traditionally hard-to-reach population that experiences high asthma morbidity and mortality.

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 for 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 will 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: 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 DNA 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 PhIP-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 PhIP-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 PhIP-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 DNA 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: Wegienka, Ganesa Rebecca 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.

Center for Health Services Research

Senior Research Staff

Jennifer Elston Lafata, Ph.D.

David Nerenz, Ph.D., Director
Manel Pladevall, M.D.

Research Summaries

Principal Investigator: Elston Lafata, Jennifer, Ph.D.

Physician Recommendation and Colorectal Cancer Screening (NCI 1R01CA112379-01A1)

Data from our own efforts and those of others indicate that different physicians discuss different things when recommending cancer screening. The U.S. Preventive Services Task Force (USPSTF) while not endorsing a specific style of physician-patient interaction, recently advocated for the use of shared decision-making when making preventive service recommendations to individual patients. We propose to use a mixed-method approach that includes both qualitative and quantitative data collection and analyses to understand the use and utility of different aspects of shared decision-making when physicians recommend CRC screening in primary care. First, we will use direct observation and audio-recording of routine health maintenance visits (n=900) to characterize the nature and content of CRC screening discussions in primary care (Aim 1). Results from these qualitative efforts will be used to derive quantitative measures characterizing physician-patient discussions of CRC screening in primary care. In the second stage, we will join these qualitatively derived measures characterizing physician-patient discussions of CRC screening with automated claims/laboratory data to determine their relationship to 12-month post-visit CRC screening use (Aim 2). A combined pre- and post-visit patient survey will allow us to assess the concordance of patient preferences for screening modality, information, and participation in decision-making with what occurs in the observed visit. We will then be able to evaluate the effect of these concordances on 12-month post-visit CRC screening use (Aim 3). We will use the Henry Ford Health System (HFHS), a large integrated delivery system serving Detroit and its surrounding suburbs, as the setting for these efforts. The diversity and size of the HFHS primary care physician and patient populations combined with the comprehensive, existing automated data systems makes this an ideal environment in which to conduct the proposed work. By joining detailed accounts of the contribution of both physicians and patients to CRC screening discussions in the real world of primary care with subsequent CRC screening use and patient reported preferences, results from the proposed project will inform a new generation of interventions aimed at improving CRC screening participation. They will provide valuable information for training both physicians and patients how to effectively discuss CRC screening as well as facilitate the development of decision aides and policies for diverse populations.

Principal Investigator: Pladevall, Manel, M.D.

The Clinical Effectiveness of Pharmacy Adherence Information For Diabetes Control (NIDDK 2R01 DK064695-04A1)

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 (MI) 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 glycemetic and/or lipid control. Primary care providers will be randomized to one of the following two study arms: 1) usual care - PCPs will write prescriptions electronically but will not be provided patient adherence information or MI 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.

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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- Dermatology
- Eye Care Services
- Family Medicine
- Neurology
- Neurosurgery
- Obstetrics & Gynecology
- Orthopedics (Bone & Joint Center)
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Part III: Publications – Hospital Based Departments

- **Anesthesiology**
- **Diagnostic Radiology**
- **Emergency Medicine**
- **Medical Genetics**
- **Pathology**
- **Pharmacy**
- **Radiation Oncology**

Anesthesiology

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Part IV: Publications – Health and Health Care Research

- **Biostatistics & Research Epidemiology/Cancer Epidemiology**
- **Center for Health Services Research**

Biostatistics & Research Epidemiology/Cancer Epidemiology

1. **Alford, S. M. H.**, R. E. Lappin, L. Peterson and C. C. Johnson (2009). "Pregnancy Associated Smoking Behavior and Six Year Postpartum Recall." Maternal and Child Health Journal **13**(6): 865-872.
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Center for Health Services Research

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Books:

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