2017 RESEARCH ANNUAL REPORT

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SUMMARIES OF 2017 NATIONAL INSTITUTES OF HEALTH AND OTHER FEDERAL GRANTS AWARDED TO HFHS

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Part I – Department of Internal Medicine

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- Cardiology/Cardiovascular Research
- Endocrinology and Metabolism
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- Hypertension and Vascular Research
- Infectious Disease
- Pulmonary
- Sleep Medicine
- General Internal Medicine

Allergy and Immunology

Principal Investigator: Edward Zoratti, M.D.

ICAC 3 - Inner City Asthma Consortium Infrastructure (UM1AI114271) Subcontract

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

Principal Investigator: Edward Zoratti, M.D.

Pets and the Infant Microbiome: Effect on Immune Maturation & Atopic Asthma – Project 2 (P01A1089473)

The Program Project Grant (PPG) application seeks an increased understanding of the relationships between dog or cat exposure during infancy and a lower risk of allergic asthma. We believe that this protective association is related to different patterns of microbial stimulation during immune development. Four synergistic Projects will examine our hypothesis that the presence of pets in a home results in a more diverse bacterial community composition (BCC) of the dust in the home which in turn influences the development of the gut BCC of a newborn infant living in the home. A more diverse gut BCC shifts the maturation of the infant's immune system such that later immune responses are less likely to produce IgE antibody responses and allergic asthma. Project 2 will recruit a new birth cohort of children either living with or without a dog, measure infant stool BCC, and follow the cohort with detailed studies of immune function until 18 months of age to determine the impact of dog exposure on immune maturation. The Projects are supported by five Cores which each provide essential services to all four Projects.
Heart failure (HF) remains an enormous public health problem despite advances in treatment. Disease progression and response to therapy in HF varies widely between individuals, but breakthrough technologies such as genomics and metabolomics are helping to unravel the disease heterogeneity that confounds patient management. Perturbed energy metabolism may be a key contributor to cardiac dysfunction and the development of clinical HF. Evidence from a variety of sources indicates that impaired structure and function of the energetic apparatus in the myocardium contributes to disease severity, progression, and may influence response to treatment. However, in order to advance these observations toward meaningful interventions for HF patients, several key steps are still needed: 1) confirming the importance of metabolic variation in human HF, 2) developing noninvasive markers of myocardial energetic status, and 3) identifying promising targets for intervention. Our proposed project is a series of interwoven translational investigations in humans and dogs with HF to define the association of plasma metabolite levels with disease severity, myocardial energetics, and disease progression. This project leverages substantial infrastructure already in place, a large existing genetic cohort study, available plasma samples suitable for metabolomic profiling, comprehensive translational laboratory capabilities, and a cohesive multidisciplinary research group focused on HF. Together the planned studies will address the overarching hypothesis that the peripheral metabolomic signature can indicate disease progression/treatment responsiveness in HF patients and that this is driven by altered myocardial energy metabolism. If true, then these data will help advance personalized therapy and identify novel targets for HF intervention, leading to improved outcomes for HF patients.

Principal Investigator: Dee Dee Wang, M.D.
Cardiac Computed Tomography and Ultrasound Core Laboratory: NHLBI DIR LAMPOON Study: Intentional Laceration of the Anterior Mitral Leaflet to Prevent Left Ventricular Outflow Tract Obstruction during Transcatheter Mitral Valve Implantation (HHSN268201700225A)

Transcatheter mitral valve replacement (TMVR) is an option to treat mitral valve failure when no surgical options exist. In as many as half of patients, TMVR can cause life-threatening blockage of the left ventricle by displacing the existing mitral valve leaflet. For these patients the only options appear to avoid TMVR or in some to cause a focused heart attack and to wait 6 weeks. The investigators have developed and tested a technique to tear the existing mitral valve leaflet and enable TMVR in patients who have no other options. The procedure is called intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction (LAMPOON). Although there are no dedicated TMVR devices commercially available, there has been short-term success with implanted transcatheter aortic valve devices in the mitral position for TMVR.

The purpose of this study is to perform LAMPOON and TMVR in patients who have no good options to treat their mitral valve failure, using heart valve devices designed to implant in the aortic valve position.

Endocrinology and Metabolism

Principal Investigator, Arti Bhan, M.D.
Epidemiology of Diabetes Interventions and Complications (U01DK094157) Subcontract

The Diabetes Control and Complications Trial (DCCT, 1983-1993) compared intensive therapy aimed at near normal glycemia versus conventional therapy with no specific glucose targets in 1441 subjects with type 1 diabetes (T1DM). In 1993, after a mean follow-up of 6.5 yrs, the study showed conclusively that intensive therapy reduced the risks of retinopathy, nephropathy, and neuropathy by 35-76%, and that hyperglycemia was a primary determinant of complications. We also described potential adverse effects of intensive therapy; assessed its effects on cardiovascular disease (CVD) risk factors, neurocognition and quality of life; and projected the lifetime health-economic impact. DCCT intensive therapy was then
adopted worldwide as standard-of-care for T1DM. The Epidemiology of Diabetes Interventions and its Complications (EDIC, 1994-present) is the observational follow-up study of the DCCT cohort, with 95% of those surviving actively participating. Most outcomes are evaluated annually. CVD events and deaths are carefully documented and adjudicated. EDIC has notably discovered that the early beneficial effects of intensive treatment on complications have persisted for over 10 years despite the similar HbA1c levels during EDIC in the two groups, termed metabolic memory. Remarkably, former intensive therapy also greatly reduced the risk of CVD events. DCCT/EDIC collaborators have also conducted numerous ancillary studies, with separate funding, most recently including measurement of cardiac function on cardiac MRI and measurement of biomarkers of oxidative stress and inflammation as determinants of complications. The overarching goals for the next 5 years are to follow at least 90% of the surviving cohort; to describe accurately the study-long effects of glycemia (HbA1c) and other established and putative risk factors on diabetes complications and the metabolic memory effects of prior DCCT intensive therapy; and to expand knowledge regarding T1DM and its complications by supporting collaborations for new research funding applications to maximally utilize the cohort, phenotypic data set, and collected biologic and genetic samples. The specific scientific aims are to 1) evaluate effects of risk factors, biomarkers and glycemia on risk of clinical CVD; 2) assess the long-term changes in CVD risk factors; 3) describe effects of DCCT intensive versus conventional therapy on mortality; 4) evaluate risk factors for severe retinopathy/nephropathy; 5) assess effects of diurnal glycemic variation on complications; and 6) conduct eight new research projects involving new measurements and analyses.

Principal Investigator: D. Sudhaker Rao, M.D.
Pathogenesis of Atypical Femaur Fractures on Long Term Bisphosphonate Therapy (R01AR062103)

Bisphosphonates (BP) have been used successfully for over a decade to prevent and treat osteoporosis and reduce osteoporotic fractures. However, since 2005 there have been many reports of atypical femoral fractures (AFF) in patients on prolonged BP therapy. Recently, it has been found that a prodromal bone deterioration (PBD) usually appears before the development to AFF. However, many PBDs may be asymptomatic, not necessarily progress to AFF, and heal spontaneously after discontinuation of BP therapy. Therefore, the prevalence of PBD may be much higher than AFF. To date, there is no evidence to support this hypothesis. It has been reported that many patients with PBD and AFF have severely suppressed bone turnover (SSBT). However, since not all patients with PBD/AFF also have SSBT, factors other than SSBT might contribute to the development of PBD/AFF. Our preliminary study suggests that PBD/AFF may be associated with osteocyte death, bone hypermineralization, and microdamage accumulation which compromise bone mechanical properties. These facts collectively led us to formulate the hypothesis that BP treated patients who develop SSBT and consequent increase in bone age, in conjunction with previous osteocyte deficiency, are predisposed to micropetrosis, accumulation of fatigue microdamage, PBD, and eventually to stress fracture manifested as AFF. To pursue this hypothesis we propose the following specific aims: Aim 1 is to determine the prevalence of PBD and AFF in 1,000 patients with postmenopausal osteoporosis, either treated with BP for more than 2 years (500 subjects), or never BP treated (500 subjects). X-rays of the femurs will be performed to systematically screen the patients for PBD/AFF. PBD can be defined as an X-ray finding of focal cortical thickening associated with a fracture line at the lateral femoral cortex.

Suspected PBD patients, whose x-ray does not show clear fracture line at focally thickened cortex, will be evaluated further using x-ray tomosynthesis, isotope bone scan or MRI. Aim 2 will determine the contribution of osteocyte deficit to PBD/AFF and SSBT in iliac bone biopsies obtained from long term BP treated patients. Degree of bone mineralization and bone nano-mechanical properties will also be assessed on these biopsies.

Gastroenterology

Principal Investigator: Stuart Gordon, M.D.
Chronic Hepatitis Cohort Study II (CHeCS-II) (U18PS005154)
Hepatitis B (HBV) affects over 1.25 million Americans, and hepatitis C (HCV) over 3.2 million Americans. In the decades to come, more than 150,000 Americans are expected to die from these conditions unless steps are taken to increase awareness, diagnosis, and access to necessary care and treatment. Emerging interferon-free, direct-acting all-oral antiviral (DAA) treatments have changed the landscape of HCV treatment and care. These treatments appear to be safer than interferon-based treatments and provide exceptionally high rates of sustained virological response (SVR). Both HBV and HCV treatment guidelines have been updated to reflect evidence regarding initiation of new therapies; however, the evidence for those recommendations is largely based on clinical trials conducted under highly controlled conditions in restricted patient populations with limited data collection. Significant health disparities—across race, sex, age, and co-infection (with HIV or dual hepatitis)—may limit the generalizability of these populations. Data from longitudinal cohorts of “real world” hepatitis patients are needed to assess the population impact of rapidly evolving antiviral therapies, to understand the spectrum of disease and its natural history, and to evaluate the public health impact of chronic viral hepatitis.

The Chronic Hepatitis Cohort Study (CHeCS) is the first comprehensive longitudinal cohort study of chronic viral hepatitis in the US, and has served as a model platform for observational data collection in this population. Since 2010, CHeCS has reported valuable information and expanded knowledge on many facets of hepatitis disease and policy. We propose to build upon CHeCS to develop “CHeCS-II,” in order to achieve the long-term goal of applying this rich data and infrastructure resource to inform public health planning, policy decisions, and clinical management of HBV and HCV. To achieve this, we will leverage the established CHeCS infrastructure, which has: (1) a diverse, real-world, non-veteran-based US cohort of >3,000 HBV, >11000 HCV, and >500 HIV co-infected patients receiving care through four U.S. health systems; (2) an experienced multidisciplinary team; (3) an efficient system for patient identification and data collection.

We will provide scientific leadership to identify research findings and priorities by: (1) Offering seamless collaboration across study sites and with the Centers for Disease Control (Aim 1); (2) Expanding our HCV cohort to over 14,000 patients with >2 years’ follow-up; (3) Increasing follow-up of HBV patients to >5 years; (4) Collecting additional data regarding social determinants of health, including access to and uptake of care (Aim 2); (5) Applying rigorous analytical approaches to develop an in-depth understanding of health disparities and comorbidities, as well as investigating how these differences impact access to and uptake of antiviral therapy; (6) Advancing translation of this research to inform hepatitis-related policy and practice (Aim 3).

Hematology/Oncology

Principal Investigator: Frederick Valeriote, Ph.D.
Merging Marine-Derived Cytotoxic Natural Products with Experimental Therapeutics (R01CA047135) Subcontract

Our long-term objective is to discover and develop leads for new anticancer agents. This research utilizes a collaboration between the Marine Bioorganic Chemistry group at U. of California Santa Cruz (UCSC) led by Prof. P. Crews and the Developmental Therapeutics Program at the Josephine Ford Cancer Center (JFCC) led by Dr. F. A. Valeriote. The hypothesis is that small molecule natural products (<2000 amu), can be identified and used, to selectively inhibit the growth of solid cancer tumors. The aims outlined below will provide a foundation to discover and explore new biomolecules that will be of broad interest while also addressing general hypotheses guiding this research. Our focus is on tumors with relative insensitivity to most of the standard anticancer drugs. Thus, the overall aim is to obtain new compounds with effective activity against solid tumors, especially pancreatic, colo-rectal, breast, prostate, brain, ovarian, and lung cancers. The general aims for the next grant period are:

1. To mine our repository of unstudied sponges either to continue or to begin new studies on both known and new bioactive, small biomolecules.
2. To use marine-derived fungi cultured in various media as a source for new active small biomolecules.
3. To use and refine our sponge-inspired hypothesis as the rationale for pursuing culture of Gram-positive and Gram-negative bacteria as a source of new active small biomolecules.

4. To utilize the in vitro cytotoxicity disk diffusion assay network to identify extracts obtained from Aims 1, 2, and 3 with solid tumor selectivity for follow-up fractionation and SAR expansion in Aim 6.

5. To make use of promising analytical methodologies, especially DART MS and DANS NMR, to guide further work on marine extracts, fractions, and library pure compounds obtained from Aims 1, 2, and 3.

6. To efficiently isolate, characterize and/or dereplicate compounds by focusing on the priority hits identified in Aims 4 and 5.

7. To continue capstone studies of solid tumor selective compounds through pharmacology evaluations and therapeutic assessment.

Hypertension and Vascular Research

Principal Investigator: Oscar A. Carretero, M.D. Project 1 and Project 3
Principal Investigator: Pamela Harding, Ph.D. Project 2
Autacoids in Hypertension: Pathogenesis and End Organ Damage (2P01HL028982-35)

This PPG was started in September, 1982. The central theme is "the study of the role of vasoactive systems (autocrine, juxtacinr, paracrine and endocrine) in the regulation of renal function and blood pressure (BP) and mediation of end organ damage (EOD)". The general hypothesis to be tested is that there is a balance between systems that promote water and sodium retention, hypertension and EOD, including Angiotensin II (Ang II), prostanoids, reactive oxygen species and inflammation, and systems that antagonize these effects like Ac-SDKP, activation of the Ang II type 2 receptor (AT2), kinins, NO, PGE2/EP4, and the newly discovered cross-talk between the connecting tubule and the afferent arteriole (CTGF) which may participate in both natriuresis and renal damage. Alterations of this balance in favor of the former are responsible for retention of water and sodium and development of hypertension and EOD, 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 in hypertension in rats and various transgenic and gene knockout mice. We will mainly use Dahl salt-sensitive rats (Dahl SS) and Ang ll-induced hypertensive rats as models. In Project I, using Dahl SS rats, we will study whether N-acetyl-seryl-aspartyl-lysyl-proline protects against EOD by decreasing adaptive immunity. In Project II we will study whether expression of cyclooxygenase-2 and generation of PGE2 via the EP4 receptor protects against EOD in Ang ll-induced hypertension. In Project III, using Dahl SS rats, we will study whether CTGF causes glomerular damage via afferent arterole dilatation and increases in capillary glomerular pressure. In Project IV, using Dahl SS rats, we will study whether a decrease in the renal thick ascending limb AT2-signaling participates in the pathogenesis of hypertension. The Four Cores - Administrative (A), Analytical and Morphological (B), Mutant Mouse (C), and Biostatistics (D) - will support the scientific efforts of the investigators. This PPG provides integration of our efforts, collaboration, sharing of ideas and expertise, thus accelerating acquisition of knowledge on the causes of hypertension and EOD. Project 4, which is subcontracted to Case Western Reserve University in Cleveland, and the 4 Cores are not described in the abstracts below.

Principal Investigator: Oscar A. Carretero, M.D.
Project 1:

In hypertension, end organ damage (EOD) is due in part to the mechanical forces exerted by high blood pressure (BP); however, other mechanisms such as inflammation, oxidative stress, the RAS, and genetic predisposition, all play key roles in its pathogenesis. In hypertension, Acetyl-Ser-Asp-Lys-Pro (Ac-SDKP), a naturally occurring peptide hydrolyzed mainly by ACE, reduces cardiovascular and renal inflammation and fibrosis without lowering BP. We have evidence that Ac-SDKP mediates some of the anti-fibrotic and anti-inflammatory effects of ACE inhibition and also prevents experimental autoimmune
myocarditis in rats. Thus we propose to test the general hypothesis that in hypertension Ac-SDKP shifts the balance between pro-inflammatory/pro-oxidative and anti-inflammatory/anti-oxidative systems in favor of the latter by decreasing innate and adaptive immunity and thus slowing the development of EOD. Furthermore, the effects of Ac-SDKP on BP and EOD are related to the degree of participation of innate and adaptive immunity in the pathogenesis of hypertension and EOD. This hypothesis will be studied in 3 aims. **Aim I:** In hypertensive Dahl salt-sensitive rats (Dahl SS) and in mice with systemic lupus erythematosus and hypertension, a model of autoimmune disease, Ac-SDKP acts as an immune modulator, reducing innate and adaptive immunity and thus EOD. Some of the effects of Ac-SDKP depend on the degree of participation of innate and adaptive immunity in the pathogenesis of hypertension and EOD. **Aim II:** The effects of ACE inh on the pro-inflammatory transcription factor NF-kB, TH cells and Treg cells are mediated by an increase in Ac-SDKP. **Aim III:** The effects of Ac-SDKP are multiphasic; central to these effects are decreases in: 1) the pro-inflammatory transcription factor NF-kB, 2) differentiation and maturation of dendritic cells (DCs), 3) DC transformation of T cells in effector T cells, and 4) TH cell proliferation, activation, migration, and differentiation into pro-inflammatory phenotypes. The effects of Ac-SDKP on TH are partly due to an increase in Treg cells. Project I is related to III and IV which also study Dahl SS; 2) II and III, which also study the pathogenesis of EOD; and 3) II and IV which also study Ang II. Project 1 will use all 4 Cores.

**Project 3:**

In hypertension, high glomerular capillary pressure (PGC) leads to glomerulosclerosis. In African-Americans with salt-sensitive (SS) hypertension, high salt intake causes an increase in estimated PGC, which could explain their high rate of hypertensive renal disease. Dahl SS rats on high salt intake have hypertension, high PGC and significant glomerular injury compared to SHR with similar blood pressure. Connecting tubule glomerular feedback (CTGF) is a cross-talk that dilates the afferent arteriole (Af-Art) when Na is increased in the connecting tubule (CNT). General hypothesis: In SS hypertension, during high salt intake there is an imbalance between factors that cause Af-Art constriction (myogenic response and TGF) versus dilatation (CTGF) in favor of the latter, leading to an increase in PGC and glomerular damage. **Aim I,** Hypothesis: In normotensive animals, chronic high salt intake causes TGF resetting due to heightened CTGF via increased release of EETs and PGE2 by the CNT. Mice with a gain-of-function mutation of ENaC have increased CTGF and reduced TGF, while mice with deletion of ENaC in the CNT have decreased or no CTGF and enhanced TGF. **Aim II,** hypothesis: In hypertensive Dahl SS rats CTGF is increased, causing TGF resetting leading to increases in PGC and glomerular damage. Conversely, in SHR CTGF is decreased, causing an enhancement of myogenic response and TGF which in turn decreases PGC and protects the glomerulus from damage. In SHR, high salt will increase CTGF, causing attenuation of the myogenic response, TGF resetting, increased PGC, and glomerular damage. In Ang II-induced hypertension in mice with increased ENaC activity, glomerular damage will be greater due to an increase in CTGF, while in mice with selectively decreased ENaC in the CNT glomerular damage will be lower, due to a decrease in CTGF. **Aim III,** hypothesis: In hypertensive Dahl SS rats, CTGF is augmented due to increases in ENaC, COX-2 and PGE2. In contrast, in SHR CTGF is attenuated due to increased soluble epoxide hydrolase and decreased EET release. Project III is closely related to 1): I and IV which also study Dahl SS; I and II which also study arachidonic acid metabolites. Project III will use all 4 Cores.

**Principal Investigator: Pamela Harding, Ph.D.**

**Project 2:**

Uncontrolled hypertension (HTN) is a major cause of end organ damage (EOD) and a risk factor for cardiovascular morbidity and mortality. Although prostaglandin E2 (PGE2) was historically thought to be a mediator of inflammation, more recent evidence suggests that it may be pro or anti-inflammatory, depending on the involvement of specific PGE2 EP receptor sub-types that signal through divergent signaling pathways. We previously reported that aged male mice lacking the EP4 receptor on cardiomyocytes develop heart failure characterized by reduced ejection fraction, left
ventricle dilation and fibrosis, coupled with elevated expression of chemokines (fractalkine and MCP-5) in the left ventricle. This proposal examines whether the protective and anti-inflammatory effects of PGE2 via EP4 are mediated by reduced fractalkine and MCP-5. It tests the general hypothesis that EP4, activated by PGE2, reduces the EOD that occurs in Angiotensin II (Ang II)-dependent hypertension and myocardial infarction (MI) by inhibiting the production and/or release of the inflammatory chemokines fractalkine and MCP-5. **Aim I** will study whether PGE2 via its EP4 receptor reduces production and/or secretion of fractalkine and MCP-5 via its EP4 receptor and cAMP in cardiac myocytes and fibroblasts and opposes the deleterious effects of Ang II. **AIM II** will study whether EP4-dependent reductions in fractalkine and/or MCP-5 improve cardiac function both in vivo and in vitro. **Aim III** will study whether PGE2 via its EP4 receptor and inhibition of fractalkine and/or MCP-5 synthesis and/or release prevents EOD by reducing infiltration of inflammatory cells into the myocardium in models of Ang II-dependent HTN and myocardial infarction (MI). The proposal will utilize a novel mouse model coupled with state-of-the-art molecular techniques to address these aims. These studies are of utmost importance in determining the role of PGE2 and EP4 in cardiac hypertrophy and EOD. Project II is closely related to: 1) Projects I and III which also study the pathogenesis of EOD; 2) Project IV which also studies AT1 receptors and superoxide; and 3) Project III which also studies arachidonic acid metabolites. Project II will use all 4 Cores.

**Principal Investigator:** Mariela Mendez, Ph.D.

**Hydrogen Peroxide Stimulates Renin Release: Role in Hypertension and Diabetes (R03DK105300)**

Hypertension and diabetes are the principal cause for chronic kidney disease (CKD). In both diseases, a high percentage of patients show activation of the renin angiotensin system (RAS). Renin is the rate-limiting enzyme in the activation of the RAS. Thus, understanding the mechanism and proteins involved in the release of renin may offer alternative targets for hypertension and CKD. Renin is stored in dense-core granules in juxtaglomerular (JG) cells, located at the pole of the renal afferent arteriole, in the kidney cortex. In hypertension and diabetes, reactive oxygen species, including hydrogen peroxide (H2O2), are enhanced in the kidney cortex. We found that hydrogen peroxide stimulate renin release from JG cells. However, the enzymes responsible for production of hydrogen peroxide in JG cells have not been identified. Hydrogen peroxide is mainly a product of superoxide dismutation or enzymatic formation by NADPH oxidases (NOX1-5). The NOX4 isoform preferentially produces hydrogen peroxide and its expression in the renal cortex is enhanced in diabetes and hypertension. Our preliminary data shows that NOX4 is expressed in renin granules in JG cells, suggestive of intragranular production of H2O2. However it is not known whether NOX4 produces the pool of hydrogen peroxide that stimulates renin release from JG cells; and whether NOX4/H2O2-induced renin release contributes to increase blood pressure and kidney damage in diabetic nephropathy. In addition the mechanism by which H2O2 stimulate renin release is unknown. In other cells H2O2 induces signaling by oxidation of protein thiols. In this proposal we will test the hypothesis that the NADPH oxidase isoform NOX4 produces hydrogen peroxide in juxtaglomerular cells and stimulate renin release, thereby increasing blood pressure and contributing to glomerular damage. We will also explore the protein targets by which H2O2 stimulates renin release. In Aim 1 we will use primary cultures of juxtaglomerular cells, isolated afferent arterioles and Akita mice to test the role of NOX4-derived hydrogen peroxide in renin release in vitro and in vivo. In Aim 2 we will use a proteomics approach and subcellular fractionation of renin granules, to identify proteins that are oxidized by hydrogen peroxide in juxtaglomerular cells. This approach will allow us to collect critical preliminary data for an RO1 submission and focus on new protein targets of hydrogen peroxide that mediate renin release.

**Principal Investigator:** Pablo Ortiz, M.D., Ph.D.

**Fructose Induced Salt-Sensitive Hypertension: Role of Thick Ascending Limb Transport (R01DK107263)**

A high-fructose diet is linked to the epidemic of hypertension, diabetes, and obesity. Up to 25 million
Americans consume up to 20% of their calories from added fructose. We found that feeding rats a fructose-enriched diet for 4 weeks did not increase blood pressure. However, a fructose-enriched diet combined with high salt (4% Na) caused salt-sensitive hypertension within 1 week (Figures 1,11); prior to the development of metabolic abnormalities. The initial phase of salt-sensitive hypertension is in part mediated by a renal defect that prevents NaCl excretion during high salt intake. The thick ascending limb (TAL) reabsorbs 25% of filtered NaCl. Enhanced TAL NaCl absorption is related to salt-sensitive hypertension in humans and rodents. However, the mechanism by which a fructose-enriched diet rapidly (1 week) causes salt-sensitive hypertension is not clear and the role of TAL NaCl absorption in this process is completely unknown.

NaCl reabsorption by the TAL depends on the apical Na/K/2Cl cotransporter NKCC2, the target of loop diuretics. Our preliminary data show that a fructose-enriched diet enhanced NKCC2 phosphorylation at Threonine (Thr)96,101. NKCC2 phosphorylation at Thr96,101 activates NKCC2. Our data show that NKCC2-mediated NaCl transport is abnormally elevated in rats fed fructose plus a high salt diet. However, the effects of fructose and the signaling induced in the TAL and the distal nephron have not been studied. Our data show that plasma and urine fructose increase rapidly after fructose intake. Thus, fructose reaching the nephron may be transported in by a fructose channel, activating protein kinase signaling. The only kinases known to phosphorylate Thr96,101 of NKCC2 are SPAK (STE20/SPS1-related proline-alanine-rich kinase) and OSR1 (Oxidative Stress Responsive 1) kinases. In the TAL, these kinases specifically phosphorylate NKCC2. In the distal convoluted tubule (DCT), these kinases specifically phosphorylate the thiazide-sensitive NaCl transporter NCC. We found that a 20% fructose diet increases SPAK/OSR1 phosphorylation in TALs. In addition, stimulation of β-adrenergic receptors (β-AR) in the TAL activates NKCC2. A fructose-enriched diet may increase sympathetic activity by 2 weeks, or enhance the sensitivity or signaling of β-AR. Our preliminary data show that β-AR stimulation increases SPAK/OSR1 phosphorylation in TALs. In the Dahl salt sensitive (SS) rat, NKCC2 and SPAK/OSR1 phosphorylation are abnormally enhanced in a normal salt diet. It is not known whether this increases the effect of fructose on blood pressure and NaCl absorption. We hypothesize that a fructose-enriched diet enhances thick ascending limb (TAL) and distal tube (DCT) NaCl absorption by inducing NKCC2 and NCC phosphorylation via SPAK/OSR1 kinases and enhanced β-AR signaling. These effects occur within 1 week, prior to metabolic alterations, and are maintained chronically (16 weeks), promoting salt-sensitive hypertension in normal rats.

Principal Investigator: Suresh Palaniyandi, Ph.D.

4-hydroxy-2-nonenal in Mitochondrial DNA Damage and Contractile Dysfunction in Diabetic Heart: A Role for Aldehyde Dehydrogenase 2 (R56HL131891)

Diabetes mellitus (DM) afflicts 26 million people in the US. 40-70% of these diabetics die of cardiovascular complications. We and others found that DM increases reactive oxygen species (ROS)-mediated aldehydes like 4-hydroxy-2-nonenal (4HNE) generation. 4HNE forms covalent bonds with macromolecules known as adducts, which lead to cellular damage and decreased cardiac function. Aldehyde dehydrogenase (ALDH2) is a mitochondrial enzyme that detoxifies 4HNE in the heart. We and others reported that in streptozotocin-induced hyperglycemic models, ALDH2 levels and activity in the heart are reduced, whereas 4HNE protein adducts are increased. Although we think this causes cardiac dysfunction, the exact mechanism is unclear. However, most diabetic patients have type-2 DM. Thus, it is imperative to investigate whether hyperglycemia-induced 4HNE and lower ALDH2 activity contribute to cardiac dysfunction in type-2 DM models. We recently demonstrated that high glucose stress or 4HNE administration decreased mitochondrial respiration with increased mitochondrial DNA (mtDNA) damage in cultured cardiomyocytes. In our preliminary study using type-2 diabetic mouse heart, we found an increase in mitochondrial levels of 8-hydroxyguanine (8OHG), an oxidized mtDNA product. 8-oxoguanine glycosylase (OGG)-1 is responsible for identification and excision of 8OHG. Next, we found increased 4HNE adduct formation on OGG-1 and reduced OGG-1 levels. These data suggest that 4HNE adduction on OGG-1 reduces its level and activity thereby raising the unmetabolized 8OHG level. Thus we postulate that 4HNE-mediated mtDNA damage is part of the mechanism by which lower
ALDH2 activity causes mitochondrial respiratory dysfunction. To test our idea, we will use a high-fat diet induced type-2 DM model in wild type (WT) C57BL/6 and ALDH2*2 mutant mice. This mutation mimics East Asians with the E487K variant (ALDH2*2), which exhibits lower ALDH2 activity. We will treat our diabetic mice with Alda-1, the only specific drug available to improve the catalytic activity of both WT and mutant ALDH2. We propose following three specific aims: **Aim 1**: Hyperglycemia in models of type-2 diabetes reduces ALDH2 activity in the heart by increasing 4HNE adduction with ALDH2, further leading to cardiac dysfunction. **Aim 2**: Reduced ALDH2 activity leads to increased 4HNE adduct formation on mtDNA and 8-oxoguanine glycosylase (OGG)-1, a mtDNA repair enzyme, thereby causing mtDNA damage and poor mitochondrial respiration in type-2 DM. **Aim 3**: Augmenting ALDH2 activity ameliorates cardiac function in type-2 DM. This study will identify a novel role of ALDH2 in hyperglycemia mediated cardiac dysfunction and establish that ALDH2 could be a therapeutic target for restoring cardiac function in DM patients.

**Principal Investigator: Tengis Pavlov, Ph.D.**

**Regulation of ENaC in Salt-Sensitive Hypertension via Inflammation-Induced ROS Production (R00HL116603)**

Reduced ability to maintain sodium homeostasis and normal levels of arterial pressure is the hallmark of salt-sensitive hypertension (SSH). In the kidney, discretionary Na+ reabsorption mediated by epithelium sodium channel (ENaC) is a determinant of the pressure-natriuresis relationship which is of fundamental importance in the long-term control of arterial pressure. According to the initial proposal we continue developing specific aims focused on regulation of ENaC by reactive oxygen species (ROS) in this pathological condition. Our data indicate that ENaC-mediated Na+ reabsorption in the distal nephron contributes to salt-sensitive hypertension in and I hypothesize here that excessive H2O2 production mediates this effect. Using genetically modified strains derived from Dahl Salt-Sensitive rats, we found that ROS production by renal tissue NADPH oxidase significantly contributes to upregulation of ENaC activity associated with high salt consumption. As planned initially, the current proposal is focused on Aim 2 studying cellular and molecular mechanisms by which ROS modulate ENaC activity and complete Aim 1. We hypothesize here that H2O2 production increased in response to high salt diet results in destroying of the actin cytoskeleton and activation of ENaC activity. Moreover, we propose that cortactin and MIM proteins are required for proper regulation of the channel by the actin cytoskeleton. Also, we shall continue studies on the role of different NADPH oxidase subunits and T-cell infiltration in the development of hypertension in Dahl SS rats. This work provides mechanistic insight on the relationships between high salt consumption, development of high blood pressure, inflammation and kidney damage and the role of sodium reabsorption. Such approach allows generating clinically relevant data interesting for broad scientific community.

**Infectious Disease**

**Principal Investigator: Marcus Zervos, M.D.**

**A Phase 2 Randomised, Double-blind, Placebo-controlled, Single-dose, Dose-ranging Study of the Efficacy and Safety of MEDI4893, a Human Monoclonal Antibody Against Staphylococcus aureus Alpha Toxin in Mechanically Ventilated Adult Subjects (UM1AI104681) Subcontract**

**A Phase 2 Proof-of-concept Study to Evaluate the Efficacy and Safety of MEDI3902 in Mechanically Ventilated Patients for the Prevention of Nosocomial Pneumonia Caused by Pseudomonas aeruginosa (UM1AI104681) Subcontract**

Our goal is to create and implement an Antibacterial Resistance Leadership Group (ARLG) that will develop, design, implement, and manage a clinical research agenda that will increase knowledge of and mitigate the important factors that drive resistance. We will pair an unprecedented team of over two dozen of the world's top investigators with the organizational excellence of the Duke Clinical Research Institute (DCRI), one of the world's largest Academic Research Organizations. Because of the complexity of integrating multiple components of such a large-scale clinical research network, our submission features centralized leadership through an Executive Committee and a dual PI approach.
One PI (Fowler) focuses primarily on operations and the other (Chambers) focuses largely on scientific agenda. The organizational structure, modeled after that of the ACTG, also features Scientific Subcommittees devoted to four priority areas: Gram-negative bacterial infections, Stewardship and infection prevention, Gram-positive bacterial infections, and Diagnostics and devices. These Subcommittees are supported by three Special Emphasis Panels (SEPs) (Pediatrics, Pharmacokinetics, and Special Populations) and a Mentoring Core. Each Subcommittee, SEP, and Core contains internationally recognized investigators, ensuring expertise. To complement the current research activities of both NIH and the pharmaceutical biotechnology industry, our ARLG has established collaborative ties with members of both communities. Our long-term goals are 1) to complete a superiority trial of new anti-infectives (either new agent or new dosing regimen of existing agent) for MDR-Gram negative bacterial infections; 2) to define shorter course, narrow-spectrum therapeutic regimens for common infections as a principal means to support stewardship; 3) to test a rapid diagnostic that identifies antimicrobial resistance based on genotypic markers in bacteria; and 4) to identify a more effective alternative to vancomycin for MRSA infections. The research agenda reflects our overall strategy of making realistic, incremental steps in early phase studies upon which to build toward more complex transformational trials that will change clinical practice and reduce the impact of antibacterial resistance.

Pulmonary

Principal Investigator: Bruno DiGiovine, M.D.

CC for NHLBI Prevention and Early Treatment of Acute Lung Injury PETAL Network: VIOLET: Vitamin D to Improve Outcomes by Leveraging Early Treatment (U01HL123009) Subcontract

This proposal is a response to the RFA-HL-14-015 for the coordinating center of the Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network. We propose to provide leadership in the design, analysis and conduct of the studies of the PETAL Network and to provide the infrastructure and communications that will create a cohesive and productive group. Over the past 18 years we have served as the coordinating center of the Acute Respiratory Distress Syndrome (ARDS) Network under the leadership of an experienced clinical trials statistician and an acute care physician. We recently published our approach to the statistical and logistics issues of the ARDS Network. We propose to enhance those methods to improve performance of these activities for PETAL. Our proposal for the PETAL network focuses on the novel challenges of prevention trials. We suggest that the feasibility of a prevention trial depends on the choice of endpoint, in particular that studies using mortality as the primary endpoint would not be feasible with a conventional trial design and other clinical endpoints may be problematic. The optimal endpoint would be the occurrence of ARDS or a measure of the clinical consequences of ARDS. The proposal discusses the issues of cluster randomized trials and adaptive designs. We discuss the statistical and scientific issues in creating a biomarker resource for the PETAL Network. We also describe our proposals to increase productivity of the network by implementing an efficient IRB review process, plans for applying a computer-assisted technique to set network priorities, and plans for soliciting community involvement on an ongoing basis. We describe the methods we will use to provide the needed infrastructure (such as a remote data and trial management system) and the coordination of all network activities: data quality control, protocol compliance, protocol initiation, randomization, drug distribution, sample management, adverse event reporting, statistical reporting, data dissemination, communication, and logistics.

Principal Investigator: Bruno DiGiovine, M.D.
Clinical Centers (CC) for the NHLBI Prevention and Early Treatment of Acute Lung: Reevaluation of Systemic Early Neuromuscular Blockade (U01HL123031) Subcontract

Purpose: This study is evaluating whether giving a neuromuscular blocker (skeletal muscle relaxant) to a patient with acute respiratory distress syndrome will improve survival. Half of the patients will receive a neuromuscular blocker for two days and in the other half the use of neuromuscular blockers will be discouraged.
**Trial Summary:** Study Design: This is a multi-center, prospective, 2-arm, unblinded, randomized clinical trial of two management strategies of neuromuscular blockade (also called skeletal muscle relaxant and muscle relaxant). Purpose: To assess the efficacy and safety of early neuromuscular blockade in reducing mortality and morbidity in patients with moderate-severe ARDS in comparison to a control group with no routine early neuromuscular blockade. Sample Size: This trial will enroll approximately 1400 subjects from PETAL network hospital ICUs.

**Principal Investigator:** Jennifer Swiderek, M.D.

**Testing a Nurse-led Algorithmic Approach to Terminal Ventilator Withdrawal (R01NR015768) Subcontract**

Terminal ventilator withdrawal is a process that entails the cessation of mechanical ventilatory support with patients who are unable to sustain spontaneous breathing and is commonly performed in the ICU. Ventilator withdrawal is undertaken to allow a natural death. Opioids and/or benzodiazepines are administered before, during, and after as an integral component of the ventilator withdrawal process to prevent or relieve respiratory distress, but there are few guidelines to determine how much to administer or when. Insufficient opioid and/or benzodiazepine administration places the patient at risk for unrelieved respiratory distress and preventable suffering. Conversely, excessive medication administration may hasten death, an unintended consequence, and one that concerns clinicians. The effective doses of medications given during ventilator withdrawal are unknown. We hypothesize that an algorithmic approach to ventilator withdrawal, relying on a biobehavioral instrument to measure and trend distress, will ensure patient comfort, and guide effective opioid and/or benzodiazepine administration. We plan to use a stepped wedge cluster randomized controlled trial with all clusters providing unstructured usual care until each cluster is randomized to implement the algorithmic approach (intervention). The proposed study is innovative because there is no standardized, evidence-based approach guided by an objective measure of respiratory distress to this common ICU procedure. The study has broad clinical significance to provide knowledge that can potentially reduce patient suffering.

**Sleep Medicine**

**Principal Investigator:** Philip Cheng, Ph.D.

**Clinical Translation of Phenotypes of Shift Work Disorder (1K23HL138166)**

Shift work disorder (SWD) is a significant threat to public health and safety; over 6 million shift workers in the United States experience the debilitating symptoms of excessive sleepiness and insomnia, and suffer functional impairments that increases the risk of catastrophic industrial accidents. However, patients with SWD are often inadequately treated because the pathophysiology is not well-characterized, and current diagnostic assessments do not identify specific treatment targets. Consequently, clinicians are unable to deliver precise interventions that target the underlying causes of SWD. The proposed project in this career development award will address these gaps by taking the initial steps of translating two phenotypes of SWD for clinical use. Previous research has indicated that SWD can arise from two independent pathways that can be categorized as pathophysiological phenotypes. The first is the circadian misalignment phenotype, characterized by poor adjustment of the biological clock to the nocturnal work schedule. The second is the sleep reactivity phenotype, characterized by a trait vulnerability to sleep disturbance triggered by environmental stressors. Both phenotypes lead to symptoms of sleepiness and insomnia in SWD, and is not currently distinguished in the clinic; however, the requisite treatments for each pathophysiological phenotype are entirely different. As such, the appropriate intervention of SWD requires that these phenotypes be adequately characterized and identified in the clinic. The proposed aims will complete the requisite foundational research to launch the translation of these phenotypes of SWD for clinical use. The first research aim will examine the stability of each phenotype in shift workers to characterize them as either state or trait phenotypes, which will impact both assessments of interventions. The second research aim will identify the specific clinical attributes that can be used to index the phenotypes in a brief, accurate, and cost-effective assessment tool. Finally, the third research aim will identify differences in cognitive and
performance deficits between the two phenotypes so that accidents and injuries can be preempted with targeted interventions. To successfully complete the research aims, and to support my long term goal of conducting translational research to improve the health and productivity of shift workers, this career development award will provide further training in the following areas: (1) development of clinical screening tools, (2) advanced methodologies in clinical and translation research, (3) feasibility of real-world behavioral interventions for shift work disorder, and (4) advanced field measurement of circadian phase. In combination, the training activities outlined in this career development award will provide the necessary expertise for a sustained career in translational research and circadian medicine.

Principal Investigator: Christopher Drake, Ph.D.
Behavioral Treatment of Menopausal Insomnia; Sleep, Depression, Daytime Outcomes (R01NR013959)

Insomnia is recognized as one of the most prevalent and costly sleep disorders and is associated with considerable morbidity including significantly reduced quality of life, impaired work performance, and increased risk for major depressive disorder. Insomnia is a key symptom of the menopausal transition with 40-50% of postmenopausal women (> 17 million) having insomnia. Insomnia associated with menopause has a pattern of sleep disturbance predominantly characterized by sleep maintenance difficulties including frequent awakenings and arousals, reduced sleep efficiency, and overall fragmented sleep. It has recently been demonstrated that this pattern of sleep disturbance, difficulty maintaining sleep, increases throughout the progression of menopause. We have recently found sleep maintenance problems in menopause are associated with reduced work performance, increased healthcare utilization, and impaired quality of life. Historically, menopausal symptoms including sleep disturbance, were treated using hormone replacement therapy (HRT). However, evidence linking HRT to increased risks of heart disease and cancer have led to a 40% reduction in the use of sex steroid hormones by postmenopausal women and highlight the need for alternative approaches to treatment. Importantly, the American Association of Clinical Endocrinologists guidelines for management of menopause do not address treatment of menopausal-related insomnia due to the absence of research findings in this area. Cognitive-behavioral therapy for insomnia (CBT-I) yields equivalent short-term efficacy and superior long-term durability to pharmacological treatment of insomnia. However, the efficacy of cognitive behavioral therapy for insomnia comorbid with menopause, one of the primary focuses of the present proposal, has not been tested. Traditional CBT-I has disadvantages however, including the need for a trained therapist and significant time commitment on the part of the patient. Therefore, widespread availability of multicomponent CBT-I is limited by the relatively low number of CBT sleep specialists, complexity of therapy, and patient burden. Thus, another aim of this project is to test the acute and long-term efficacy of a single component behavioral therapy for menopausal-related insomnia. Given the significant daytime impairment present in insomnia comorbid with menopause including depression, quality of life, and fatigue, a final aim of this proposal is to determine the efficacy of CBT-I on these measures in women with menopausal-related insomnia.

The project will test the efficacy of cognitive-behavioral therapy for insomnia (CBT-I), as a safe and effective evidence-based alternative to medication for sleep disturbance associated with menopause. Because CBT-I is costly and time intensive, we will also test the efficacy of abbreviated single component sleep restriction therapy (SRT) in the treatment of menopausal-insomnia. Importantly, we will also test the efficacy of each of these treatments on improvements in depression, fatigue, and quality of life.

Principal Investigator: Timothy Roehrs, Ph.D.
Risks for Transition from Therapeutic Hypnotic Use to Abuse (R01DA038177)

The acknowledged drugs of choice for the pharmacological treatment of insomnia are the benzodiazepine receptor ligand hypnotics (BzRL). Our nighttime studies show that with therapeutic doses used either short-term or chronically, the abuse liability of BzRLs in insomnia is not seen
universally and is relatively low. The data from our last grant, a first-ever study, showed the abuse liability of chronic zolpidem use in insomniacs was low. Yet case reports and retrospective studies continue to report BzRL dependence and for the majority of these cases the abuse developed through initial therapeutic use. In our study some subjects showed an increase in dose across time. Understanding the transition from therapeutic use to abuse and identifying risk factors, such as specific patient and drug characteristics, is both mechanistically and clinically important. Our preliminary data have shown that a subset of insomniacs, those insomniacs that have signs of hyperarousal as reflected by elevated Multiple Sleep Latency Test (MSLT) scores, increased their nightly zolpidem dose across time. BzRLs have differential receptor binding affinities and associated anxiolytic or antidepressant properties. Zolpidem has selective alpha 1 BzRL affinity and little mood activity and thus may show less risk for transition from therapeutic use to abuse than another currently frequently prescribed BzRL with less alpha subtype selectivity such as eszopiclone. We propose to study the abuse liability of a selective (zolpidem) vs nonselective (eszopiclone) hypnotic during chronic use (six months) in an at-risk sub-population (insomniacs with hyperarousal shown by elevated MSLTs). The proposal is highly innovative as it reflects a paradigm shift in understanding the abuse liability of hypnotics. In the end, this proposal will generate a unique set of data addressing a number of previously clinically important unanswered questions regarding hypnotic abuse by insomniacs (i.e., its likelihood as a function of arousal state and specific hypnotic pharmacology, of dose escalation over time and change in mood/drug effect ratings over time). It will provide clinicians with behavioral indicators of abuse risk.

General Internal Medicine

Principal Investigator: Michelle Schreiber, M.D.

eASSIST A Post-Visit Patient Portal Tool to Promote Colorectal Cancer Screening (R01CA197205) Subcontract

Colorectal rectal cancer (CRC) is the third most common cancer in the US with over 50,000 individuals dying annually from the disease. Despite multiple effective screening tests, CRC screening remains underutilized relative to other cancer screening. A driving factor behind this underutilization among insured populations is the gap that exists between a physician recommendation for care and the patient's receipt of screening. How best to support patients in CRC screening once they have a physician recommendation for care remains unknown. The proposed project will test the effectiveness and impact of a post-visit, patient portal tool, e-Assist, for engaging and supporting primary care patients in their decision making regarding, and ultimately in their obtaining, CRC screening. The tool purposely leverages the cue to action provided by a physician recommendation for care as well as the secure patient portal platform now commonly found within primary care practices. It seamlessly combines important patient-physician decision making content with assistance in removing personal and structural barriers to screening. Our research will answer four overarching questions: (1) Can a post-visit, patient portal tool, e-Assist, increase adherence to physician-recommended CRC screening? (2) How does e-Assist engage primary care patients in the CRC screening decision making process? (3) Are there subgroups of the primary care population for whom e-Assist is more engaging and effective? and (4) What adaptations are needed to e-Assist to improve its reach, and ensure its adoption, implementation, and ultimately its impact on evidence-based CRC screening use among diverse primary care patients and clinics? These questions will be addressed using a two-arm, practical randomized trial supplemented with findings from focus groups and in-depth interviews with patients, clinicians and other clinic staff to ensure a comprehensive understanding of not only program effectiveness and implementation, but the factors driving overall program impact. Results will illustrate how e-tools can be used following an office visit to support both patient decision making, and the dissemination and implementation of evidence-based cancer screening services in primary care.
Part II – All Other Clinical Departments

- Dermatology
- Neurology
- Neurosurgery
- Orthopaedics/Bone & Joint
- Pathology
- Radiation Oncology

Dermatology

Principal Investigator: Qing-Sheng Mi, M.D., Ph.D.

microRNAs and NKT Cell Development and Function (R01AI119041)

Natural killer T (NKT) cells are an evolutionarily conserved subset of T cells that are developmentally and functionally distinct from conventional T cells. The ability to quickly secrete large quantities of a variety of cytokines upon activation enables NKT cells to be potent regulators of diverse immune responses. The deficiencies in NKT cell number and function have been linked to the development of many diseases. However, a significant gap remains in our understanding of how the development and function of NKT cells are precisely regulated. MicroRNAs (miRNAs), a recently discovered class of evolutionarily conserved small non-coding RNAs, negatively regulate the expression of protein-coding genes and thereby control essential biological functions and contribute to the development of many diseases. We were the first to report that the deletion of Dicer (a key enzyme for miRNA biogenesis) during hematopoiesis results in a significantly reduced NKT cell number and impaired NKT cell maturation and function, without alternating conventional T cell development in the thymus, suggesting that miRNAs are required for NKT cells. Our long-term goal is to understand how miRNAs regulate NKT cell development and function. While more than 1000 experimentally reported miRNAs, very few specific miRNAs are linked to NKT cells so far. Our objective here is to define specific miRNAs and their targets that regulate NKT cell development and function. Using miRNA arrays, we recently identified dynamic expression of miRNAs, including miR-155, and miR-17-92 cluster, during NKT cell development and activation. These findings plus our recent other report lead to our central hypothesis that these dynamically expressed miRNAs serve as critical regulators controlling NKT cell development and function through fine-tuning of specific target genes. Here we will further test this hypothesis. We will investigate how dynamic and miR-155 and miR-17-92 expression regulates NKT cell development and function using specific miRNA mutant mice with the gain or loss of miRNA gene. The results from proposed studies may not only illuminate the new immunological and molecular mechanisms underlying NKT cell development, but may also facilitate the development of new and more efficient intervention strategies for autoimmune diseases, infection, and cancer based on the NKT cell therapy.

Principal Investigator: Qing-Sheng Mi, M.D., Ph.D.

Roles of HDAC3 in Epidermal Langerhans Cell Ontogeny and Function (R01AR069681)

Langerhans cells (LCs), the skin residing dendritic cells (DCs), form a contiguous immune network in skin and are involved in allergy, infection, cancer, and autoimmune disease development. However, the regulatory mechanisms involved in the development and functions of LCs have not been completely elucidated. Histone deacetylases (HDACs) are enzymes that regulate gene expression by modifying chromatin structure through removal of acetyl groups from target histones or directly deacetylating nonhistone proteins, and represent a key epigenetic regulatory mechanism. HDAC inhibitors (HDI) are shown to have anti-tumor and anti-inflammatory effects in a variety of diseases, in which LCs play an important role. However, the mechanisms underlying the clinical effectiveness of HDI remain largely unknown. We recently reported that the inhibition of Class I/II HDACs by Trichostatin A (TSA) regulates the homeostasis and function of LCs in vitro and in vivo and modulates the non-coding miRNA expressions in LCs, while miRNAs also control LC development and function.
Our preliminary data indicate that LCs express all Class I/II HDACs. To evaluate the role of individual HDACs in LC development and function, we generated knockout (KO) mice with selective deletion of HDAC3 (Class I) or HDAC4 (Class II) in epidermal LCs. Interestingly, LC number was significantly reduced in LC-HDAC3KO mice, but unaffected in LC-HDAC4KO mice. Furthermore, LC maturation and function were altered in LC-HDAC3KO mice. Thus, we hypothesize that HDAC3 is a key epigenetic component that controls LC development and function. In Aim 1, we will investigate the roles of HDAC3 in LC development and homeostasis, using LC-HDAC3KO mice for homeostasis after birth and using constitutive Csf1r-specific HDAC3-deletion mice (Csf1r-HDAC3) and inducible Csf1r-specific HDAC3-deletion (Csf1r.Mer-HDAC3) mice for early embryonic LC development; Aim 2, we will investigate the roles of HDAC3 in LC function, using inducible LCER. HDAC3KO mice. In Aim 3, we will elucidate the molecular mechanisms and signaling pathways by which HDAC3 regulates LC development and function, by combining cDNA array, miRNA array and ChiP-Seq techniques. The proposed studies will uncover the epigenetic regulatory mechanisms of HDAC3 in LC development and function, and may also elucidate new mechanisms for HDI therapy.

Principal Investigator: Qing-Sheng Mi, M.D., Ph.D.
Serum MicroRNA Biomarkers of Islet Autoimmunity (R01AI123258) Subcontract

Under Dr. Mi’s leadership, the team at Henry Ford Health System will perform miRseq profiles and quantitative miRNA analysis on serum samples using the Exiqon RT-PCR platform. Based on preliminary data, a custom panel of 188 microRNAs will be used. This strategy will allow greatly reducing the cost of measuring microRNAs by almost 50% and yet allow to study serum microRNA extensively; making it possible to measure a larger number of samples for increased statistical power. Over the course of the four year program, we anticipate measuring microRNA levels in 600 serum samples from the DPT cohort, as described in the experimental plan. In addition to this, the team at Henry Ford Health System will perform miRseq to define potential candidates that may be missed by the Exiqon platform.

Neurology

Principal Investigator: Gregory Barkley, M.D.
Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (U01NS038455) Subcontract

There is a compelling need for prospective, properly controlled studies in women with epilepsy (WWE) during pregnancy to improve maternal and child outcomes. The proposed investigations are pertinent to the NINDS Epilepsy Research Benchmarks and will address multiple gaps in our knowledge noted by the recent American Academy of Neurology guidelines. This multicenter investigation will employ a prospective, observational, parallel-group, cohort design with an established research team. The specific aims are to: 1) Determine if WWE have increased seizures during pregnancy and delineate the contributing factors; 2) Determine if C-section rate is increased in WWE and delineate contributing factors; 3) Determine if WWE have an increased risk for depression during pregnancy and post-partum period and characterize risks factors; 4) Determine the long-term effects of in utero AED exposure on verbal intellectual abilities and other neurobehavioral outcomes in the children of WWE; 5) Determine if small for gestation age and other adverse neonatal outcomes are increased in children of WWE; 6) Determine if breastfeeding when taking AEDs impairs the child’s verbal intellectual and other cognitive abilities. An overall goal of the proposed research is to establish the relationship between AED exposure and outcomes in the mother and child as well as describe and explain the variability in AED exposure and response. Anticonvulsant blood levels (ABLs) and area-under-the-concentration-time-curves (AUCs) will be used as direct measures of drug exposure. The results will enable clinicians to prospectively calculate individual dosing regimens for the mother in order to optimize dosing and limit unnecessary drug exposure to the child. In addition, genetic samples will be collected, which will provide a valuable resource for future pharmacogenetics studies to further delineate individual variability across patients.
Diabetes mellitus (DM) leads to a 3-4 fold higher risk of experiencing ischemic stroke. Hyperglycemia and diabetes instigate a cascade of events leading to vascular endothelial cell dysfunction, increased vascular permeability and poor recovery after ischemic stroke. Diabetic animals exhibit more severely injured white matter (WM) than non-DM animals after stroke. There is also a differential response to treatment of stroke between DM and non-DM subjects. Effective therapy of stroke in the non-DM population may not necessarily transfer to the DM population, prompting the need to develop therapeutic approaches specifically designed to reduce neurological deficits after stroke in the DM population. Our preliminary data show that T2DM significantly decreases microRNA-126 (miR-126) and Angiopoietin-1 (Ang1) expression in the circulation and in the ischemic brain of mice. Human umbilical cord blood cell (HUCBC) treatment of stroke in T2DM mice starting at 3 days after stroke significantly improves recovery of neurological function as well as increases miR-126 and Ang1 expression in the ischemic brain. Therefore, based on our robust preliminary data, we propose to use HUCBCs for the treatment of stroke in the T2DM mice and to investigate the role of intercellular communication via miR-126 encapsulated within Exosomes/Microvesicles (EMVs) in mediating the therapeutic benefit on HUCBCs for ischemic stroke. This application includes three Aims. Aim 1 will test if miR-126 mediates HUCBC treatment induced neurorestorative effects after stroke in T2DM mice. We hypothesize that miR-126 mediates HUCBC treatment and vascular integrity, axonal outgrowth, and WM remodeling, and improves functional outcome after stroke in T2DM mice. Aim 2 will test whether miR-126 generated by HUCBCs is transferred to brain endothelial cells (BECs) and parenchymal cells via EMVs. We hypothesize that HUCBCs secrete EMVs containing miR-126 which are taken up by BECs and parenchymal cells. Aim 3 will investigate whether miR-126 regulation of Ang1 promotes the HUCBC-induced neurorestorative effects after stroke in T2DM mice. We hypothesize that: 1) HUCBC treatment of stroke in T2DM mice increases Ang-1 signaling activity in the ischemic brain; 2) miR-126 regulates Ang1 expression and thereby regulates vascular remodeling, axonal outgrowth and oligodendrocyte survival and differentiation; 3) Restoration of Ang1 with an Ang1 mimetic peptide will rescue the neurorestorative effects of knockdown of miR-126 in HUCBC after stroke in T2DM mice. In this application, we are the first to propose that, generation of miR-126 encapsulated in EMVs by HUCBCs contributes to its robust therapeutic restorative effects and that miR-126 and its regulation of Ang-1 regulate HUCBC-induced neurovascular and WM remodeling, and thereby improve stroke functional recovery in T2DM mice. This proposal is highly clinically relevant and if successful, will significantly impact the treatment of diabetic and possibly all stroke patients.
conditional knockout of EC miR-126 (MiR-126EC-/-) and in non-miR-126 knockout control (miR-126fl/fl) T2DM mice with EC-Exo derived from miR-126EC-/- brain ECs (miR-126EC-/- EC-Exo) or EC-Exo derived from wild type miR-126fl/fl brain ECs (miR-126fl/fl-EC-Exo) on vascular and axonal/WM remodeling and neurological and cognitive functional outcome. **Aim-3:** To test whether ABCA1, an indirect target of miR-126, contributes to EC-Exo treatment induced neurorestorative effects after stroke in adult male T2DM mice, mice with specific knockout of brain ABCA1 (ABCA1-B/-B) and WT ABCA1 knockout control (ABCA1fl/fl) mice will be employed. In this application, we are the first to propose that, generation of miR-126 encapsulated in EC-Exo contributes to its robust therapeutic restorative effects and that miR-126/ABCA1 pathway mediates EC-Exo-induced neurovascular and WM remodeling, and thereby improves stroke neurological and cognitive functional recovery in T2DM mice. This proposal is highly clinically relevant and if successful, will significantly impact the treatment of diabetic stroke, and possibly all stroke patients.

**Principal Investigator:** Michael Chopp, Ph.D.

**miR-17-92 Exosome Treatment of Stroke (R01NS088656)**

Exosomes, small lipid microvesicles (30-150 nm), are active biological containers, which transport regulatory genes and proteins between cells and form a major biological communication conduit, facilitating a plethora of biological responses. The regulatory molecules contained in the exosomes include microRNAs (miRNAs), short (22-25 nt) non-coding RNAs which regulate gene translation and play primary roles in mediating a vast range of biological functions. In this proposal, based on strong preliminary data, we propose to manufacture a distinct exosome population which contains increased levels of the miR-17-92 cluster as a proof-of-principle and a mechanistic demonstration of a new method of treating stroke and possibly other neurological diseases and injury. We test the premise, that by modulating their miRNA content, exosomes can be designed to enhance plasticity of axons and thereby further promote neurological recovery post stroke. Success of this novel approach may lead to a new designer-based paradigm for the treatment of stroke and neurological disease. The following Specific Aims and associated Hypotheses are proposed: **Specific Aim 1:** To employ exosomes derived from multipotent mesenchymal stromal cells (MSCs) to treat stroke in order to enhance neurovascular remodeling and thereby, functional recovery post stroke. **Hypothesis:** Exosomes, derived from MSCs when administered to rats after stroke promote neurovascular remodeling which improves functional outcome. **Specific Aim 2:** To alter specific miRNAs contained within exosomes generated by MSCs as a means to enhance axonal plasticity and neurological recovery post stroke. **Hypothesis:** Administration of exosomes with increased miR-17-92 cluster to rats post stroke promotes axonal remodeling and enhances functional outcome. There are multiple layers of innovation in our application: we generate biological exosome carriers tailored for specific miRNAs; we use these exosomes to treat stroke, without the administration of exogenous cells; we employ electrophysiological methods, laser capture, fiber track tracing, a battery of neurological tests, and an array of novel approaches, e.g. microfluidic chambers, and ex vivo slice cultures, to mechanistically determine the molecular pathways of the target exosomes which mediate axonal outgrowth. Development of this designer exosome-based therapy, also serves as a prototype for capitalizing on the characteristics of exosomes to transport specific miRNAs and for the manufacture of designer exosomes. Developing a therapy for stroke that is exosome-based opens up a wide variety of means to deliver targeted regulatory genes to enhance multifaceted aspects of central nervous system (CNS) plasticity and to amplify neurological recovery for neural injury and neurodegenerative diseases.

**Principal Investigator:** Xu Cui, Ph.D.

**ABCA1 Regulates White Matter Remodeling and Oligodendrogenesis after Stroke (R01NS092917)**

Stroke is a major cause of white matter (WM) damage which induces long-term disability. There is limited WM remodeling in the adult brain. Many neuroprotective treatments of stroke have failed in clinical trials because they cannot protect WM. Therefore, there is a compelling need to investigate the mechanism underlying WM remodeling and oligodendrogenesis of the adult brain and to develop
effective long-term stroke therapy. Cellular cholesterol modulates axonal and dendritic outgrowth and is required for myelination. The level of HDL-cholesterol is related to the progression and recovery of stroke patients. ATP-binding cassette transporter A1 (ABCA1) is a major cholesterol transporter and plays critical roles in regulation of HDL-cholesterol and ApoE synthesis and metabolism in the central nervous system. Brain specific- ABCA1 deficient (ABCA1-B/-mice have very low brain HDL-cholesterol/ApoE level, and exhibit neuronal ultrastructure changes and functional deficits. Both HDL-cholesterol and ApoE increase neurite outgrowth in culture conditions. Our preliminary study shows that ABCA1-/-B mice exhibited increased WM damage and reduced oligodendrogenesis and exacerbated neurological functional deficits after stroke. Primary cultured neurons derived from ABCA1-/-B mice show decreased neurite outgrowth, which can be attenuated by HDL treatment. ABCA1-B/-B astrocyte-conditioned media also decreased wild type neurite outgrowth after hypoxic ischemia. Therefore, we propose the following three specific aims: Aim1 To investigate whether brain-deficient in ABCA1 exhibits decreases in WM-remodeling and axonal growth after stroke. ABCA1-B/-B and floxed-control mice will be subjected to stroke, WM-changes and oligodendrogenesis will be measured. Aim2 To investigate molecular mechanism underlying ABCA1 in regulation of WM-remodeling and oligodendrogenesis after stroke, we will examine whether ABCA1 regulates brain HDL and ApoE level, and whether brain HDL and ApoE levels mediate ABCA1-induced WM-remodeling and oligodendrogenesis after stroke. Aim3 To investigate cellular mechanisms of ABCA1 in regulation of WM-remodeling and oligodendrogenesis, we will examine neurons and oligodendrocytes and the cross talk of astrocytes with neurons and oligodendrocytes on ABCA1-induced WM-remodeling and oligodendrogenesis in vitro and in vivo. We expect that ABCA1 deficient brain will exhibit significant decreases in HDL and ApoE level, and decreases WM-remodeling and oligodendrogenesis as well as reduced functional outcome after stroke. The level of HDL/ApoE in brain or cerebrospinal fluid will, at least partially, mediate ABCA1-induced WM-remodeling and oligodendrogenesis in the ischemic brain after stroke. To our knowledge, no one has investigated the functional effect of ABCA1 on oligodendrogenesis and WM-remodeling post-stroke recovery, especially by using ABCA1- B/-B mice. The new insights gleaned from this study will contribute to our understanding of the beneficial role of ABCA1/HDL-C/ApoE in brain plasticity which will impact development of rational restorative approaches to improve neurological outcome for stroke patients.

Principal Investigator: Shailendra Giri, Ph.D.

Role of AMP-Activated Protein Kinase in Bacterial Endophthalmitis (R01EY026964) Subcontract

The role of myeloid cells such as neutrophils in providing host defense to microbial infections is well-established; however, the contribution of monocytes/macrophages (M¿) to the pathophysiology of bacterial endophthalmitis is less clear. Our preliminary studies revealed that M¿ depletion results in increased inflammatory mediators at the resolution phase, suggesting their involvement in the resolution of endophthalmitis. The M¿ perform multiple tasks, including sensing pathogens, tissue repair, and, in response to host-derived mediators, they differentiate into distinct functional phenotypes; a feature termed "plasticity". The "classically activated" M¿ (M1) produce inflammatory cytokines and nitric oxide, contributing to host tissue damage. Conversely, the "alternatively activated" M¿ (M2) mediate tissue repair through the elimination of damaged cells/tissue and the production of anti-inflammatory molecules to resolve inflammation. Therefore, understanding the mechanisms governing the phenotypic switch of M¿ can be utilized to develop novel therapeutic strategies. Our transcriptome and metabolomics analyses of the bacteria-infected retina directed us to the identification of adenosine monophosphate-activated protein kinase (AMPK), a metabolic gene, which modulates the infiltrating myeloid cell phenotype in endophthalmitis. We discovered that mice with global deletion (knockout) of AMPKa1 (KO) developed severe endophthalmitis and pathology compared to wild type (WT) mice. M¿ lacking AMPKa1 maintained a low metabolic state, even in the hyper-inflammatory state. To precisely examine the role of AMPK in myeloid cells, we induced endophthalmitis in myeloid cell specific KO of AMPKa1 (LysM-KO) and observed that LysM-KO displayed exacerbated inflammation and reduced retinal function compared to WT mice, suggesting an essential role of AMPK in myeloid cells in the pathogenesis of bacterial endophthalmitis. Building on these findings, we propose to test our central hypothesis that AMPK exerts protective effects in bacterial endophthalmitis by modulating the polarization of infiltrating monocytes/M¿ to promote inflammation resolution and that metabolic reprogramming is an underlying mechanism of the
monocytes/M\(\mu\) phenotype switch. To test our hypothesis, in Aim 1, we will investigate the mechanisms underlying reduced AMPK activity in bacterial endophthalmitis by examining the modification of LKB1 via nitrosylation or chemical adduct formation. Aim 2 tests the hypothesis that AMPKa1 ablation enhances the activation state of myeloid cells and maintains their proinflammatory (M1) state during the resolution phase of the disease. In Aim 3, we will decipher the bioenergetic events, regulated by AMPK in M\(\mu\), that polarize and maintain their pro-inflammatory nature. The anticipated results of this study will demonstrate that defective AMPK activity in myeloid cells, mainly in monocytes/M\(\mu\), impacts the resolution of endophthalmitis via regulation of cellular metabolism. Also, it may provide novel therapeutic targets for the development of anti-inflammatory therapies for endophthalmitis and other microbial infections.

**Principal Investigator: Quan Jiang, Ph.D.**

**Impairment of the Glymphatic System in the Aged Diabetic Brain (R21AG052735)**

Type II diabetes mellitus (T2DM) is a common metabolic disease and an established risk factor for cognitive dysfunction in the elderly population. However, the pathological mechanisms that underpin the development and progression of DM-related deficits remain unclear. Recent investigations have altered the traditional model of cerebrospinal fluid (CSF) hydrodynamics. The brain lacks specialized organ-wide anatomic structure to facilitate lymphatic clearance although the brain has complex architecture and high metabolic activity. However, a newly identified glymphatic system has been shown to modulate the CSF-interstitial (ISF) exchange, which facilitates clearance of interstitial solute from the brain parenchyma. Impairment of the glymphatic system is involved with the development of neurodegenerative conditions, including Alzheimer’s disease and sleep disorders, etc. Although the impact of the glymphatic system is being investigated in Alzheimer’s disease and sleep disorders, with promising results, there are no reported data related to diabetes and the glymphatic system. Using a model of T2DM in middle-aged rats and noninvasive MRI methodologies, our preliminary data indicate that compared with age-matched non-DM rats, the T2DM rats reduced clearance rate of interstitial Gd-DTPA agent from brain parenchyma by approximately 84% and increased clearance time by 4.2 time of Non-DM rats in the hippocampus, leading to accumulation of Gd-DTPA agent in these regions and consequently high MRI signal intensity in T1 weighted MRI (T1WI). In parallel, ex-vivo confocal imaging analysis revealed that in Non-DM rats, the concentration of interstitial Texas Red-conjugated dextran (TR-3, MW 3kD) reached a plateau in the brain interstitium approximately 3h after injecting TR-3 into the cisterna magna and after that TR-3 began to clear and was almost completely cleared from brain parenchyma at 6h after the injection, whereas in middle-age T2DM rats TR-3 accumulated in the hippocampal interstitium with time and exhibited strong fluorescent signals at 6h after the injection. These ex-vivo data are consistent with in vivo MRI findings, indicating that T2DM impairs the glymphatic clearance of interstitial solutes in the brain. In addition, T2DM rats exhibited microvascular thrombosis and blood brain barrier (BBB) leakage in the hippocampus in immunofluorescent analysis and also showed spatial learning deficits compared to Non-DM rats. Based on our novel preliminary data, we will employ MRI and 3D confocal microscopy to evaluate for the first time, temporal and spatial profiles of paravascular CSF-ISF exchange throughout the brain during the development of T2DM. We propose to further develop MRI protocol and analysis modeling as an effective means to evaluate the function and status of the glymphatic system (Aim 1). We will then use the optimized MRI protocol and analysis to explore the relationships between impairment of glymphatic system, vascular damage, and functional deficits during develop of DM (Aim 2). Data generated from this application will provide new insights into the progression of DM associated impairment of the glymphatic system.

**Principal Investigator: Quan Jiang, Ph.D., Jieli Chen, Ph.D.**

**Investigation of D4-F Effects on Neurovascular Remodeling after Diabetic Stroke (R01NS097747)**

Ischemic stroke patients with Diabetes mellitus (DM) exhibit a distinct risk-factor and etiologic profile and a worse neurovascular prognosis than non-DM patients. Therefore, there is a compelling need to investigate neurovascular changes after stroke in the DM and non-DM population and to develop therapeutic approaches specifically designed to reduce neurological deficits after stroke. Type 2 diabetes (T2DM) constitutes 90% of diabetic patients and is associated with low high-density lipoprotein cholesterol (HDL-C), impairment of the anti-oxidative capacity of HDL-C, low phosphorylation of
endothelial nitric oxide synthase (p-eNOS), and with reduced ATP-binding cassette transporter A1 (ABCA1) gene expression. D-4F is an economical apolipoprotein A-I (ApoA-I) mimetic peptide, presently employed in clinical trials to reduce coronary atherosclerosis in patients with acute coronary syndrome. However, the therapeutic effects of D-4F in post-ischemic stroke have not been investigated. Our preliminary data show that D-4F treatment of stroke starting 2h or 24h after ischemic stroke improves recovery of neurological function in both T2DM and non-DM mice and also increases p-eNOS and ABCA1 in the ischemic brain. In a novel and clinically relevant approach, based on our robust preliminary data, we propose to use D-4F in the treatment of stroke in the non-DM and T2DM population in mice. We seek to develop D-4F as a novel neurorestorative therapy to reduce white matter (WM) dysfunction and vascular damage, in T2DM and non-DM mice when treatment is initiated at 24h after onset of ischemic stroke. In addition, most development of stroke treatments has focused on young adult animals, but not on old animals, the prevalent population with stroke. Increased age also increases neurological impairment after stroke. We have also developed and implemented multimodality MRI imaging which can dynamically monitor neurovascular remodeling in both the animal and the patient. In the current study, we will measure WM and vascular changes and elucidate the mechanisms of action of D-4F in young adult and aged animals with and without T2DM after stroke. Our hypothesis is that D-4F increases ABCA1 and p-eNOS signaling activity which mediates vascular and WM remodeling and in concert improve functional outcome after stroke. We, therefore, propose two highly integrated and longitudinally designed Specific Aims. Aim 1 will investigate the delayed (24h after stroke) therapeutic effects of D-4F in non-DM and T2DM in young adult and aged mice after stroke. The differences in cerebral WM and vascular changes, and neurological functional outcome after stroke between non-DM and T2DM mice treated with or without D-4F will be analyzed. MRI will be employed to measure the dynamics of neurovascular reorganization underlying therapeutic response and recovery. In Aim 2, using eNOS knockout mice and specific loss of brain ABCA1 mice, we will investigate the mechanisms by which D-4F promotes neurovascular remodeling and hence, neurological recovery. The long-term objective of this RO1 is to develop a neurorestorative treatment for stroke in patients with or without diabetes.

Principal Investigator: Quan Jiang, Ph.D.
Glymphatic and Cognitive Impairment of Aging and Diabetes (RF1AG057494)

The objective of this application is to investigate glymphatic impairment and cognitive deficits during progression of aging with and without diabetes. Emerging data1-5 indicate that the glymphatic system in the brain mediates the cerebrospinal fluid (CSF)-interstitial (ISF) exchange and solute clearance from the brain parenchyma. However, despite the well-described dysfunction of the glymphatic system in the development of neurodegenerative conditions, there is still no reported study that focuses on the role of the glymphatic system in the development of cognitive impairment during aging and aging with type-2 diabetes (DM). Using noninvasive MRI methodologies to investigate cerebral solute waste clearance in middle-age control and type-2 diabetic (DM) rats, we have found increased impairment of the glymphatic system, as indicated by reduced clearance of interstitial Gd-DTPA in brain parenchyma, primarily in the hippocampus and hypothalamus in DM rats (Fig.2&3). In parallel, 3D confocal microscopic analysis of the brain-wide distribution of fluorescent tracers revealed increased delayed clearance of ISF in the hippocampus and hypothalamus from DM rats (Fig.2&3). Impairment of the glymphatic system in DM rats was shown to be highly correlated with cognitive deficits as measured by an array of cognitive tests including the Morris Water Maze (MWM) for hippocampal related learning and memory. Importantly, histopathological analysis shows that delayed clearance of interstitial solutes is associated with sporadic cerebral microvascular thrombosis in the hippocampus 2 months after hyperglycemia (15 months from birth), while extensive microvascular thrombosis and para-vascular accumulation of beta-amyloid (Aβ) are detected at 4 months after induction of hyperglycemia (17 months from birth), suggesting that the impairment of the glymphatic system leads to Aβ accumulation. Collectively, our preliminary data, for the first time, demonstrate that non-invasive MRI methodologies can detect DM-induced early impairment of the glymphatic system which is highly correlated with hippocampal related dysfunction of learning and memory. Based on our novel preliminary data, we will employ MRI and 3D confocal microscopy to evaluate and quantitatively measure kinetic clearance parameters of the glymphatic system during progression of aging with and without DM(Aim 1). We will then investigate: whether impairment of the glymphatic system predicts cognitive dysfunction, the sensitivity and association between impairment of
the glymphatic system, the onset of brain vascular dysfunction, and cognitive deficits during aging with and without DM (Aim 2). Data generated from this application will provide new insights into aging and age-matched DM associated impairment of the glymphatic system and the relationship of the glymphatic system with vascular and cognitive dysfunction.

**Principal Investigator: Xianshuang Liu, M.D.**
**Translational Study of miR-146a Gene Therapy for Diabetic Peripheral Neuropathy (R01DK102861)**

Peripheral neuropathy is the major complications of diabetes. There is a compelling need to develop effective therapeutic approaches specifically designed to improve neurological function in the damaged peripheral nervous system after diabetes. MicroRNA-146a (miR-146a) has been implicated in the regulation of multiple immune diseases. However, the role of miR-146a in diabetic peripheral neuropathy (DPN) has not been investigated. In a novel set of experiments, our preliminary data show that intravenous administration of miR-146a remarkably improved sciatic nerve vascular function, axonal myelination and peripheral nerve function in diabetic mice, indicating that miR-146a may have a beneficial effect on the clinical treatment of DPN. In this application, we therefore seek to investigate the mechanisms underlying the therapeutic effects of miR-146a on DPN. We propose that miR-146a by improving vascular function and suppressing pro-inflammation factors ameliorates DPN. The associated hypotheses are: 1. Treatment with chemically engineered miR-146a improves neurological outcomes in DPN in dose and therapeutic window dependent manners. 2. Elevation of miR-146a levels suppresses its target genes, IRAK1/TRAF6 and their down-stream pro-inflammatory factors in vascular endothelial cells and monocytes of type II diabetic mice, thereby, leading to the improvement of neurovascular function and consequently ameliorating peripheral neuropathy. To investigate the effect of miR-146a on neurological outcomes, type II diabetic mice which develop severe peripheral neuropathy will be treated with miR-146a at various time points and doses after onset of DPN. To investigate the underlying molecular mechanisms, the effects of miR-146a overexpression and knockdown on target genes and inflammatory genes that mediate miR-146a-enhanced neurovascular function will be determined. These studies are innovative and will provide novel insights into mechanisms underlying the neurological dysfunction of DPN and likely lead to the development of a new miRNA-based gene therapy.

**Principal Investigator: Hongqi Xin, Ph.D.**
**Exosome Transfer of miR-133b Mediates MSC Induced Neurological Recovery after Stroke (R01NS081189)**

Multipotent mesenchymal stromal cells (MSCs) have potential therapeutic benefit in many diseases including neurological diseases and injury. MSC-based therapies enhance recovery from stroke. We have previously demonstrated that exogenously administered MSCs interact with neural cells, increase the production of neurites, reduce expression of axonal inhibitory molecules and stimulate the production of growth and plasticity positive factors in neural cells which promote neurorestoration and recovery of neurological function. However, it is unknown how MSCs interact with neural cells, alter their protein expression, and thereby promote functional recovery. In the present proposal, we provide fundamental and novel mechanistic insight into how cell-based therapies promote recovery. MicroRNAs (miRNAs) act as master switches regulating the translation of many genes, and exosomes are membrane vesicles, 40-100nm in diameter, that are secreted by a wide range of cell types. We propose that MSCs increase specific miRNA levels in neural cells via exosomes, which subsequently stimulate neurite outgrowth and functional recovery. Based on our preliminary data, we will primarily focus on miR-133b, as an important target miRNA. Two specific aims are proposed. Aim 1: To investigate whether exosomes primarily mediate cell-cell communication by direct transfer of miR-133b to neural cells and/or indirectly by stimulating miR-133b expression in neural cells, which subsequently promote neurite outgrowth and functional recovery after stroke. Aim 2: To investigate the mechanisms by which miR-133b promotes neurite remodeling after treatment of stroke with MSCs. This study opens up important and novel ways to elucidate how exogenously administered cells communicate with and alter neural cells to activate restorative events. Confirming our hypothesis represents a major leap forward in our understanding of cell-cell communication and will lead to novel ways to augment brain
Stroke is one of leading causes of death and disability worldwide, mainly affecting elderly. Tissue plasminogen activator (tPA), the only Food and Drug Administration (FDA) approved treatment, is limited in its use to < 8.5% of stroke patients. Therefore, there is a compelling need to develop new and broader utility therapies for acute ischemic stroke. Vepoloxamer is a well characterized proprietary amphipathic copolymer with rheological properties, which is currently under investigation in a global phase III clinical trial for patients with sickle cell disease. Our preliminary studies demonstrate that administration of Vepoloxamer in combination with tPA 4h after embolic stroke facilitates recanalization and thrombolysis reduces ischemic neuronal damage and improves neurological outcome, but does not increase cerebral hemorrhage in young adult rats. We also found that platelet-derived exosomes contribute to the therapeutic effect of Vepoloxamer on enhanced tPA-thrombolysis. In this application, we propose to investigate effect of Vepoloxamer in combination with tPA on acute stroke and molecular mechanisms underlying the combination therapy on the thrombolysis and neurovascular function in the aged male and female rats. Data generated from this application may provide a novel and potentially useful treatment strategy for patients with acute stroke.

Diabetes mellitus (DM) is a common metabolic disease in the middle-aged and older population, which is associated with cognitive decline and an increased risk of developing dementia in the elderly. Given the growing size of the aging population and increased prevalence of DM, development of specific interventions to maintain cognitive integrity by counteracting DM induced pathophysiological processes is of major clinical importance. Clinical trials show that the achievement of improved glycemic control may not prevent progression of cognitive impairment. The underlying cause of DM-induced cognitive deficits remains unknown. Exosomes are nanovesicles with a size of 40 to 120 nm in diameter and mediate intercellular communication by transferring proteins, lipids, and genomic materials including mRNAs and microRNAs (miRNAs) between source and target cells. Our preliminary data demonstrated aged-DM rats exhibit substantial cognitive impairment, which is associated with dysfunction of cerebral endothelial cells and neural stem cells. We also found that exosomes derived from dysfunctional cerebral endothelial cells induced by DM communicated with and damaged neural stem cells. More importantly, administration of exosomes isolated from cerebral endothelial cells of healthy young adult brain to aged-DM rats effectively improved cognitive function and minimize DM-induced dysfunction of cerebral endothelial cells and neural stem cells. In this application, we therefore, propose to develop the endothelial exosomes as a mechanism-based therapy for DM-induced cognitive decline in aged population. Our hypotheses are: 1) The cerebral endothelial exosome (CEE) treatment reduces cognitive deficits in the aged-DM rat, 2) The CEE treatment improves cerebral vascular patency and integrity, and promotes neurogenesis and oligodendrogenesis in the aged-DM rat, and 3) Engineered exosomes carrying elevated miR-1 and -146a have enhanced effects on cerebral vascular function, neurogenesis and oligodendrogenesis as well as cognitive function. Aim 1 is to investigate whether the CEE derived from young adult rats improve cognitive function in the aged-DM rat, when the CEE is administered at an early (2 months) or advanced (4 months) stage of DM in aged male and female rats. Aim 2 is to investigate whether the CEE treatment improves cerebral vascular function and enhances neurogenesis and oligodendrogenesis in the aged-DM rat. Cerebral vascular patency and integrity, neurogenesis and oligodendrogenesis will be measured. Aim 3 is to investigate whether treatment of the aged-DM rat with tailored endothelial exosomes carrying elevated miR-1 and miR146a further enhances vascular function, neurogenesis and oligodendrogenesis as well as cognitive function. We will generate the tailored CEE and then administer the tailored CEE to aged-DM rats. These studies are innovative and highly clinically relevant.
Principal Investigator: Zheng Gang Zhang, M.D., Ph.D.
Ac-SDKP for Treatment of Acute Stroke (R01NS079612)

Stroke is a leading cause of death and disability worldwide and approximately 72% of people who suffer a stroke are over the age of 65. Tissue plasminogen activator (tPA) is the only drug approved by the Food and Drug Administration (FDA) for treatment of acute stroke (within 4.5h). The most feared complication after tPA treatment of stroke is an increased risk of cerebral hemorrhage. Our preliminary data indicate that N-acetylseryl-aspartyl-lysyl-proline (Ac-SDKP), a peptide normally presented in human plasma, in combination with tPA reduced infarct volume by more than 50% and improved neurological outcome, but did not increase the incidence of hemorrhagic transformation in young adult rats. In this application, we propose to develop a combination therapy of Ac-SDKP and tPA for treatment of acute stroke in aged rats and to investigate molecular mechanisms underlying the combination therapy on the neurovascular unit. In Specific Aim 1, using MRI and 3D laser confocal microscopy, we will investigate the effect of Ac-SDKP alone and Ac-SDKP in combination with tPA on recanalization of the occluded MCA, cerebral microvascular perfusion and vascular integrity, brain hemorrhage, and ischemic neuronal damage in aged rats subjected to embolic middle cerebral artery occlusion (MCAO). In Specific Aim 2, we will examine whether Ac-SDKP suppresses the ischemia- and tPA-activated nuclear transcription factor-κB (NF-κB) pathway in cerebral vessels, which leads to enhancement of cerebral microvascular patency and integrity by reduction of thrombosis. In Specific Aim 3, we will examine whether Ac-SDKP blocks the ischemia- and tPA-activated transforming growth factor β (TGFβ) signaling pathway in cerebral vessels and astrocytes, which leads to reduction of thrombosis by down regulation of plasminogen activator inhibitor1 (PAI-1). These studies could potentially provide a new therapy to minimize the adverse effect of tPA on ischemic neurovascular damage, leading to improved neurological outcomes after acute stroke.

Neurosurgery

Principal Investigator: Meser Ali, Ph.D.
Treatment of Glioma with Nanocombretastatin with MRI Monitoring (R01CA206190)

Glioblastoma (GBM) is a highly aggressive hypervascularized brain tumor characterized by high recurrence rates and poor prognosis despite advanced treatment. The vasculature of GBM is fundamentally different from that of normal vasculature and offers a unique target for anti-cancer therapy. Therefore, direct targeting of tumor vasculature with vascular disrupting agents (VDAs) is distinctly different from anti-angiogenic strategies, and offers a complementary approach to standard therapies. Combretastatin A4 (CA4) is a potent vascular disrupting drug. CA4 induces rapid shutdown of tumor blood supply, typically promoting a necrosis at the core of the tumor, but leaves a rim of viable tumor cells at the periphery which can then rapidly re-grow. However, CA4 is not effective in inducing necrosis at the core of GBM tumor. The ineffectiveness of small molecule chemotherapy drugs in treating malignant brain tumors has been attributed to the blood-brain barrier (BBB) being a significant impediment to the transvascular extravasation of drug fraction across the barrier into the extravascular compartment of tumor tissue and the high tumor interstitial fluid pressure also presents an additional delivery barrier. Nanotechnology is already benefiting to deliver drugs across the BBB and into brain tumors. We have engineered a nano-sized polymeric CA4 conjugate which demonstrates high water solubility. Preliminary intravenous (i.v.) delivery of G3-CA4 in an orthotopic glioma model demonstrated necrosis at the core of the tumor leaving a rim of viable tissue. By applying the designed nano-prodrug strategy and tumor-specific prodrug activation mechanism, we observed the true success of inducing necrosis at the core of the tumor in an orthotopic U-251 glioma animal model first time. Tumor-VDAs have significant potential when combined with cytotoxic chemotherapy and radiotherapy in treating other tumor models. Combined treatment with radiation is attractive, as radiation therapy (RT) represents a standard of care and RT should effectively kill the well-oxygenated cancer cells in the well-perfused tumor rim. We have shown that GBM cancer stem cells are sensitive to radiation exposure in culture and a single dose of 50Gy irradiation yielded necrosis in primary GBM rat model. Therefore, this study is extended to include SRS and standard cytotoxic temozolomide (TMZ) therapies with G3-CA4. We hypothesize that the combination of G3-CA4 with SRS and TMZ will show synergistic cytotoxic effect in
clinical relevant primary GBM model. Our objectives of the proposed research are A) To incorporate CA4 molecules with dendrimer-based nanoparticles (G3-CA4) that demonstrates full solubility in aqueous media, B) To determine the efficacy and safety of small molecule CA4, CA4-P and G3-CA4 nano-prodrug in U251 glioma tumor model, C) To determine the efficacy and safety of G3-CA4 alone or in combination with SRS in primary GBM, D) To determine the efficacy and safety of a combined G3-CA4 and standard TMZ therapy in primary GBM model. The overall therapeutic effect from G3-CA4 alone or in combination with SRS/TMZ will be evaluated by image-guided MRI monitoring of long-term survival rats.

Principal Investigator: Meser Ali, Ph.D.
Extracellular pH Mapping as Therapeutic Readout of Nanoparticle-based Drug Delivery in Glioblastoma (R01EB023366) Subcontract

Extracellular acidosis (i.e., low pHe) is a tumor microenvironment hallmark, caused by atypical metabolism and perfusion. Acidic pH enhances cancer growth, proliferation, and builds therapy resistance. The prognosis remains dismal for most brain tumor patients. Malignant gliomas, including glioblastoma multiforme (GBM), fail treatments because gliomas invade outside tumor boundaries conventionally demarked by MRI contrast and the blood-brain barrier (BBB) blocks most drugs. Furthermore conventional MRI methods are insensitive to physicochemical parameters like pHe and mainly track intratumoral volume. Among the primary MRI methods are paramagnetic agents for longitudinal (T1) contrast, where assessment of treatment response involves 2D or 3D measurement with Gd3+ enhanced MRI contrast. However, such methods are not reliable in distinguishing pseudoprogression and pseudoresponse from actual changes in tumor status. Thus there is an urgent need for alternative MR techniques sensitive to metabolic changes, which can aid in effective monitoring of therapeutic response in addition to measuring the tumor size. Because acidic pH milieu is conducive to tumor growth and builds resistance to therapies, simultaneous mapping of pHe inside and outside the tumor (i.e., intratumoral-peritumoral pH gradient) is an important cancer imaging need. A novel way to map intratumoral-peritumoral pH gradient is using lanthanide III (Ln3+) agents with BIRDS methods, where physicochemical factors like pHe contribute to shifts of non-exchangeable protons. To meet the need for MR readouts of the tumor physicochemical state, we developed BIRDS to map the intratumoral-peritumoral pH gradient, and found that it is a sensitive readout of cancer growth and treatment. Based on preliminary data obtained from GBM models (e.g., U251), including patient-derived xenograft (PDX) models, we will validate high-resolution pHe mapping with BIRDS as therapeutic readout of chemotherapy drugs delivered into human GBM models. Although we detected 1-2 mm diameter tumors with BIRDS using non-methylated agents, higher resolution mapping of intratumoral-peritumoral pH gradients will be reached with a novel methylated multiplexed agent in Aim 1. In Aim 2 we will validate intratumoral-peritumoral pH gradient mapping by BIRDS with fluorescent pH probes. We will use BIRDS to examine how intratumoral-peritumoral pH gradients change with tumor aggression (Aim 3). We will also test compatibility of pHe mapping with BIRDS for tracking response to chemotherapy drugs (e.g., Temozolomide and Sorafenib) being used to treat GBMs (Aim 4). Both of these drugs are known to cross the BBB and are used in GMB therapy. Temozolomide activates apoptosis by alkylating DNA to stall cell replication and Sorafenib is a multiple kinase inhibitor targeting several oncogenic pathways and enhances glycolysis. If successful, pHe mapping by BIRDS will enable monitoring of therapeutic response of various chemotherapy drugs for preclinical PDX models to potentially be translated clinically.

Orthopaedics/Bone & Joint

Principal Investigator: Yener Yeni, Ph.D.
A Clinically Viable Noninvasive Method for Direct Measurement of Mechanical Strains in Vertebral Bone (R21AR070363)

Mechanical strains experienced at the tissue level are intimately related to the mechanical integrity of whole bones and their response to environmental and interventional stimulus. Techniques for measurement of trabecular strains in an entire cancellous bone volume have been developed for
laboratory studies of excised bones that can be performed using high resolution imaging systems such as microcomputed tomography (μCT). These methods involve comparing high-resolution images of bones taken under loaded and no-load conditions and, through advanced mathematical computations, calculation of tissue strains (digital volume correlation, DVC). Thus far, it has not been possible to apply DVC methodologies to human spines in vivo, due to issues with resolution, radiation exposure and the need for a safe, yet effective mechanical loading protocol within the clinical imaging modality. Modern digital tomosynthesis (DTS) systems have the characteristics needed to be able to perform strain mapping in vivo but this has never been tried. With the overall hypothesis that DTS-based strain mapping is feasible and informative, the following aims are proposed to rigorously optimize, validate and demonstrate utility in human spine through a set of in vitro and in vivo experiments: **Aim 1:** Identify the strain levels that can be measured with DTS-DVC under physiologically relevant load magnitudes by using human cadaveric vertebral bodies and comparison to μCT based DVC μCT will serve as the gold standard for optimizing values of DVC analysis parameters for a DTS application, determining thresholds for admissible strain values to maximize measurement accuracy and precision and identifying strain components to be further validated in the later stages of the research. **Aim 2:** Determine the extent to which DTS-DVC performed under a clinically applicable loading protocol predict vertebral strength and energy to failure independent from bone density. Using in vitro destructive mechanical test results as gold standard outcome, this aim will determine the relative efficacy of strain components for improving prediction of mechanical failure in cadaveric vertebrae and define margins of error for these predictions. **Aim 3:** Determine the range of in vivo vertebral strains measured with DTS-DVC in a sample of human subjects with a vertebral deformity and those without. Testing the ability of DTS-DVC to discriminate between cases with a predictable strain outcome from those that are normal will provide in vivo proof of concept. Through comparison of in vivo and in vitro strains, it will be possible to estimate the error in predictive models to be tested in future clinical studies. Development of the DTS-DVC methodology through the proposed aims is expected to substantially improve understanding of etiologies of age- and disease-related bone and joint degeneration, assessment of fracture risk and assessment of efficacy of therapeutic and surgical interventions aiming to restore bone function.

**Pathology**

Principal Investigator: Azadeh Stark, Ph.D.,
Molecular Markers of Risk of Subsequent Invasive Breast Cancer in Women with Ductal Carcinoma In Situ (R01CA218429) Subcontract

Ductal carcinoma in situ (DCIS) is considered to be a non-obligate precursor of invasive breast cancer (IBC). Use of screening mammography has led to a substantial increase in detection of DCIS over the past 2-3 decades. About 5-14% of patients diagnosed with DCIS and treated with breast-conserving therapy, with or without radiation, develop an ipsilateral IBC and 1-6% develop a contralateral IBC over a period of 10 years. However, natural history studies have shown that, in the absence of treatment, 14-53% of DCIS cases develop IBC if followed for up to ~30 years. Treatment of DCIS is variable, and many DCIS patients are either under- or over-treated. Elucidation of the molecular changes detectable in DCIS lesions that are associated with risk of IBC development is critically needed, as this may help not only to reduce risk of development of IBC but also to prevent overtreatment of patients with lower risk of IBC. In this regard, a multigene expression assay, consisting of genes related to proliferation, as well as PR and GSTM1, was recently shown to predict risk of subsequent ipsilateral IBC in women with DCIS. Similarly, immunohistochemically-detected expression of p16, COX-2, and Ki67 has also been associated with increased risk of IBC development. However, these findings require confirmation. Furthermore, novel prognostic (and ultimately predictive) markers may emerge from assessment of gene expression patterns on a global scale. In this regard, microRNAs (miRNAs), which are noncoding RNAs that are master regulators of gene expression, are thought to contribute to the development of invasive cancer. Against this background, our overarching goal is to facilitate early detection of patients with DCIS at risk of IBC development. To this end, building upon our previous work, we propose to use clinical data and archived formalin-fixed paraffin-embedded (FFPE) tissue from a large, population-based multi-center cohort of 7,275 patients initially diagnosed with DCIS in community-based health plans and followed for subsequent IBC development, to identify and then validate miRNA expression changes associated with risk of subsequent IBC, to evaluate risk of IBC in association with 2 previously
identified sets of markers (Oncotype DX DCIS score; positivity for p16, COX-2, and Ki67 protein expression), and to examine the association between clinical factors and risk of subsequent IBC in the largest such study to date. Our molecular epidemiologic study, which proposes to apply state-of-the-art technologies to archived DCIS FFPE specimens for the detection of molecular changes associated with risk of IBC development in a large, multi-center population-based cohort of women initially diagnosed with DCIS, has the potential to lead to approaches that will help to refine identification of women who need enhanced surveillance and early aggressive treatment.

**Radiation Oncology**

**Principal Investigator: Mohamed Elshaikh, M.D.**

**Molecular Classification of High Grade Endometrial Cancers: Extending TCGA Findings to a High Risk Population (R01CA200864) Subcontract**

To update the Henry Ford Health System database for patients with endometrial cancer that includes more than 1,900 women in regards to the different prognostic factors including treatment factors in addition to survival data. Additionally, to identify the patterns of recurrence for those who receive no treatment after surgery compared to those who received radiation treatment chemotherapy for a combination of both. To identify patients who are at higher risk for recurrence based on the known prognostic factors. To conduct data analysis and reporting of the results.

**Principal Investigator: Carri Glide-Hurst, Ph.D.**

**Development of Anatomical Patient Models to Facilitate MR-only Treatment Planning (1R01CA204189)**

Accurate delineation of targets and organs at risk for radiation therapy planning (RTP) remains a challenge due to the lack of soft tissue contrast in computed tomography (CT), the standard of care imaging for RTP. Radiation Oncology has addressed this limitation by registering magnetic resonance images (MRI) to CT datasets to take advantage of the superior soft tissue contrast afforded by MRI. MRI brings considerable value to RTP by improving delineation accuracy which, in turn, has enabled dose escalation to improve local control while maintaining or reducing normal tissue toxicities. However, the current integration of MRI as an adjunct to CT has significant drawbacks as it requires image registration and contour transfer between datasets. This process introduces systematic geometric uncertainties that persist throughout treatment and may compromise tumor control. Thus, we propose to translate MR-only RTP into clinical use, with the ultimate goal of improving patient outcomes accomplished via improved treatment plan design. MR-only RTP will eliminate redundant CT scans (reducing dose, patient time, and costs), streamline clinical efficiency, entirely circumvent registration uncertainties, and fully exploit the benefits of MRI for high-precision RTP. Yet, MRI is not routinely used alone for RTP, largely due to its known spatial distortions, lack of electron density, and inability to segment the bone needed for online image guidance and electron density mapping for dose calculation. The central hypothesis is that the innovative technologies that our multi-disciplinary academic/industrial (Henry Ford Health System/Philips Healthcare) collaboration develop will yield geometrically accurate patient models built from MRI data across several platforms/field strengths with CT-equivalent densities that can be used in confidence throughout the entire RTP workflow. In Aim 1, we will perform geometric distortion corrections, determine distortion variability with changing anatomy, benchmark the results in a novel modular phantom, and develop an image processing toolkit. In Aim 2, we will fully automate MR image segmentation in the brain and male/female pelvis to yield accurate synthetic CT patient models derived from novel MRI sequences, including provisions for metal implants, and benchmark the results in phantom. In Aim 3, we will conduct end-to-end testing to characterize the uncertainties in the MR-only RTP workflow. We will perform a virtual clinical trial of MR-only RTP for brain and male/female pelvis and compare to the standard of care. Final translation will include developing physician-physician practice guidelines, end-user validation of all translational steps, and dissemination of image processing tools into the Radiation Oncology community. This research will systematically address the major challenges limiting MR-only RTP and lay the groundwork for multi-institutional clinical trials across MRI platforms. It will support future work related
to MR-guided RT, functional MRI for biologically adaptive RT, and focal RT to areas of high tumor burden.

Principal Investigator: Brent Griffith, M.D.
A Pragmatic Trial of Lumbar Image Reporting with Epidemiology (LIRE) (UH3AR066795) Subcontract

Low back pain, an Institute of Medicine priority condition for comparative effectiveness research, is of major public health importance. It is one of the most common reasons for physician visits and an important cause of functional limitation and disability. Imaging is frequently performed as part of the diagnostic evaluation and is an important contributor to the cost of back pain care, which totaled more than $86 billion in 2005. It is well known that, even without back pain, magnetic resonance (MR) imaging of the lumbar spine frequently reveals findings such as disc desiccation or bulging. Patients and their providers may attribute greater importance to these findings, which are often age-related, than they should, because they do not have an appropriate frame of reference in which to interpret the findings. These incidental findings may initiate a cascade of events leading possibly even to surgery, without improving patient outcomes. We propose a pragmatic, randomized controlled trial (RCT) to determine the effectiveness of inserting epidemiological benchmarks into imaging reports at reducing subsequent tests and treatments. Our rationale is that providing a context for both physicians and patients to better interpret imaging findings may reduce concern about incidental findings and reduce unnecessary further diagnostic tests and treatments. Our intervention is simple, inexpensive and easy to deploy. We propose an efficient, novel, cluster randomized design referred to as a stepped wedgedesign, permitting longitudinal comparisons while controlling for temporal trends. As called for in the Request for Applications, we plan to passively collect primary outcome measures of healthcare utilization both pre- and post-intervention, using robust electronic medical records at our participating sites. We hypothesize that for patients of primary care providers, inserting epidemiological benchmarks in lumbar spine imaging reports will reduce subsequent diagnostic and therapeutic interventions, including MR and CT, opioid prescriptions, spinal injections and surgery. The rationale is that the epidemiologic data may provide a context for both physicians and patients to better interpret imaging findings. The long-term public health significance is high. Not only may this simple, inexpensive intervention substantially reduce unnecessary and expensive care for back pain; thee intervention can easily be generalized to all diagnostic tests, and could become the dominant paradigm for communicating diagnostic information.

Principal Investigator: Jae Ho Kim, M.D.
Improving the Radiation Therapeutic Ratio by Inhibiting Proinflammatory Cytokines (R21CA205660)

The goal of the proposal is to determine the potential of a new class of compounds, selective inhibitors of dysregulated proinflammatory cytokines/chemokines, to increase the therapeutic gain for cancer patients receiving radiotherapy for tumors that are known to be radiation resistant (e.g. malignant brain tumors, pancreatic cancer, and lung cancer - stage III/IV). The exploratory proposal builds on our previous discoveries that the lead cytokine/chemokine inhibitor mitigates radiation injury in multiple tissues and the same compound confers an enhancement in radiation tumor growth delay. Two specific aims are planned to confirm the studies in orthotopic tumor models and to elucidate the mechanism of action. In Aim 1, we test the hypothesis that the inhibitor when administered to rats with brain tumors enhances the radiotherapy efficacy and reduces the radiation injury to normal brain. We aim to determine if the therapeutic ratio of a cytokine inhibitor combined with radiation is superior to radiation alone. In Aim 2, we test the hypothesis that the inhibitor suppresses acute proinflammatory cytokines including those produced by activated macrophage in the tumor tissue and reduces neuroinflammation caused by activated microglia in the normal brain following radiation. We aim to elucidate the mechanism of action of a cytokine inhibitor's effects on the radiation response of tumor and normal brain following single and fractionated radiation. At the completion of these studies we expect that a new paradigm for improving radiation therapy will have been initiated.
Part III – Population and Health Sciences

- Center for Health Policy and Health Services Research
- Department of Public Health Sciences

Center for Health Policy and Health Services Research

Principal Investigator: Brian Ahmedani, Ph.D.

A Targeted Approach to Safer Use of Antipsychotics in Youth (HHSN271201600002C) Subcontract

The National Institute of Mental Health (NIMH) and the National Institutes of Health (NIH) seek to launch a research initiative to address the rising use of antipsychotic medications by youth who do not suffer from a psychotic disorder. Most of the antipsychotic use in communities is for the management of non-psychotic conditions. Antipsychotic use increases the risk of metabolic syndrome and consequently, higher rates of obesity and diabetes. Additionally, the long-term implications of antipsychotic use in youth are unknown. For these reasons, efforts should be made to develop successful alternative treatment approaches that allow a more targeted and appropriate use of antipsychotics with the goal to minimize their usage by youths who do not suffer from a psychotic disorder.

The objective of this study is to successfully identify alternative treatments to the use of antipsychotics in youth (ages 5-17) that are not psychotic, which can manage the emotional and behavior disturbances of these children and adolescents.

The initiative is articulated around the following specific objectives, which will function as sequential phases (i.e., contract options):

A. PHASE 1 - Develop an algorithmic approach to the treatment of non-psychotic behavioral and mood disturbances of youth that minimizes antipsychotic exposure by using non-antipsychotic interventions first and, in case of use of antipsychotics, limiting their use to acute stabilization.

B. PHASE 2 - Pilot-test the algorithm(s) for feasibility, acceptability, preliminary effectiveness.

C. PHASE 3 - Test the effectiveness of the algorithmic approach vs. usual care in practice settings, using a mental health research network, and identify moderators and mediators of treatment outcome.

Principal Investigator: Brian Ahmedani, Ph.D.

Treatment Utilization Before Suicide (TUBS) (R01MH103539)

Adult suicide rates in the United States rose by almost 30 percent between 1999 and 2010. These rates have not markedly improved in decades. To date, previous suicide attempts and psychiatric diagnoses are largely the only known clinical risk factors for suicide death. Recent research shows that most individuals who die by suicide make a health care visit in the weeks and months prior to their death. Most of these visits occur in primary care or outpatient medical specialty settings. However, over half of these visits do not include a psychiatric diagnosis.

Thus, there is limited evidence available from health care users in the US general population to inform targeted suicide screening and risk identification efforts in general medical settings. New research is needed to investigate the general medical clinical factors associated with increased suicide risk among individuals without a known risk factor. This research project uses data on more than 4000 individuals who died by suicide and made health care visits to one of eight health care systems across the United States in the year prior to their death. These health systems are
members of the Mental Health Research Network and have affiliated health plans. They are able to capture nearly all health care for their members via the Virtual Data Warehouse (VDW). The VDW consists of electronic medical record and insurance claims data organized using standardized data structures and definitions across sites. These data are matched with official regional mortality data. This project includes the following specific aims:

1) identify clinical factors from general medical visits prior to suicide across sites, 2) compare clinical factors to a matched sample of health care users across sites, and 3) investigate indications of psychiatric and other concerns in general medical chart notes prior to suicide. This is the first study with a large enough sample in the US general population to be able to study general medical treatment utilization prior to suicide death. This project will allow the identification of previously unknown factors that increase risk of suicide death, including general medical diagnoses, medications, health care procedures, and types of visits. These results will inform decisions about how to focus suicide prevention efforts in general medical settings.

Principal Investigator: Brian Ahmedani, Ph.D.
An Evaluation of the National Zero Suicide Model Across Learning Healthcare Systems (U01MH114087)

Suicide is a major public health concern – it is the 10th leading cause of death and number one cause of injury related death in the United States (US). Due to national concern about this problem, the National Action Alliance for Suicide Prevention and the US Surgeon General published the joint 2012 National Strategy for Suicide Prevention (NSSP). The NSSP outlines a series of Aspirational Goals (AG) with the specific objective to reduce the national suicide rate by 20%. AG 8 and 9 promote healthcare settings as primary targets for suicide prevention. Consistent with this message, Henry Ford Health System’s (HFHS) Perfect Depression Care (PDC) Zero Suicide Initiative was the first US program linked with a substantial decrease in the suicide rate among behavioral health patients after implementation. These findings have motivated national promotion of this model for suicide prevention in health systems. As such, the National ZS Model (NZSM) was developed, based on the HFHS PDC program, but with flexibility to allow adaptation to diverse settings and patient populations. Overall, the NZSM is founded on the realization that suicidal individuals often fall through multiple cracks in a fragmented and sometimes distracted healthcare system, and on the premise that a systematic, comprehensive approach to care is necessary for suicide prevention. The comprehensive approach of the NZSM includes implementation of a series of clinical and quality strategies within the following components: 1) Identification of those at-risk, 2) Engagement and care management; 3) Effective treatment, and 4) Care transition. Despite being a model program promoted internationally for healthcare system quality improvement in suicide prevention, the NZSM has very limited evidence outside of the findings from the HFHS PDC program. The proposed study seeks to conduct a comprehensive process and outcome evaluation of NZSM implementation in real-world clinical settings across 6 large, diverse Mental Health Research Network affiliated Learning Healthcare Systems providing healthcare for over 9 million individuals each year. The project aims are to: 1) Collaborate with health system leaders to develop EHR metrics to measure specific quality improvement targets and care processes tailored to local NZSM implementation, 2) Examine the fidelity of the specific NZSM care processes implemented in each system, and 3) Investigate suicide attempt and mortality outcomes within and across NZSM system models. Study data are captured using electronic health records and insurance claims. Given strong national support for NZSM, if it is found to be effective to reduce suicide behavior, this model will have nationwide implications for suicide prevention in healthcare settings.

Principal Investigator: Brian Ahmedani, Ph.D.
Mental Health Research Network II (U19MH092201) Subcontract

This application requests five years of funding to sustain and expand the Mental Health Research Network (MHRN), a consortium of 13 research centers affiliated with large integrated health systems. Two new members will join the network, increasing the diversity of health system organization and adding a larger rural population. Established data and informatics infrastructure will be maintained (with
reduced levels of funding). New infrastructure development will aim to address the opportunities and
challenges described above and to address specific goals described in RFA MH-14-110: * Dissemination of MHRN tools and resources to the broader mental health research community * Facilitating new research collaborations with investigators outside of MHRN member institutions * Improving capacity for ongoing surveillance of mental health treatment patterns and outcomes MHRN will be governed by a steering committee of participating investigators and representatives from NIMH. An Administrative Core will house specific infrastructure activities, including: The Informatics Unit will maintain and expand data infrastructure to support multi-site research. The Organizational Unit will continue work to streamline administrative and regulatory processes. The Outreach and External Collaboration Unit will continue engagement with health system partners and external stakeholders while expanding outreach to external investigators. Four specific research projects are proposed: Reducing cardiovascular risk in adults with SMI using EMR-based clinical decision support - This cluster randomized trial will test an informatics-based intervention to reduce risk factors for cardiovascular disease among people living with severe mental illness. Maximizing biospecimen collection from children with mental health conditions - This pilot study will evaluate strategies for collecting biospecimens from families affected by early-onset mental disorders. Next-generation assessment using mobile devices - This pilot study will evaluate the feasibility, acceptability, and potential utility of direct assessment of behavior and neuropsychological performance (including NIMH RDoC constructs) for prediction or early detection of depression treatment response. Automated outreach for depression treatment dropout - This pilot study will evaluate the feasibility and acceptability of population-based outreach to address early dropout from depression treatment.

**Principal Investigator: Jordan Braciszewski, Ph.D.**

**Promoting Smoking Cessation Among Youth Exiting Foster Care (R21CA205190)**

Each year, roughly 30,000 youth exit the foster care system due to “aging out” at age 18, losing access to support services while also becoming fully responsible for their own financial, health, employment, and housing needs. Progressing from homes disproportionately high in neglect and maltreatment, these emerging adults face independence with an increased likelihood of heavy tobacco use and, ultimately, the development of tobacco use disorders. Indeed, lifetime tobacco use is nearly ubiquitous among foster youth, while daily use rates are four times that of the general population. Services to curtail such use while young people remain in the foster care system are severely limited, if they are offered at all. Once removed from foster care, these youth have far less access to health services compared to their non-foster care peers. The proposed feasibility study seeks to address these gaps in availability, accessibility, and use of tobacco cessation services for youth aging out of the foster care system.

Computer- and mobile phone-based interventions have the capacity to provide evidence-based treatment content while reducing many of the barriers relevant to tobacco cessation service delivery for foster youth. The proposed study will begin a program of research to synthesize the benefits of these approaches in a way that addresses the needs of a vulnerable population who experience tobacco-related health disparities. More specifically, this study seeks to test an adaptation of an existing substance use intervention (iHeLP: Interactive Healthy Lifestyle Preparation) for smoking cessation among youth aging out of foster care. Rooted in motivational interviewing, the transtheoretical model, and social cognitive theory, iHeLP is a one-time computerized screening and brief intervention (SBI), supplemented by six months of tailored text messaging based on participants’ SBI results and subsequent fluctuations in their readiness to change. The goal of this pilot study is to obtain data on acceptability and feasibility of a novel intervention, as well as examine direction of effects on both overall motivation to change and actual tobacco use. As such, we will conduct a two-arm feasibility trial, testing iHeLP against a contact-control condition. The use of daily text messaging represents a novel method for delivering intervention boosters. Low-intensity, high-frequency interactions are a marked change from traditional interventions and have high potential for extending initial gains. In addition, tailoring of these messages through dynamic, text-based communication with participants is innovative. Given the potential of wide dissemination to multiple at-risk populations at low cost, the proposed study has high potential public health and clinical significance.
Alcohol use puts adolescents with suicide-related thoughts and behaviors at high risk for attempted suicide and suicide death. Typically, adolescents who make a suicide plan or attempt are admitted to an inpatient psychiatric hospital for a brief time period in order to be evaluated. These inpatient units rarely address alcohol use in a comprehensive fashion as the adolescent's suicide risk is the primary focus of treatment. Given the significant role alcohol can play in subsequent suicidal ideation and attempts, greater attention to the assessment and initial treatment of alcohol use in adolescent inpatient psychiatric settings is essential, with a post-discharge follow-up plan playing a critical role in the safety of the suicidal adolescent. The proposed study will develop and test iASIST (integrated Alcohol and Suicide Intervention for Suicidal Teens), a novel adjunctive intervention for alcohol use and alcohol-related suicidal thoughts and behaviors. iASIST involves three components: 1) one 60-90 minute individual intervention with the adolescent in which motivational enhancement techniques are used to explore alcohol use as a risk factor for continued suicide-related thoughts and behaviors, build the adolescent's motivation to reduce or stop their alcohol use, and create a change plan if the adolescent is ready, 2) a subsequent 30 minute family intervention in which the interventionist facilitates a discussion between the adolescent and the parent about the change plan using motivational enhancement techniques to align the parent with the adolescent to strengthen the adolescent's self-efficacy and commitment to the change plan as well as the parent's confidence and ability related to supporting the adolescent in the change plan, and 3) a post-discharge mHealth booster to adolescents focused on strengthening their commitment to the change plan, and to parents focused on their commitment, confidence, and ability related to supporting the adolescent in the change plan. First, we will refine the design of the mHealth booster by obtaining feedback on proposed content, interface, and functionality via in-depth interviews with 8 adolescents and 8 parents who completed the intervention arm of PI O'Brien's current pilot trial of the in-person component of iASIST. Second, we will conduct an open trial of iASIST with 10 adolescents and their parents to test the full adaptation of iASIST (i.e., in-person sessions and mHealth booster) and make subsequent changes for the final study phase. Third, we will conduct a randomized trial with 50 adolescents and their parents to test the feasibility and acceptability of iASIST as well as alcohol- and suicide-related outcomes at 3 months post-discharge. Intervention participants will be compared to adolescents and their parents who will receive an attention-matched comparison condition focused on a post-discharge mHealth control targeting the maintenance of a healthy lifestyle. The data from this project will inform the preparation of a fully powered, future trial of the intervention.

Each year, roughly 30,000 youth exit the foster care system due to aging out at age 18, losing access to support services while also becoming fully responsible for their own financial, health, employment, and housing needs. Progressing from homes disproportionately high in neglect, maltreatment, and parental substance use, these emerging adults face independence with an increased likelihood of developing substance use disorders. Once removed from foster care, these youth have far less access to health services compared to their non-foster care peers. Moreover, substance use services offered within the foster care system are often difficult to access. The proposed pilot intervention study seeks to address these gaps in availability, accessibility, and use of substance use services for youth aging out of the foster care system. Computer- and mobile phone-based interventions have the capacity to provide evidence-based treatment content while reducing many of the barriers relevant to substance use service delivery for foster youth. The proposed study will begin a program of research to synthesize the benefits of these approaches in a way that addresses the needs of a vulnerable population with many barriers to care. More specifically, this project involves the development and pilot data collection of a preventive intervention (iHeLP) targeting the reduction of problematic substance use among foster youth who are aging out of care. Rooted in motivational interviewing, the
transtheoretical model, and social cognitive theory, iHeLP is a one-time computerized screening and brief intervention (SBI), supplemented by six months of tailored text messaging based on participants’ SBI results and subsequent fluctuations in their readiness to change. The goal of this pilot study is to obtain preliminary data on acceptability, feasibility, and initial efficacy. Focus groups will be conducted in which twenty four 17-year old foster youth will provide qualitative feedback on the perceived utility, likelihood of use, and preferences for the content, interface, and functionality of the proposed intervention components. Results will be used to modify the intervention content/format, which then will be delivered to sixteen foster youth in an open trial of iHeLP. Further alterations may result from the qualitative and quantitative results of the open trial. Finally, thirty youth will participate in a pilot randomized controlled trial, testing the efficacy of iHeLP against a contact-control condition. The use of daily text messaging represents a novel method for delivering intervention boosters. Low-intensity, high-frequency interactions are a marked change from traditional interventions and have high potential for extending initial gains. In addition, tailoring of these messages through dynamic, text-based communication with participants is innovative. Given the potential of wide dissemination to multiple at-risk populations at low cost, the proposed study has high potential public health and clinical significance.

Principal Investigator: Keoki Williams, M.D.
Combined Transcriptomics and Genomics to Find Asthma Genes in Admixed Populations (R01HL118267)

African American individuals are more likely to develop asthma and are nearly three times as likely to experience serious asthma complications when compared with European American individuals. Genome wide association studies have identified a number of genetic risk markers for asthma, but many of the associations observed in European and European American patients have not replicated in African American individuals. This may be the result of allele frequencies, linkage disequilibria, or disease-related genes which differ by ancestry. Detailed characterization of the transcriptome can aid in the identification of asthma-related genes by circumventing some of the aforementioned problems associated with genotype association alone. Therefore, this proposal seeks to combine transcriptomics and genomics to identify asthma-related genes and the expression quantitative trait loci (eQTL) which appear to regulate these genes. We propose using RNA sequencing (RNA-seq) to characterize the transcriptome of African American individuals with and without asthma. RNA-seq is superior to traditional microarrays at quantifying transcript abundance, but this method has not been widely used in U.S. minority populations to date. The Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE) cohort is an ideal group in which combine these analytic approaches. In addition to being one of largest and best characterized asthma cohorts in the U.S., genome wide genotype data and banked whole blood RNA already exist for a large number of SAPPHIRE participants. In Specific Aim 1, we will use RNA-seq to identify expression differences in previously identified asthma-related genes among African American individuals by asthma status. Pre-existing genotype data will then be used to identify eQTL for these differentially expressed, asthma-associated genes. In Specific Aim 2, we will use admixture mapping to identify chromosomal regions where ancestry is associated with asthma. The genes in these regions will be interrogated for differential expression by asthma status. The resulting potentially novel, ancestry-specific asthma genes will also be assessed for eQTL. As a subset of African American SAPPHIRE participants have RNA collected at both their initial evaluation and the time of an asthma exacerbation, in Specific Aim 3 we will assess whether the genes identified in the preceding aims are also associated with asthma exacerbations. Lastly, Specific Aim 4 will attempt to replicate our findings in a separate group of African American participants with and without asthma. In summary, asthma is a complex disease with potentially distinct genetic predictors by ancestry. Persisting inequities in asthma complications by race-ethnicity underscore the need for improved disease biomarkers and therapeutic targets. As a step in this direction, we proffer an integrative approach with greater statistical power to identify asthma-related genes and their regulatory elements.
Diabetes mellitus is a modern day scourge, affecting an ever increasing proportion of individuals worldwide, including 26 million Americans currently. Moreover, type-2 diabetes (T2D) disproportionately affects historically disadvantaged U.S. minority groups, as evidenced by the much higher rates of disease and more severe complications among African American individuals. Although there are multiple therapeutic classes of oral medication available for treating T2D, metformin is currently recommended as the first-line therapy. Metformin lowers blood glucose levels by reducing hepatic gluconeogenesis, improving skeletal muscle insulin sensitivity, and limiting intestinal glucose uptake. It has also been shown to be an effective therapy for preventing incident diabetes. Despite being one of the most frequently prescribed drugs worldwide, very little is known about the biologic mechanism(s) through which metformin mediates its effect. This knowledge would be of value therapeutically to better understand and predict treatment response. By extension, even less is known about the activity of metformin among African American individuals, as few studies have included substantial numbers of non-European population groups. This application will help rectify existing knowledge gaps by studying a large and diverse patient population with T2D. Specifically, we will utilize electronic medical record (EMR) data for large-scale diabetes pharmacogenomics. These data have the advantage of being able to account for medication use and drug exposure over time; to provide substantial numbers of individuals for combined and population group specific analyses; and to assess clinical end-points both retrospectively and prospectively. In this application, we propose the following study aims: 1) To assess whether there are differences in metformin treatment response by self-reported race-ethnicity and genetic ancestry; 2) To use novel, gene-based association approaches to identify both shared and population group specific genetic variants influencing metformin's effect on blood glycemia (i.e., HbA1c levels); and 3) To replicate our findings in a separate group of patients and to include additional exploratory analyses to assess whether the identified genetic variants influence diabetes-related microvascular events, macrovascular events, and adverse drug reactions. The knowledge gained through this study will directly address the goals of Health People 2020 – "achieve health equity, eliminate disparities, and improve the health of all groups."

Department of Public Health Sciences

Principal Investigator: Gwen Alexander, Ph.D.
Encouraging Young Adults to Make Effective Nutrition Choices: MENU Gen Y Study (R01HD067314)

The MENU Gen Y Study will focus on developing an age-targeted web-based intervention designed to increase daily intake of fruit and vegetables for young adults (age 21 – 30 “Gen Y”) using features that appeal to and factors relevant to this targeted age group.

Principal Investigator: Gwen Alexander, Ph.D.
Breastfeeding Support and Weight Management for Black Women: A Dual Intervention (R21HD085138) Subcontract

Excessive pregnancy-related weight retention is an important determinant of obesity and is more common among African American women. At the same time, breastfeeding, which has been recommended as a strategy to decrease weight retention is lowest among African American women. This racial disparity in breastfeeding may partly explain the disparity in obesity, but even if the two are not causally related, a dual intervention designed to increase breastfeeding duration and decrease postpartum weight retention makes practical sense because both are associated with the same critical postpartum time window. For this study, we will incorporate a postpartum weight management component into an effective breastfeeding support program. This dual intervention will use a
combination of in-person, telephone, and interactive web/mobile-based health counseling to provide education and support for breastfeeding difficulties and postpartum weight management. The intervention will be delivered by peer counselors who will be trained to provide support using motivational interviewing techniques with consultation by experts. Additionally, the web-based platform includes tools for tracking diet and physical activity, and is accessible using mobile technology. We have designed the dual intervention to provide encouragement, information, and problem-solving assistance at the appropriate pre or postpartum stage for both breastfeeding support and maternal weight management. The mixed delivery mode has proven effective in other settings and is important to build a trusting relationship while allowing frequent and flexible methods for communicating during this vulnerable time in a new mom's life. The overall goal of this developmental/exploratory R21 proposal is to gather pilot data to effectively refine the intervention so that it can be tested in a larger, longer study using a factorial design in a future R01 phase. We will recruit, in one large inner-city prenatal care clinic (Henry Ford Health System, Detroit, MI), pregnant African American women (32-36 weeks gestation) who are considering breastfeeding (n=80), randomize them to the intervention or to a usual care group, and follow all participants to 20 weeks postpartum. Our specific aims are to: 1) test feasibility; 2) assess acceptability; and 3) estimate the effect size of the intervention at 20 weeks postpartum relative to the usual care group on (1) breastfeeding duration and (2) postpartum weight retention. This project is significant because the combined intervention is designed to work synergistically on two interrelated, highly prevalent problems that disproportionally disadvantage African American families.

**Principal Investigator:** Gwen Alexander, Ph.D.

**Automated Coding of eCoaching Exchanges to Promote Healthier Eating (R21DK108071) Subcontract**

Poor eating habits, particularly low fruit and vegetable intake, is a growing, serious public health concern, particularly among young adults age 21-30, referred to as Generation Y (GenY). GenY’s poor dietary practices are associated with the onset of obesity and many chronic diseases, such as type 2 diabetes, as well as declines in predicted health status and life expectancy. Thus, there is a need to develop effective interventions to improve GenY's eating habits. MENU GenY is a computer-based intervention to encourage increased fruit and vegetable intake among GenY. A critical component of MENU GenY is personalized eCoaching. eCoaches use email to deliver motivation-enhancing coaching to encourage healthy eating, grounded in the principles of Motivational Interviewing (MI), an evidence-based communication technique to increase intrinsic motivation and self-efficacy for behavior change. The MI model posits that counselor's use of “MI-consistent” communication techniques are responsible for eliciting behavior change through patient “change talk” (i.e., statements about one’s own desire, ability, reasons, need for or commitment to behavior change). A growing body of empirical evidence links change talk to behavior change, but research identifying the specific provider behaviors that elicit patient change talk is limited to specific populations (mainly adults who abuse substances and a couple studies of adolescents). Identifying specific communication strategies linked to behavior change and integrating these strategies into communication-based interventions (e.g., brief, motivation-enhancing interventions delivered in a variety of settings or public health initiatives) can increase these interventions’ potency. However, a significant barrier to this research is the qualitative methods traditionally used to analyze the communication process which are resource-intensive, requiring an iterative process of human (subjective) interpretation of text. Rapidly developing computational technologies, specifically machine learning combined with classification models, offer a unique opportunity to accelerate this process. Our research group has recently applied machine learning-based data mining models to similar communication data. We automated a simple communication code scheme to characterize patient communication and achieved accuracy comparable to human coders. The goals of this study are to leverage innovative computer science machine learning and classification models to fully automate the communication coding process and link patterns in eCoach-patient communication to increases in fruit and vegetable intake. We propose a secondary analysis of data collected for a NICHD randomized clinical trial (R01 HD067314). The sample is 160 members of GenY drawn from both urban and rural settings (Detroit metropolitan area and rural Pennsylvania) with outcomes measured at baseline and 3 months. Our validated approach will accelerate the pace of outcomes-oriented communication research and identify effective
Principal Investigator: Andrea Cassidy-Bushrow, Ph.D.
Delivery Mode, Environment and the Gut Microbiome: Influence on Childhood Body Size (R01HD082147)

Caesarean section (CS) delivery, which accounts for ~32% of all US births, has been associated with offspring obesity. Little is known about the mechanisms linking CS with obesity risk. The gut microbiome, which varies by mode of delivery, is also associated with childhood obesity. In our established racially and socioeconomically diverse birth cohort (WHEALS; Wayne County Health, Environment, Allergy and Asthma Longitudinal Study), the early-life gut microbiome is associated with body mass index (BMI) category at age 2 years; CS is associated with both a distinct early-life gut microbiome and with increased BMI at age 2 years; and the presence of pets in the home, which increases microbial diversity, reduces the association between CS and BMI. Our data provide evidence for a mediating role of the gut microbiome in the CS-obesity relationship. However, to provide stronger evidence requires additional study. This project builds on extant data in WHEALS and on-going data collection in a subset of these children to examine the role of the gut microbiome in the CS-obesity association. Children will be invited for a research clinic visit for comprehensive body size assessment and blood draw at age 10-12 years. Gut microbiome composition and predicted function will be measured in banked early-life (1 and 6 months of infancy) stool samples and in samples from these children at age 10-12 years using the 16S rRNA and ITS2 biomarker genes and the Illumina MiSeq platform. A metabolomics analysis will be conducted in a subset of these stool samples. Adiposity will be measured as BMI at ages 2 and 10-12 years, BMI trajectory from birth to age 10-12 years, and anthropometric, bioimpedance and inflammatory measures at ages 10-12 years. Combined, we anticipate 630 unique children will have 10-year adiposity measures and at least one early-life microbiome measure (~405 with 1 month and ~381 with 6 month stool samples, which includes ~300 children with paired 1 and 6 month samples). Of these children, 400 will also have gut microbiome measured at age 10-12 years. Our specific aims are to: (1) examine if mode of delivery is associated with childhood adiposity; (2) examine if the gut microbiome is associated with childhood adiposity; and (3) examine whether the gut microbiome mediates relationships between mode of delivery and measures of adiposity. Such a complementary “omics” approach has never been applied to the study of childhood obesity and is likely to provide critical insights into disease development in early-life as well as potential targets amenable for intervention.

Overall Principal Investigator: Christine Cole-Johnson, Ph.D. Project 3, Project 4
Principal Investigator: Ganesa Wegienka, Ph.D. Project 1
Pets and the Infant Microbiome: Effect on Immune Maturation & Atopic Asthma (P01A1089473)

This Program Project Grant (PPG) study seeks an increased understanding of the relationships between dog or cat exposure during infancy and a lower risk of allergic asthma. We believe that this protective association is related to different patterns of microbial stimulation during immune development. Four synergistic Projects will examine our hypothesis that the presence of pets in a home results in a more diverse bacterial community composition (BCC) of the dust in the home which in turn influences the development of the gut BCC of a newborn infant living in the home. A more diverse gut BCC shifts the maturation of the infant's immune system such that later immune responses are less likely to produce IgE antibody responses and allergic asthma. Project 1 examines the relationships between the presence of a dog or cat in a home, the BCC of dust in the home, the BCC of stools of infants living in homes and allergic sensitization at 2 years of age. An innovative, culture-independent microarray (G3 PhyloChip) will be used to characterize the BCCs utilizing previously collected samples from the ongoing WHEALS birth cohort study. Changes in home BCC following introduction of a dog are also examined. Project 2 will recruit a new birth cohort of children either living with or without a dog, measure infant stool BCC, and follow the cohort with detailed studies of immune function until 18 months of age to determine the impact of dog exposure on immune maturation. Project 3 uses mouse models
of allergic asthma to further examine the influence of house dust from homes with and without dogs on immune responses that result in lung inflammation. The use of mouse models allows more detailed studies of immune functions from multiple compartments of the body than are possible with human children. Project 4 again utilizes the existing WHEALS birth cohort to examine the relationships between dog or cat exposure during the first year of age, 6-month infant stool BCC, and the presence of allergic asthma at 9 years of age. The Projects are supported by five Cores which each provide essential services to all four Projects. Subcontracts to the University of Michigan, UCSF, and Georgia Regents University, as well as the summaries of the Cores are not described here.

Principal Investigator: Christine Cole-Johnson, Ph.D. Project 3:

Allergic asthma is common in Westernized countries and its prevalence has increased greatly during the last century. Interestingly, recent research has shown that exposure to pets during infancy correlates with a lower risk of developing allergy and asthma in later life. In addition, data generated by the PPG investigators have demonstrated that pets can be associated with alterations to the microbiota in house dust. It is well known that soil and dust are ingested by children, and alterations in gut microbiome have been associated with risk for allergic asthma development. In order to further our understanding of the mechanisms that lead to the alterations observed clinically, this project has established and utilized models of pulmonary disease with exposure to dust from homes with dogs versus no pets. Using two different mouse models of allergic asthma (cockroach antigen and ovalbumin), we will study pulmonary immune responses after oral exposure to house dust using samples collected from homes with dogs and without pets. We will test the overall hypothesis that the composition of the dust microbiome from homes with dogs versus no pets differentially alters pulmonary immune responses during allergen exposure by changing the GI microbiota or bacterial community composition (BCC), resulting in systemic changes in antigen presenting cell and bone marrow progenitor cell programming and allergic outcomes. To test this hypothesis, we will specifically focus on clinically relevant mechanisms involved in the ability of pulmonary-derived allergen responses to induce Th2 cytokines, mucus hypersecretion, physiologic changes (AHR), and changes in innate responses locally as well as systemically. Our studies will: 1) establish that exposure of mice to dust from homes with dogs versus no pets will result in differential changes in the GI BCC, 2) demonstrate that the dog dust-altered gut microbiome alters pulmonary allergic responses, 3) establish that the dog dust-induced changes alter dendritic cell responses in the lung, 4) identify that changes in innate responses are a systemic effect by examining bone marrow cell responses, and 5) utilize innovative mouse models to derive the cellular mechanisms of the altered responses. BCC will be measured using the G3 PhyloChip. Thus, these studies, in close collaboration with the other projects in this PPG, will clarify a number of previously unexplored questions and will guide exploration into this novel area of research.

Project 4:

The overall objective of Project 4 is to assess the relationship between exposure to pets, the infant home and gut microbiomes, and allergic asthma at 9 years of age, using an ethnically diverse, population-based general risk birth cohort (the WHEALS cohort). A premise with growing evidence is that lack of exposure to particular patterns of microbial stimuli during early infancy results in a heightened T-helper (Th) 2 response in the maturing immune system, likely due to a suboptimal regulatory capacity, which in turn is associated in childhood with increased immunoglobulin (Ig)E, allergy, and clinical allergic conditions such as asthma. Epidemiological studies have revealed that atopic conditions have increased over the latter half of the twentieth century. Humans, in earlier centuries had lifestyles associated with closer direct contact with soil, animals and other humans, suggesting exposure to environments with richer and more diverse microbiological burdens. We hypothesize that evolutionary adaptation to such microbial exposures with respect to immune recognition and regulation may result in untoward consequences when humans are presented with the different, and probably more limited, patterns of microbial exposures found in modern Westernized societies. Our theory is that in many settings, pets, as well as farm animals in close proximity, render the home microbiome, or bacterial community composition (BCC) to be more similar to early 20th century environments with respect to an increased bacterial richness, diversity and a more even distribution of taxa. This home microbiome impacts
directly through effects on the infant gastrointestinal tract BCC the immunogenesis of the infant and subsequently the development of clinically important outcomes such as childhood atopic asthma. Using a new technology (the G3 PhyloChip), capable of cost-effectively identifying, to a great depth, bacteria in environmental and biological samples, our collaborative team has preliminary data suggesting that the presence of dogs and cats is associated with distinct home and infant gut microbiomes characterized by dramatic increases in bacterial diversity, richness and evenness. Using newly measured outcome variables measured by questionnaire and clinical examinations in the WHEALS cohort, in conjunction with PhyloChip analyses of stored infant stool and dust samples, we will test whether distinct patterns of pet exposure, home microbiome and infant gut microbiome are associated with current allergic asthma at age 9 years.

Principal Investigator: Ganesa Wegienka, Ph.D. Project 1

The overarching hypothesis of Project 1 is that pet ownership is associated with exposure to a wider diversity of bacteria in house dust, and that these exposures profoundly influence the bacterial community composition (BCC) of the infant gastrointestinal microbiome, maturation of immune responsiveness and subsequently, the development of allergy and allergic asthma. This Project thus proposes two population-based studies and a longitudinal panel study to shed light upon mechanisms that may explain the observed protective effects of exposure to household pets during infancy against development of atopy and high total IgE in infancy. We propose to use an advanced, highly sensitive and semi-quantitative method for bacterial detection, the G3 PhyloChip. This method offers an unprecedented capacity for detailed, high-resolution profiling of complex microbial communities, detecting in parallel common and uncommon members of assemblages present in house dust and infant stool samples. For Aims 1 and 2, we propose to examine samples already collected and stored form a large, carefully characterized, racially and socio-economically diverse, cohort of children (the WHEALS cohort). In Aim 1 we propose using an innovative case-cohort design to compare samples from infants who became atopic at age 2 years versus samples form a randomly selected sub-cohort (serving as the control group). Using the sub-cohort in Aim 2, we will determine whether, and in what fashion, bacterial community composition of both house dust and infant stool are impacted by pet-keeping and if they are related to each other. The study of bacteria, or bacterial communities, identified as deriving from dog keeping will be enabled by a small prospective panel study proposed as Aim 3, to analyze the changes in microbial community composition of house dust in child-occupied but previously pet-free households into which a dog is introduced. Because the 16S-rRNAPhyloChipprovides information on relative abundance of every bacterial taxon detected, we aim, through statistical analyses, to take advantage of this semi-quantitative data to identify particular bacterial species as critically important in protection against atopy development.

Principal Investigator: Christine Cole-Johnson, Ph.D.
Personalizing Care for Obese Patients in an Urban Health System (R24HS022417)

Today, patients and providers are presented with more health care options than ever before. There is considerable doubt and lack of understanding of science not only among patients, but also among physicians. Without systematic, evidence-based guidance for the appropriate and efficient use of the multitude of treatment options, as well as the consideration of patient preferences, the rapid growth and complexity of treatments will only add to the existing confusion about which option is best for each individual patient. The objective of the proposed Patient-Centered Outcome Research Center (PCORC) is to fully leverage and further develop the research infrastructure and clinical assets of Henry Ford Health System (HFHS) in order to conduct Patient-Centered Outcomes Research (PCOR). The PCOR evidence will guide care in order to achieve patient-desired outcomes in our urban and suburban patient populations located throughout Metropolitan Detroit. The Center will be organized into four different Cores (Patient Engagement Core, Study Design and Analysis/Measurement Core, Patient Data Network Core, and Implementation/Dissemination Core) with different functions. The Center currently has three PCOR projects proposed that are focused on our selected theme of caring for the obese patient. The HFHS PCORC will maximize programmatic and scientific efficiency within our health care system setting, promote shared use of resources and standardization of processes and
procedures, promote training in PCOR/Comparative Effectiveness Research (CER) methods, and facilitate rapid dissemination of research findings to the medical community and translation of those results into our system's clinical practice.

The Center will build on existing research capabilities by developing expertise in novel PCOR methods through didactic course work, educational sessions at national meetings and content-specific educational seminars. These educational experiences will allow the Center staff to learn how to develop and conduct innovative PCOR studies that will provide evidence for the many pressing issues in patient care. The Center will demonstrate its proficiency through the conduct of the proposed projects.

The proposed PCORC is relevant to public health because it provide research infrastructure and methods for the design and conduct of patient-centered outcome research (PCOR) projects in patients within our health care system. The results of those projects will provide evidence-based and patient-centered guidelines available to physicians in their offices, on a real-time basis in order to ultimately provide care that places each individual patient and his/her preferences at the center of decision-making.

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

Trans-America Consortium of the Health Care Systems Research Network for the Precision Medicine Initiative Cohort Program (1OT2OD024610)

Aim 1: Using our existing network of Patient Advisors and experts, finalize the TACH governance and establish an oversight structure to a) continuously conduct rapid assessments of recruitment, enrollment and retention goals, and b) rapidly deploy and test interventions and apply modifications as necessary, for the following processes: 1. Engagement of all recruitment site facilities and staff in our initial designated catchment areas; 2. Outreach and enrollment of research-empowered Patient Partners; 3. Collection and transfer of Patient Partners’ consent, survey and physical exam data, and biospecimens; 4. Periodic compilation and transfer of Patient Partners’ EHR data to the PMI-CP Coordinating Center and return of data to Patient Partners. Aim 2: Fully enroll within a 12 month period 10,000 Patient Partners (defined as completion of informed consent, baseline exam and survey, biospecimen collection, and initial and recurring extraction of their EHR data). Submit specimens daily to the PMI-CP Biobank and EHR data as one pipeline to the PMI-CP Data and Research Support Center (DRSC) on the schedule determined by the PMI-CP Steering Committee (PMI-CP SC). Return individual and comparative data to Patient Partners as specified.

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

Children's Respiratory and Environmental Workgroup (CREW) (UG3OD023282)

The grant is part of $157 million in awards announced yesterday by the NIH that launches a seven-year initiative called Environmental Influences on Child Health Outcomes (ECHO). The ECHO program will investigate how exposure to a range of environmental factors in early development – from conception through early childhood – influences the health of children and adolescents.

Study Highlights

The CREW consortium will be tasked with identifying specific asthma subtypes and overcome shortcomings of individual cohorts by: Providing a large and diverse national data set of nearly 9,000 births and long-term follow-up for 6,000-7,000 children and young adults. Harmonizing data related to asthma clinical indicators and early-life environmental exposures. Developing standardized measures for prospective data collection across CREW cohorts and other ECHO studies. Conducting targeted enrollment of additional subjects into existing cohorts.

Experiences during sensitive developmental windows, including around the time of conception, later in pregnancy, and during infancy and early childhood, can have long-lasting effects on the health of children. These experiences encompass a broad range of exposures, from air pollution and chemicals in our neighborhoods, to societal factors such as stress, to individual behaviors like sleep and diet.
They may act through any number of biological processes, for example changes in the expression of genes or development of the immune system.

Principal Investigator: Christine Cole-Johnson, Ph.D.
Center for Urban Responses to Environmental Stressors (P30ES020957) Subcontract

Situated in the heart of Detroit, the environmental health sciences “identity” of the Center for Urban Responses to Environmental Stressors (CURES) is to understand the health impacts of environmental exposures to complex chemical and non-chemical contaminants in Detroit's urban landscape. Our strategic vision is to provide leadership to identify, evaluate, and mitigate environmental health concerns in close collaboration with the community and environmental policy makers. CURES has assembled a unique interdisciplinary team of established and new environmental health scientists and community partners to address major environmental health challenges facing Detroit's racially and ethnically diverse population. We hypothesize that “modern-era” diseases (e.g., cardiovascular disease, cancer, diabetes) that compromise the quality of life of residents living in an industrialized urban environment, such as Detroit, occur as a consequence of dynamic interactions among an individual's genetic and epigenetic make-up, nutritional status, and environmental stressors, which re-program key cellular networks to favor pathogenesis. CURES advances the NIEHS 2012-2017 Strategic Plan by nurturing strong bonds with Detroit's urban community, applying translational and interdisciplinary team-research approaches to solve complex environmental health problems, and by seeking the sources of environmental health disparities. CURES is making an impact in our region. Our researchers and community partners responded rapidly and coordinately to a serious emerging health crisis in our immediate vicinity; the 2015-2016 lead watershed contamination disaster in Flint, Michigan. To create a gateway to a healthy Detroit, CURES' short-term goals are to: 1) strengthen existing partnerships and continue to develop new ones between CURES and the Detroit community; 2) in collaboration with them, identify the chief environmental health threats to Detroit's vulnerable populations; 3) conduct highly integrated mechanistic, epidemiological, and community-engaged research that addresses the impact of urban environmental exposures on human health; 4) build the capacity of CURES to accomplish its research goals by providing facility cores that are optimized to meet the needs of its members and seed funds to support pilot projects to explore the feasibility of new areas of study; and 5) enhance the impact of CURES on the field of environmental health science by providing mentoring to new and established investigators that supports their professional goals and prepares them for leadership roles in environmental health research. Our long-term goals are to 1) enhance our community partners' efforts to increase community awareness and facilitate programs for a healthier community and 2) develop appropriate strategies, based on CURES research, to inform policy so as to mitigate the risks associated with urban environmental exposures. We believe that CURES is optimally positioned on "the ground floor" of innovative team science opportunities that have the greatest promise to realize the early detection, prevention, and eventual eradication of urban environmental disease in our lifetime.

Principal Investigator: George Divine, Ph.D.
Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance: Randomized Controlled Trial for Treatment of Extensively Drug-Resistant Gram-Negative Bacilli (Option 5) (HHHSN272201600049C) Subcontract

The Gram-negative bacilli organisms Acinetobacter baumannii, Klebsiella spp., Escherichia coli, Enterbactor spp. and Pseudomonas aeruginosa have become a frequent cause of bloodstream infection and pneumonia in the hospital and other healthcare settings. Among these pathogens, antimicrobial resistance has emerged to many classes of antimicrobial agents. Most concerning, has been the emergence of resistance to group 2 carbapenems (such as imipenem). In several regions of the world, including Southeastern Michigan, strains of extensively-drug resistant Gram-negative bacilli (XDR-GNB) that exhibit resistance to most, and in some cases all types of available antimicrobial agents, including group 2 carbapenems, have emerged and disseminated. Treatment options for XDR-GNB typically include Colistimethate sodium (referred to as colistin in this study), used alone (monotherapy) or in combination with other agents. Unfortunately, resistance to colistin has begun to emerge in some strains
of XDR-GNB, which is a truly concerning development, since colistin is one of the last remaining treatment options for XDR-GNB. No prospective, randomized controlled trials have been conducted to evaluate the clinical efficacy of colistin monotherapy versus colistin-containing combination therapy or the impact of these therapeutic modalities on the emergence of colistin resistance among XDR-GNB. We plan to conduct a double-blind randomized controlled trial including patients with pneumonia and bloodstream infection due to XDR-GNB. After enrollment, subjects will be randomized to receive 14 days of either colistin monotherapy or colistin plus meropenem.

In the Detroit metro area, infections due to XDR-GNB have developed into a regional challenge and common problem. We have assembled a multi-disciplinary team that includes Infectious Diseases researchers, clinicians, infectious diseases pharmacists, microbiologists, epidemiologists and statistical experts to address critically important questions and challenges regarding the management of bloodstream infection and pneumonia due to XDR-GNB. Specifically, we hypothesize that the combination of colistin and imipenem will provide superior efficacy in the treatment of XDR-GNB pneumonia and bloodstream infection and will prevent the emergence of decreased susceptibility to colistin among XDR-GNB strains. We also aim to analyze tools that could be used in "real time" to aid clinicians treating patients with infection due to XDR-GNB. For example, we aim to analyze the association between the presence of in vitro synergy of the colistin and carbapenem (imipenem or meropenem) combination (as determined by E-test) and clinical outcomes; and the association between colistin plasma levels and clinical outcomes and the development of nephrotoxicity.

Principal Investigator: George Divine, Ph.D.
Pulsed UV Xenon Disinfection to Reduce Multidrug Resistant Hospital Infections (R01HS024709) Subcontract

The objective is to conduct a prospective, sham controlled, double-blinded, interventional crossover trial to compare standard terminal cleaning plus PX-UV (intervention) with standard terminal cleaning plus sham PX-UV (control) with crossover at 12 months, following a 6-month washout period. Outcome measures include the rates of HAIs, as well as the recurrence of genetically identical clinical strains of HAIs among patients on study units. The study will be conducted in 2 hospitals covering 16 total hospital units at Detroit Medical Center. Our central hypothesis is that the addition of PX-UV to standard terminal cleaning will be associated with a significant reduction in the rate of HAIs, as well as a reduction in the recovery of genetically identical strains of MDROs. The impact of PX-UV disinfection on rates of HAIs on study units will be determined by comparing rates of HAIs on a) study units where PX-UV is added to standard terminal cleaning practices to b) units where a sham UV disinfection system is added to standard terminal cleaning; and by comparing rates of HAIs on the same medical ward during each of two 12-month phases of a crossover study (one phase when a PX-UV device is added and one when a sham device is added to standard terminal cleaning).

The long-term goal of this project is to establish the efficacy of terminal cleaning plus PX-UV in reducing rates of HAIs due to the following multi-drug resistant organisms (MDROs): C. difficile, vancomycin-resistant enterococci (VRE), Klebsiella pneumoniae and Escherichia coli producing extended-spectrum beta-lactamases (ESBLs), methicillin-resistant Staphylococcus aureus (MRSA) and Acinetobacter baumannii.

At the conclusion of the proposed project, novel data will be generated from this rigorously controlled study regarding the effectiveness of PX-UV in reducing HAIs in a representative, real-world healthcare setting.

Principal Investigator: Michael Flynn, Ph.D.
CT Dose Collaboratory (R01CA181191) Subcontract

The objective is to conduct a prospective, sham controlled, double-blinded, interventional crossover trial to compare standard terminal cleaning plus PX-UV (intervention) with standard terminal cleaning plus sham PX-UV (control) with crossover at 12 months, following a 6-month washout period. Outcome
measures include the rates of HAIs, as well as the recurrence of genetically identical clinical strains of HAIs among patients on study units. The study will be conducted in 2 hospitals covering 16 total hospital units at Detroit Medical Center. Our central hypothesis is that the addition of PX-UV to standard terminal cleaning will be associated with a significant reduction in the rate of HAIs, as well as a reduction in the recovery of genetically identical strains of MDROs. The impact of PX-UV disinfection on rates of HAIs on study units will be determined by comparing rates of HAIs on a) study units where PX-UV is added to standard terminal cleaning practices to b) units where a sham UV disinfection system is added to standard terminal cleaning; and by comparing rates of HAIs on the same medical ward during each of two 12-month phases of a crossover study (one phase when a PX-UV device is added and one when a sham device is added to standard terminal cleaning).

The long-term goal of this project is to establish the efficacy of terminal cleaning plus PX-UV in reducing rates of HAIs due to the following multi-drug resistant organisms (MDROs): C. difficile, vancomycin-resistant enterococci (VRE), Klebsiella pneumoniae and Escherichia coli producing extended-spectrum beta-lactamases (ESBLs), methicillin-resistant Staphylococcus aureus (MRSA) and Acinetobacter baumannii.

At the conclusion of the proposed project, novel data will be generated from this rigorously controlled study regarding the effectiveness of PX-UV in reducing HAIs in a representative, real-world healthcare setting.

Principal Investigator: Lois Lamerato, Ph.D.
Central Data Collection Center (CDCC) (HSN26100001) Subcontract

The PLCO Central Data Coordinating Center (CDCC) is an extension of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. To reduce costs, the extension has one data collection site under the direction of the National Cancer Institute (NCI) rather than the original ten PLCO Screening Centers. PLCO participants were invited to be transferred to the CDCC for continued, active follow up. Other participants agreed to be passively followed at the PLCO sites through tumor registry searches. PLCO was designed to determine if screening for prostate, lung, colorectal and ovarian cancer can reduce mortality from these cancers. In addition, PLCO has a collection of pre- and post-diagnostic biological samples stored in the PLCO Biorepository, and epidemiological data from questionnaires. These data are a valuable resource for cutting-edge molecular epidemiologic research. The study was extended in this streamlined fashion to increase the value of the resource. The study will continue to update key exposure data by collecting additional risk and lifestyle information, including medication use and medical conditions that are common in older adults. Also, the CDCC will collect additional clinical data and tumor tissue of selected cancers, such as that of the colon and ovaries. This extension of the PLCO Cancer Screening Trial enhances the value of the PLCO resources through the substantial increase in the number of incident cancers accrued within the Trial, strengthens the Trial's ability to clarify further the long-term effects of screening on cancer mortality, and provides a final opportunity to collect additional exposure data and expand the existing tumor pathological resource within the PLCO.

Principal Investigator: Lois Lamerato, Ph.D.
US Hospital Vaccine Effectiveness (VE) Network (U01P000974) Subcontract
US Influenza Vaccine Effectiveness Network (U01IP001034) Subcontract

Prevention of hospitalization has long been viewed as a major health benefit of the use of influenza vaccine. This was, in large part, the rationale for the initial vaccination programs targeting the elderly and those with underlying health conditions. However, in the last decade, questions have been raised about the value of such programs. Modern study designs to assess vaccine effectiveness (VE) have required laboratory confirmation of influenza infection, as well as documentation of vaccine receipt and the use of a test-negative design to control for differences in healthcare-seeking behavior between vaccinated and unvaccinated patients. There is a need for current estimates of VE in preventing influenza-associated hospitalization using these methods. We propose estimation of influenza vaccine effectiveness in preventing influenza hospitalization in two health systems in Michigan, where we have been conducting annual assessments of VE in various populations since 2008. We will conduct surveillance at two hospitals, and will enroll adult in-patients with acute respiratory infection. Vaccination status will be
reported and documented, and considered with laboratory-confirmed influenza outcomes to estimate vaccine effectiveness for prevention of hospitalization. Analyses will use a test- negative design; those testing positive for influenza or cases, those testing negative are controls. Modifiers and confounders of vaccine effectiveness such as age, health status, high-risk health conditions, functional status, frailty, education, tim from illness onset to specimen collection, calendar time, and propensity for vaccination will be assessed. In addition to our proposed influenza surveillance and VE assessment, we propose an estimation of the incidence of hospitalization in adults due to respiratory syncytial virus (RSV) and other respiratory viruses. This will allow for the evaluation of bias in influenza VE assessment due to interaction between influenza vaccination, infection, and non-influenza respiratory viruses, and will establish a platform for the future evaluation of RSV vaccines. We will accomplish these additional objectives by expanding our surveillance to months before and after the typical influenza season and evaluating specimens by molecular methods for RSV and other respiratory viruses.

Principal Investigator: Albert Levin, Ph.D.
Comprehensive Analysis of Gene-Environment Interaction in Sarcoidosis (R21HL129023)

Sarcoidosis is a multi-organ granulomatous, inflammatory disease of uncertain etiology, with 90% of cases presenting pulmonary involvement. Despite convincing evidence that sarcoidosis likely arises when a genetically-susceptible host is exposed to a causative environmental agent, studies of environmental agents and disease risk suggest that there is more than one single environmental trigger. Further, there have been few gene-environment interaction (GxE) studies of disease etiology published to date; those few have focused on the class II genes within the Human Leukocyte Antigen (HLA) region, the most studied and validated region associated with sarcoidosis risk. In the United States, African Americans are at highest risk for sarcoidosis; the adjusted annual incidence among African Americans is roughly three times that of European Americans (35.5/100,000 versus 10.9/100,000). Among African Americans, the disease is also more likely to be chronic and severe. We recently performed the first gene-environment-wide interaction study (GEWIS) of insecticide exposure and sarcoidosis risk in the Ancestry Mapping of Sarcoidosis Study (AMASS), a large study of sarcoidosis in African Americans. Using our recently-developed methodology, we identified a genome-wide significant GxE association in the FUT9 gene. To build on this effort, the current proposal will focus on the family-based portion of AMASS (503 families, including 818 sarcoidosis cases and 632 healthy family members), which has a rich resource of both environmental exposure and genetic (genome-wide genotyping, targeted/full exome sequencing, and imputed HLA Class I and II genes) data available. First, we propose to identify environmental exposures associated with sarcoidosis risk (Aim 1). Where existing sarcoidosis studies have been limited to investigating environmental exposures in isolation, we will move beyond this trend by using latent-class analysis (LCA) to identify patterns across multiple environmental exposures. Associated environmental exposures (individual and/or LCA-identified multi-exposure groups) will be evaluated for GxE effects (Aim 2). Current family-based GEWIS have focused on the exhaustive strategy of testing all genetic variants. To attempt to improve power, we will extend a two-step strategy to our study of related and admixed individuals and compare both exhaustive and two-step GEWIS strategies via simulation. The strategy with the highest power that also controls the type-1 error rate will be selected for GxE testing for the environmental factors from Aim 1. In summary, we propose multiple innovations to the fields of both GxE analysis and sarcoidosis research that increase the chance for better understanding of the etiology of this debilitating disease.

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

Chronic inflammation, which is caused by infectious agents or exposure to environmental factors such as heterocyclic amines, is believed to play a role in up 20% of adult cancers. In prostate, genetic, molecular pathology, and toxicology data suggest that inflammation-related processes are involved in cancer development, but these data conflict with results of epidemiological studies that show an inverse correlation between inflammation and prostate cancer risk. This may be due to bias in the
factors that lead men to undergo prostate biopsy, as well as complexity of the inflammatory phenotype itself. Our proposed study will address this paradox by dissecting inflammation at the cellular, molecular, and clinical level. The Henry Ford Health System biorepository contains benign prostate tissue specimens collected from over 9,000 men over the past 20 years, including over 1,000 men who subsequently developed prostate cancer. Using this unique cohort with its annotated clinical baseline and follow-up data, we will conduct a nested case-control study of 700 prostate cancer case-control pairs. Characterizing inflammatory markers in these pre-disease specimens will allow us to determine the nature of tumor-suppressive vs. tumor-supportive inflammatory signatures. We will also measure telomere length in the same benign prostate tissue specimens in which we characterize inflammation to assign a malignancy-potential signature to each specimen. Approximately 1 million prostate biopsies are performed annually in the US, two thirds of which reveal benign condition. Our cohort includes a large group of patients who are at high risk of prostate cancer despite a negative biopsy. An in-depth characterization of inflammation in the benign prostate, before histologic signs of malignancy become apparent, will provide insight into the type of inflammatory milieu associated with eventual tumor development as well as cancer progression and recurrence. A better understanding of the clinical implications of chronic inflammation of the prostate so often observed in older men can have significant impact upon millions of men where currently a negative biopsy offers little reassurance in terms of prostate cancer outcomes.

Principal Investigator: Ganesa Wegienka, Ph.D.
Epidemiology of Allergic Disease Endotypes (R01AI110450)

Pediatric allergy and asthma are a costly public health burden, but so far substantial research efforts have yielded no prevention strategies. A likely reason is that despite longstanding recognition by the medical community that the term ‘asthma’ refers to a collection of diseases, researchers have historically treated the syndrome as a single disease entity. Epidemiologically, the collapse of different phenotypes (observed disease patterns) and endotypes (phenotypes further delineated by pathophysiological processes), into a single category corrupts associations between risk factors and diseases. Thus, progress in allergic disease research has been hampered. Prior attempts have been made to identify such phenotypes and endotypes, but a combination of incomplete data and oversimplified statistical methods have limited progress. We propose to apply sophisticated latent class analyses in a large general risk cohort combined with immunological markers to finely discriminate asthma and allergy disease phenotypes and endotypes and then use this information to conduct risk factor analyses. Using this approach in our WHEALS birth cohort, we have already characterized four classes at age 2 years: 1) Low to No Sensitization; 2) Highly Sensitized; 3) Milk and Egg Dominated Sensitization; and 4) Peanut and/or Inhalant allergen – No Milk Sensitization. Total IgE levels varied between the groups, as did the rates of eczema and doctor diagnosis of asthma (at age 4 years). The Highly Sensitized had the greatest rates, the Low to No Sensitization had the lowest rates, and the other two classes had rates intermediate between the Low and High Sensitization groups. These data suggest the use of latent classes, rather than the use of the “traditional” definition of atopy (any allergen-specific IgE (sIgE) _0.35 IU/mL), more specifically identifies those on a trajectory for allergic disease, yielding advancement in both allergic disease research and clinical care. Using the predominantly (62%) African American birth cohort WHEALS, we will: Aim 1) Determine which early life allergic disease phenotypes identified at age 2 years are associated with lung function (spirometry and methacholine challenge) at age 10 years; Aim 2) a) Identify the allergic disease endotypes for 10 year old children based on annual report of wheeze; lung function, eNO, obesity, cytokines, and white cell counts and extensive immunophenotyping [assessment of cellular markers to identify and quantify activation of regulatory T cells (Tregs), basophils and dendritic cells (DCs)] at age 10 years; and total IgE and sensitization (sIgE and skin prick tests) at ages 2 and 10 years; and, b) Estimate associations between early life risk factors (e.g., delivery type, pet exposure, etc.) and the identified Aim 2a endotypes; and, 3) Compare and contrast the risk factor associations with the endotypes in Aim 2 to the risk factor associations determined using “traditional” definitions of atopy and asthma (doctor diagnosis and medication use and/or symptoms in the last year). Analyses will be performed for all 900 WHEALS cohort children and separately for Black children and White children to assess racial differences.
Uterine leiomyomata (UL), or fibroids, are the most common neoplasms of the uterus and are a major source of gynecologic morbidity. In the United States (U.S.), the lifetime risk of symptomatic UL is approximately 25-30%. UL are the leading indication for hysterectomy, and UL-related costs exceed $34.4 billion annually. Black women are disproportionately affected by UL, with a 3-fold greater risk of diagnosis, earlier age at diagnosis and surgery, and more symptomatic tumors on average than white women. Despite the large public health burden of UL, little is known about its natural history or pathogenesis. Animal data and cross-sectional human studies have provided compelling preliminary evidence of a role for vitamin D in UL development and growth. Exposure to heavy metals such as lead, mercury, and cadmium is widespread, with reproductive-aged women, African Americans, and those of lower socioeconomic status having higher exposure levels than other groups. Funded by the National Institute of Environmental Health Sciences (NIEHS), the Study of Environment, Lifestyle and Fibroids (SELF) is a multi-year prospective cohort study of UL determinants in black women from the Detroit area. In 2011-2012, SELF enrolled 1,696 black women aged 23-34 years who had never been diagnosed with UL. At baseline and every 20 months for a total of 5 years (4 total clinic visits), SELF participants complete interviews, have blood collected for biological measurements, and undergo transvaginal ultrasounds for precise identification and mapping of UL at each visit facilitating accurate determination of UL development and growth (cohort retention >85%). The final planned clinic visits are underway. In this application, we propose to extend follow-up of SELF for an additional five years. One more clinic visit with transvaginal ultrasound, biospecimen collection and detailed exposure assessments via interview will be conducted to achieve the following specific aims: 1) Describe the natural history of UL initiation and growth; calculate age-specific UL incidence; and evaluate changes in tumor characteristics (size, number, and location) over a 10-year period; 2) Assess whether vitamin D status influences UL incidence and growth over a 10-year period; and 3) Evaluate the influence of selected environmental toxicants on UL incidence and growth. Specifically, we will examine the influence of active and passive cigarette smoking on UL incidence and growth; assess exposure to a panel of 13 metals and metalloids (and their mixtures) measured in whole blood and UL incidence and growth over a 10-year period; and determine whether vitamin D status modifies the associations between environmental toxicants and UL incidence. With its prospective design, population of young black women, serial ultrasounds, repeated collection of data on exposures and covariates, and careful analysis of chemical mixtures, SELF is ideal for identifying environmental risk factors for UL. Using methods that overcome the limitations of prior studies, this will be the most definitive study of modifiable environmental risk factors of UL and is likely to have high impact on science, clinical care, and public health policy.

The broad, long-term objective of this project is to enable patients with uterine fibroids (UF) to make informed decisions about management options based on the highest possible quality evidence. To help achieve this objective, we propose a multi-center registry of a geographically, racially, ethnically, and clinically diverse group of women who have received medical or surgical treatment for UF, Comparing Options for Management: Patient-Centered Results for Uterine Fibroids (COMPARE-UF), designed to address the following specific aims: AIM 1) Develop the infrastructure necessary to implement large-scale observational comparative effectiveness research (CER) studies of management options for women with UF, including (a) a governance structure, policies, and procedures conducive to collaborative research involving patients, clinicians, methodologists, and other stakeholders, (b) an experienced Research and Data Coordinating Center, and (c) nine geographically diverse Clinical Centers (CCs) representing a broad range of patients and providers. AIM 2) Use this infrastructure to implement 3 projects addressing high-priority evidence gaps related to the effect of different management strategies on patient-centered outcomes. These include PROJECT 1: Comparing management options for symptom relief PROJECT 2: Comparing management options for preserving
reproductive function

PROJECT 3: Comparing effectiveness in different subpopulations. AIM 3) Evaluate innovative methods for the design, conduct, and analysis of observational comparative effectiveness research in this population. AIM 4) Translate research results into improved patient care, through both traditional peer-reviewed publications and collaborations with stakeholders to integrate the research findings into evidence-based patient decision making tools, clinical practice guidelines, and quality measures.

Principal Investigator: Ganesa Wegienka, Ph.D.
Study of Ovarian Aging and Reserve in Young Women (SOAR) (R01HD088638) Subcontract

The average age for a woman to have her first child has been increasing for the last three decades in the United States, making our understanding of ovarian aging and its negative effect on the ovarian reserve, a measure of the capacity of the ovary to produce eggs capable of fertilization. Yet, we know very little about other factors in reproductive-age women that might affect the ovarian reserve, beyond aging itself. This proposal, titled Study of Ovarian Aging and Reserve in Young Women (SOAR), seeks to address the significant gap in our knowledge of factors, particularly modifiable factors, that affect ovarian reserve and might accelerate its decrease in young women. To achieve this goal, we will leverage the ongoing NIEHS Study of Environment, Lifestyle and Fibroids (SELF), which is following a cohort of 1,696 African-American women between the ages of 23-34 years over a five-year period. In this group of young women, we will assess changes in the ovarian reserve by tracking three different measures of the ovarian reserve: anti-Mullerian hormone (AMH), early follicular phase follicle-stimulating hormone (FSH), and antral follicle count (AFC). In addition to collecting survey data, we will also perform oral glucose tolerance testing (OGTT) and anthropometric and bioelectrical impedance analysis (BIA) measurements to more precisely determine the roles of glucose metabolism and obesity on the ovarian reserve. The results of our study will be clinically significant as we currently have limited longitudinal data for counseling women on risk factors for decreased ovarian reserve. Our study design is innovative in that we will use overlapping measures of the ovarian reserve and group-based trajectory modeling to determine correlates associated with decreased ovarian reserve. Specifically, we will determine the demographic, health-behavior, reproductive, and environmental factors associated with decreased AMH (as a measure of the ovarian reserve) over time (Aim 1), determine the association between various measures of obesity and decreased ovarian reserve (Aim 2), and determine the association between glucose dysregulation and decreased ovarian reserve (Aim 3). The proposed prospective longitudinal cohort study will determine the natural history of and factors associated with the change in ovarian reserve over time. Further, it will add to the extremely limited data by generating the largest set of longitudinal data on AMH and ovarian reserve in the United States to date, which will benefit all women.
ADMINISTRATION


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**RESEARCH ADMINISTRATION**

**Image Analysis Program**


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**SURGERY**


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**BEHAVIORAL HEALTH SERVICES/PSYCHIATRY**


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**Psychology/Neuropsychology**


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CLINICAL QUALITY AND SAFETY


COMMUNITY HEALTH EQUITY AND WELLNESS


DERMATOLOGY


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**DIAGNOSTIC RADIOLOGY**


**EMERGENCY MEDICINE**


FAMILY MEDICINE


GLOBAL HEALTH INITIATIVE


INTERNAL MEDICINE

Allergy and Immunology


Cardiology/Cardiovascular Research


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**Sleep Medicine**


**General Internal Medicine/Palliative/Other**


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OPHTHALMOLOGY


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RADIATION ONCOLOGY


RESEARCH ADMINISTRATION

Cytogenetics


Image Analysis Program


SURGERY


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