# 2016 Research Annual Report

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Summaries of 2016 National Institutes of Health and other Federal Grants Awarded to HFHS

Part I – Department of Internal Medicine

- Allergy and Immunology
- Endocrinology and Metabolism
- Gastroenterology
- Hypertension and Vascular Research
- Sleep Medicine

Allergy and Immunology

Principal Investigator: Edward Zoratti, M.D.

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

Endocrinology and Metabolism

Principal Investigator: D. Sudhaker Rao, M.D.

Pathogenesis of Atypical Femur Fractures on Long Term Bisphosphonate Therapy (NIH 1R01AR062103)

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 micropetosis, 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 hepatits 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).

**Hypertension and Vascular Research**

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

This PPG was started in September, 1982. The central theme is "the study of the role of vasoactive systems (autocrine, juxtacrine, paracrine and endocrine) in the regulation of renal
function and blood pressure (BP) and mediation of 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), prostanooids, 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 II-induced hypertensive rats as models. In Project I, using Dahl SS rats, we will study whether N-acetyl-ser-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 II-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 inh 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 the pathogenesis of EOD; and II which also studies 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 (NIH 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 stimulates 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 fructose1,2. We found that feeding rats a fructose-enriched diet (20%) 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 rodents3-5. 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 NKCC213. A fructose-enriched diet may increase sympathetic activity by 2 weeks12, 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 tubule (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. In Dahl SS rats, abnormally elevated SPAK/OSR1 in the TAL, enhances the effect of fructose on
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.

Sleep Medicine

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 (NIH 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 LatencyTest (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 subpopulation (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.
Part II – All Other Clinical Departments

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Dermatology

Principal Investigator: Qing-Sheng Mi, M.D., Ph.D.
microRNAs and NKT Cell Development and Function (NIH 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 (NIHR01AR069681)

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 (NIH R01AI123258)

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
cPCR 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 DPT1 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.

Imaging Research Program

Principal Investigator: Soltanian-Zadeh, Hamid, Ph.D.
Decision Support System for Temporal Lobe Epilepsy (NIH R01EB013227)

With the ever-increasing role of medical images in diagnosis, treatment planning, and evaluation of treatment effects, extraction of quantitative information from these images and efficient use of the results have become a necessity. In recent years, we have developed novel three-dimensional (3D) knowledge-based methods to segment brain structures from magnetic resonance images (MRI) automatically. These methods need to be optimized, fine-tuned, and compared to other methods for the segmentation of specific brain structures that may be involved in medical temporal lobe epilepsy (mTLE). Feature extraction methods also need to be developed and optimized to characterize (i.e., determine local and global multi-parametric intensity distribution, texture, shape, surface area, surface curvatures, and volume of) the brain structures. Multi-modality analysis using multi-parametric MRI and SPEC needs to be developed for improved sensitivity and specificity. We have also developed our preliminary version of a content-based human brain image database system to hold the image analysis results with other clinical information (e.g., textual data) in a manner that can be searched, retrieved, and queried conveniently from any computer station. This system needs integrated methods for data preparation, missing value treatment, interactive rule-extraction, visualization, and user- inference to serve as a decision support system in clinical practice. A user-friendly, web-based interface will be critical for the ultimate use of the system by researchers and clinicians. Last but not least, the database needs to be populated with data from a large number of patients so that it can be confidently used for hypothesis testing and clinical applications. The goal of this project is to develop novel approaches for the above needs. Image analysis and feature extraction methods will segment and characterize hippocampus, amygdala, entorhinal cortex, thalamus, putamen, and other brain structures from MRI. The methods will be tested, evaluated, and validated using clinical data of epilepsy patients. Clinical diagnosis based on EEG studies and surgery outcome will be used as “god standards” for evaluation and validation of the image analysis methods. The proposed decision support system will be populated with multi-modality data of 350 epilepsy patients to evaluate correlation between a variety of risk factors, imaging features, clinical diagnosis (lateralization), and post-operative outcomes, and to assist physicians with improved clinical diagnosis, reduced intracranial EEG studies (reduced risk and suffering of patients as well as their
healthcare cost), optimal treatment options, and prediction of outcome in prospective studies. The proposed research will be a breakthrough in the application of computerized methods for medical image quantification and object characterization, and will advance image analysis science in the direction of integrating knowledge-based image segmentation and characterization methods with pattern recognition and data mining technology in decision support systems. The proposed approaches are applicable to the identification, segmentation, and characterization of other biological structures. They are also applicable to virtually any image analysis task for which object segmentation, quantification, and characterization are used. This project will develop a decision support system for assisting physicians to improve diagnosis and prognosis of epilepsy patients while reducing the healthcare cost. It will process multi-modality medical images and extract quantitative information from them. The image analysis results will be used along with the results of other clinical tests as well as the patients’ history and characteristics to reduce the need for intracranial electrographic studies, predict post-operative outcomes, and suggest optimal treatment options for the new patients.

Neurology

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 nanoprodug strategy and tumorspecific 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 nanoprodug 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: Jieli Chen, Ph.D.
Neurorestorative Therapy of Stroke with HUCBC in Type Two Diabetic Mice (NIH 1R01NS083078)

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–induced 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 mediate 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.

Principal Investigator: Jieli Chen, Ph.D.

MiR-126/ABCA1 Mediates Exosome Induced Neurorestorative Effects after Stroke in T2DM Mice (1R01NS099030)

Diabetes mellitus (DM) leads to a 3-4 fold higher risk of experiencing ischemic stroke. Stroke in type two DM (T2DM) patients and in animal models increases vascular and white matter (WM) damage in the ischemic brain, and stroke in T2DM patients has a distinct clinical pattern and a poor prognosis compared to non-DM stroke. Exosomes (Exo), are active nano size biological lipid 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 exosome include microRNAs (miRs), which regulate gene translation and play primary roles in mediating a vast range of biological functions. MicroRNA-126 (miR-126) is an angiogenic microRNA and primarily expressed in endothelial cells (EC). Specific conditional knockout of EC miR-126 (miR-126EC-/-) mice have significantly worse functional outcome after stroke as well as decreased brain miR-126 and ATP-binding cassette transporter A1 (ABCA1) expression. Exosomes derived from EC (EC-Exo) have a high level of miR-126. Based on our robust preliminary data, in this pioneering study, we propose that treatment of stroke with EC-Exo will enhance neurorestorative effects after stroke in T2DM mice, possibly, via the miR-126/ABCA1 signaling pathway. This application includes three Aims. Aim-1: To test the therapeutic effects of EC-Exo on cerebral ischemic stroke in adult male and female T2DM mice. Aim-2: To evaluate whether miR-126 mediates EC-Exo treatment induced neurorestorative effects, we will evaluate the therapeutic effects of treatment of stroke in specific conditional knockout of EC miR-126 (MiR-126EC-/-) and in non-miR-126 knockout control (miR-126EC-fl/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-126EC-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 ( NIH 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, lasercapture, 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 ( NIH 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 A 1 (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/-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. **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: 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 investigations1-4 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 Alzheimers disease and sleep disorders, etc2, 4. Although the impact of the glymphatic system is being investigated in Alzheimers 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.
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-inflammatory 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: Lei Wang, M.D.
Thymosin Beta4 Promotes the Recovery of Peripheral Neuropathy in Diabetic Mice (NIH R01DK097519)

Peripheral neuropathy is one of 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. Thymosin Beta4 (Tβ4), a major intracellular G-actin sequestering peptide, has multiple biological functions, including promotion of remodeling of injured and damaged tissues, and increasing angiogenesis after myocardial infarction. However, the role of Tβ4 in diabetic peripheral neuropathy has not been investigated. In a novel set of experiments, our data show that Tβ4 remarkably improved sciatic nerve vascular function and peripheral nerve function in diabetic mice, indicating that Tβ4 may have a beneficial effect on the clinical treatment of diabetic peripheral neuropathy. In this application, we therefore seek to investigate the mechanisms underlying the therapeutic effects of Tβ4 on the treatment of diabetic peripheral neuropathy. We propose that Tβ4 by improving vascular function ameliorates diabetic peripheral neuropathy. Our hypotheses are: 1. Treatment with Tβ4 improves neurological function of peripheral neuropathy in diabetic mice. 2. The Ang/Tie2 signaling pathway mediates the therapeutic effect of Tβ4 on neurovascular function in diabetic peripheral neuropathy. 3. The PI3K/Akt signaling pathway underlies the effect of Tβ4 on Ang1/Ang2 expression. To investigate the effect of Tβ4 on neurological outcome, type II diabetic mice which develop severe peripheral neuropathy will be treated with Tβ4 at various time points after onset of diabetes. To investigate the molecular mechanisms that mediate Tβ4-enhanced neurovascular function in diabetic mice, the effect of Tβ4 on expression of Ang/Tie2, and activation of PI3K/Akt signaling pathway will be examined. Using pharmacological inhibitors and siRNA gene knockdown techniques, we will investigate the cause-effect of the Ang/Tie2 and PI3K/Akt signaling pathways on regulating Tβ4-enhanced neurovascular function and axonal outgrowth. These studies are innovative and will provide new insight into mechanisms underlying the neurological dysfunction of diabetic peripheral neuropathy and lead to the development of a new treatment using Tβ4. Peripheral neuropathy often stemming from diabetes is a major disability affecting millions of Americans. In this proposal, employing preclinical studies in the diabetic animal, I seek to develop a novel treatment for peripheral neuropath using Tβ4. Tβ4 is currently in a phase II clinic trial for the treatment of patients with acute myocardial infarction. In this proposal, I also elucidate the molecular mechanism by which Tβ4 is therapeutically effective. This research will provide the essential pre-clinical data for translation to a
phase 1 clinical trial.

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

Principal Investigator: Zheng Gang Zhang, M.D., Ph.D.
MicroRNAs and Neurogenesis after Stroke (NIH 1R01NS075156)

MicroRNAs (miRNAs) regulate biological function of neural progenitor cells and oligodendrocyte progenitor cells (OPCs). Our preliminary data show that stroke substantially changed miRNA expression profiles in adult neural progenitor cells and oligodendrocytes. In this application, we propose to test the hypothesis that miRNAs in neural and OPCs play a pivotal role in mediating adult neurogenesis and oligodendrogenesis in the ischemic brain. In Specific Aim 1, we will investigate the effect of inactive miRNA processes in neural progenitor cells and OPCs on stroke-induced neurogenesis and oligodendrogenesis by conditional and inducible Dicer ablation in Ascl1 lineage cells (Ascl1-reTM/Dicerflox/flox). In Specific Aim 2, we will investigate whether the sonic hedgehog (Shh) signaling pathway interacts with the miR-17-92 cluster to increase neurogenesis and oligodendrogenesis. In Specific Aim 3, we will investigate the effect of the miR17-92 cluster on biological function of neural and oligodendrocyte progenitor cells in the ischemic brain by deletion or overexpression of the miR17-92 cluster in neural progenitor cells and OPCs after stroke.

These studies will provide novel insights into miRNAs in regulating stroke-induced neurogenesis and oligodendrogenesis, which could potentially lead to new therapies to amplify neurogenesis and oligodendrogenesis in injured brain. Neurogenesis and oligodendrogenesis are associated with functional recovery after stroke. Molecular mechanisms underlying generation of new neurons and oligodendrocytes in ischemic brain have not been fully understood. Our preliminary data suggest that MicroRNAs (miRNAs), short noncoding RNA molecules, could be essential components in mediating stroke-induced neurogenesis and oligodendrogenesis. In this application, we propose three experiments to investigate the role of miRNAs in regulating adult neurogenesis and oligodendrogenesis in the ischemic brain. We will first delete Dicer to inactive miRNA processes in neural progenitor cells and oligodendrocyte progenitor cells (OPCs) after stroke. We will then examine a linkage between the sonic hedgehog (Shh) signaling pathway and miR17-92 expression in mediating neurogenesis and oligodendrogenesis. Finally, we will ablate or overexpress the miR17-92 cluster in neural progenitor cells and OPCs. These studies will provide novel insights into miRNAs in regulating stroke-induced neurogenesis and oligodendrogenesis, which could potentially lead to new therapies to amplify neurogenesis and oligodendrogenesis in injured brain.

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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.

Pathology

Principal Investigator: Chunhai (Charlie) Hao, M.D.
SUMO1 Inhibition Compound as a New Anticancer Drug for Glioblastoma Therapy (R01CA20389301)

Our long term goal is to develop novel and effective treatments of glioblastoma, the most common and lethal human brain cancer. To achieve this goal, we propose to develop the SUMO1 inhibition compound (SMIC1) as a new anticancer drug for glioblastoma therapy. In our recent studies, we have demonstrated for the first time that SUMO1 modification is overactive in human glioblastoma and drives the cell cycle and tumor growth through its conjugation of the cell cycle control protein termed cyclin-dependent kinase-6 (CDK6). SUMO1-CDK6 conjugation inhibits CDK6 ubiquitination and the ubiquitin-mediated proteolysis, thus stabilizes CDK6 protein and kinase activity and drives the cell cycle for glioblastoma progression. To target this pathway in glioblastoma, we designed and carried out the tumor cell-based screening of NCI pharmacological compounds. The screening led to the discovery of a SUMO1-specific inhibitor that we named and patented as the SUMO1 inhibition compound (SMIC1). In preliminary studies, we have shown that SMIC1 is rapidly absorbed into the system circulation and distribution in brain tissues through the blood brain barrier after administration in animal models. SMIC1 treatment blocks SUMO1-CDK6 conjugation and suppresses the progression of glioblastoma cells and xenograft animal models. These preliminary data indicate the potential of SMIC1 in the treatment of human glioblastoma. To develop this potential of SMIC1, we will follow the US Food and Drug Administration guidance in nonclinical evaluation of anticancer pharmaceuticals. In Aim 1, we will examine the pharmacology, i.e. mechanism of action of this new drug in treating glioblastoma cells. In preliminary studies, we have shown that SMIC1 is rapidly absorbed into the system circulation and distribution in brain tissues through the blood brain barrier after administration in animal models. SMIC1 treatment blocks SUMO1-CDK6 conjugation and suppresses the progression of glioblastoma cells and xenograft animal models. These preliminary data indicate the potential of SMIC1 in the treatment of human glioblastoma. To develop this potential of SMIC1, we will follow the US Food and Drug Administration guidance in nonclinical evaluation of anticancer pharmaceuticals. In Aim 1, we will examine the pharmacology, i.e. mechanism of action of this new drug in treating glioblastoma cells. In preliminary studies, we have shown that SMIC1 treatment eliminates SUMO1 protein through its ubiquitination and degradation. In this study, we will further identify the ubiquitination site on SUMO1 protein and the ubiquitination regulatory enzyme that is targeted by the drug. These studies will test the hypothesis that through induction of the ubiquitination and degradation of SUMO1 protein, SMIC1 treatment inhibits SUMO1-CDK6 conjugation and blocks the cell cycle progression in glioblastoma cells. In Aim 2, we will test the drug toxicology and pharmacokinetics. Through the analyses, we will identify a dose window in which SMIC1 can effectively inhibit SUMOylation and tumor growth without causing any damage to normal tissues. The data will provide valuable information in dose selection and schedule for clinical trails of SMIC1 treatment of cancer patients. In Aim3, we will evaluate the therapeutic efficacy of this new drug in treating the cancer stem cells-derived xenograft models of human glioblastoma and...
determiner whether SMIC1 treatment can effectively suppress the tumor progression. Upon completion, this proposal will lead to the genesis of a new anticancer drug for clinical treatment of patients suffering this deadly human cancer.

**Radiation Oncology**

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

**Molecular Classification of High Grade Endometrial Cancers: Extending TCGA Findings to a High Risk Population (NIH R01CA2000864)**

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 or 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: Svend Freytag, Ph.D.**

**Gene Therapy and Radiation Therapy for Prostate Cancer (NIHR01CA160289)**

Our translational research program has been developing a multi-modal, gene therapy-based approach for the treatment of cancer. We have evaluated the toxicity and preliminary efficacy of our investigational approach in five clinical trials of non-metastatic prostate cancer. Our early stage results indicate that our approach is safe and has the potential to improve local tumor control. Although local tumor control is important, new therapies for high-risk prostate cancer must also target metastatic disease if they are to have an impact on survival. Hence, we have added a fourth modality to our investigational approach by generating a third-generation adenovirus armed with interleukin 12 (IL-12) that has the potential to eradicate both local and metastatic disease. This new adenovirus has generated encouraging preliminary results in preclinical studies, and we plan to move it into the clinic targeting high-risk prostate cancer. In specific aim 1, we will test the hypothesis that IL-12 will improve the efficacy of replication-competent adenovirus-mediated suicide gene therapy and radiation in an immune-competent, orthotopic model of prostate cancer.

C57BL/6 male mice bearing intraprostatic TRAMP-C2 tumors will receive an intratumoral injection of Ad5- yCD/mutTKSR39rep-mIL12 followed by 2 weeks of 5-fluorocytosine (5-FC) + ganciclovir (GCV) prodrug therapy and pelvic radiation. Primary endpoints are local and metastatic tumor control. Secondary endpoints include T cell activation, NK and CTL activity, serum and tumor cytokine levels, and development of anti-tumor immunity. In specific aim 2, we will test the hypothesis that cyclophosphamide (CP) can be combined safely with replication-competent adenovirus-mediated suicide and IL-12 gene therapy and that the combined therapies exhibit synergy in vivo. Efficacy will be examined in the immune-competent, orthotopic TRAMP-C2 tumor model without and with CP. Efficacy endpoints are identical to those in specific aim 1. Toxicity will be examined in C57BL/6 male mice and Syrian hamsters, the latter of which are permissive for human adenovirus replication. In specific aim 3, we will test the hypothesis that replication-competent adenovirus-mediated suicide and IL-12 gene therapy can be combined safely with intensity modulated radiation therapy (IMRT) and androgen suppression therapy (AST) in men with newly-diagnosed, high-risk prostate cancer. Fifteen men (5 cohorts, 3 patients each) with high-risk prostate cancer (Stage e T3 or Gleason e 8 or PSA >20 ng/mL) will receive a single injection of Ad5- yCD/mutTKSR39rep-hIL12 at five dose levels (1 x 1010 vp to 1 x 1012 vp in half-log increments). The adenovirus will be injected intraprostatically under transrectal ultrasound-guidance. Two days later, men will receive 2 weeks of 5-FC + valganciclovir (vGCV) prodrug therapy concomitant with 80 Gy IMRT and e 2 years of AST. The primary endpoint is toxicity through day 90. Secondary endpoints are: 1) prostate biopsy at 2 years, 2) freedom from biochemical/clinical failure (FFF), 3) disease-specific survival, 4) overall survival, and 5) serum cytokine levels. We believe this research will have high impact because it may lead to better treatments for aggressive forms of prostate cancer. Public Health Relevance: The broad, long-term goal of the proposed research is to develop better cancer treatments. This research will improve further an investigational therapy that has already demonstrated promising activity in early stage...
trials of prostate cancer. We believe this research will have high impact because it will lead to better treatments for aggressive forms of prostate cancer.

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

**Development of Anatomical Patient Models to Facilitate MR-only Treatment Planning (NIH 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-physicist 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.

**Surgery**

**Principal Investigator: Jeffrey Johnson, M.D.**

**ATB-202: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Study of AB103 as Compared to Placebo in Patients with Necrotizing Soft Tissue Infections (NSTI) (HHSO1002014000013C)**

The purpose of this study is to determine whether AB103 is safe and effective in the treatment of patients with necrotizing soft tissue infections receiving standard of care therapy.

The primary hypothesis of this study is that in addition to standard of care treatment (which includes surgical intervention, antimicrobial therapy and critical care support for organ dysfunction or failure), AB103 will demonstrate a clinically significant treatment benefit over placebo.
Urology

Principal Investigator: Nallasivam Palanisamy, Ph.D.
Comprehensive Molecular Profiling of Prostate Cancer in African American Population; Unraveling Molecular Heterogeneity (Dept. of Defense W81XWH-16-1-0544)

Prostate cancer is a complex disease with multiple tumors originating independently at different stages of growth. Although morphological differences has been well recognized, the underlying molecular complexity in each tumor foci has not been well studied. Tumor growth in each foci can be determined by independent driver molecular aberration(s). Understanding the molecular level of differences in each tumor foci would help to differentiate the patients who may undergo indolent or aggressive disease course. Further, morphological differences mostly help to understand the stage of the disease, but it is not possible to select appropriate targeted therapy. If different tumor foci carry different driver molecular aberrations, targeted therapy for single molecular aberrations may not yield the curative benefit to the patients. Conventionally, systematic sampling of large tumor foci or high Gleason grade tumor foci have been considered for various genetic and molecular studies. In this approach smaller tumor foci with important driver molecular aberration and high metastatic potential can be easily missed. Therefore, using our novel approach, we propose to screen the entire prostate tissue to assess molecular differences in each tumor foci using well characterized prostate cancer specific molecular markers.
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.
Treatment Utilization Before Suicide (TUBS) (NIH 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.
ER/LA Opioid Post-Marketing Requirement Studies: Observational Study (FDA 1A 2065)

Estimate incidence of misuse, abuse, and addiction among patients treated longterm with ER/LA opioids for chronic pain overall and by the following factors: a) Clinical characteristics, product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness). b) Demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors.

Principal Investigator: Jordan Braciszewski, Ph.D.
Promoting Smoking Cessation Among Youth Exiting Foster Care (NIH 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.

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

Department of Public Health Sciences

Principal Investigator: Gwen Alexander, Ph.D.
Encouraging Young Adults to Make Effective Nutrition Choices: MENU Gen Y Study (NIH 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 (NIH R21HD085138)

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; 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 disproportionately disadvantage African American families.

Principal Investigator: Andrea Cassidy-Bushrow, Ph.D.
Delivery Mode, Environment and the Gut Microbiome: Influence on Childhood Body Size (NIH 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 (NIH 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 (lg)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 from 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 from 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-rNAPHyloChip provides 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 (Agency for Healthcare Research and Quality 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 (NIH 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) (NIH 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: Albert Levin, Ph.D.**

*Comprehensive Analysis of Gene-Environment Interaction in Sarcoidosis (NIH 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 \textit{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.

\textbf{Principal Investigator: Benjamin Rybicki, Ph.D.}
\textit{A Nested Case-Control Study of ProstateCarcinogenesis (NIH 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.

\textbf{Principal Investigator: Ganesa Wegienka, Ph.D.}
\textit{Epidemiology of Allergic Disease Endotypes (NIH 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.
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Image Analysis Program


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Full Text

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RESEARCH ADMINISTRATION

Cytogenetics


Image Analysis Program

SURGERY


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