



Seed Grant Research Program – 2011 Recipients

Cardiovascular/Pulmonary Diseases

Name: Bonny Bardhan, MBBS
Institution: University of Tennessee Health Science Center College of Medicine
Memphis, TN
Project Title: Steroids for Pediatric Acute Lung Injury Trial
Grant Amount: \$2,500

Name: Adrienne Barry
Institution: University of Illinois College of Medicine, Urbana-Champaign
Urbana, IL
Project Title: Tension Sensing at Vascular Endothelial Cell Adherens Junctions
Grant Amount: \$2,500

Name: Katherine Berg, MD
Institution: Beth Israel Deaconess Medical Center
Boston, MA
Project Title: The effect of thiamine on VO₂ in critical illness
Grant Amount: \$2,500

Name: Kalkidan Bishu, MD
Institution: Mayo Clinic
Rochester, MN
Project Title: Renalase Regulation and Heart Failure
Grant Amount: \$2,500

Name: Katja Gist, DO
Institution: University of Colorado School of Medicine
Denver, CO
Project Title: Evaluation of low cardiac output syndrome by Near Infrared Spectroscopy (NIRS) and organ specific biomarkers in children following cardiac surgery
Grant Amount: \$2,500

Name: Yashar Kalani, MD, PhD
Institution: Barrow Neurological Institute
Phoenix, AZ
Project Title: Identification of novel molecular markers for vasospasm from the cerebrospinal fluid of patients with subarachnoid hemorrhage
Grant Amount: \$2,500

Name: Sarah Kim
Institution: Drexel University College of Medicine
Philadelphia, PA
Project Title: Identification and Characterization of Novel Inhibitors of Protein Disulfide Isomerase
Grant Amount: \$2,500

Name: Donald Lynch, MD
Institution: Johns Hopkins University School of Medicine
Baltimore, MD
Project Title: Investigation of Cyclooxygenase-1 N-Glycosylation as a Novel Mechanism of Platelet Function Regulation in Aspirin Treated Diabetic Patients
Grant Amount: \$2,473

Name: Matthew Painschab
Institution: Washington University in St. Louis School of Medicine
St. Louis, MO
Project Title: The Role of Hypoxic-Responsive Plasma Biomarkers in Chronic Mountain Sickness: EPO, VEGF, and Endothelin-1
Grant Amount: \$2,500

Name: Vimal Ramjee, MD
Institution: Emory University School of Medicine
Atlanta, GA
Project Title: Inflammatory and Lipid Markers Pre- and Post-LDL Apheresis: A Multimodal Experience (The INFLAME Study)
Grant Amount: \$2,500

Name: Casey Rebholz, MPH
Institution: Tulane University School of Medicine
New Orleans, LA
Project Title: The effect of soybean protein on novel cardiovascular disease risk factors
Grant Amount: \$2,500

Name: Monica Rodriguez, MD
Institution: Northwestern University, Feinberg School of Medicine
Chicago, IL
Project Title: Effect of Nitric Oxide on the Ubiquitination of Insulin Receptor Substrate-1 in Type 1 and Type 2 Diabetes
Grant Amount: \$2,500

Name: Theresa Tran, MD
Institution: Los Angeles Biomedical Research Institute
Los Angeles, CA
Project Title: The Effect of Subclinical Hypothyroidism and Impact of Treatment with Levothyroxine on Exercise Capacity in Young and Elderly Patients
Grant Amount: \$2,500

Name: Anand Vaidya, MD
Institution: Brigham and Women's Hospital
Boston, MA
Project Title: Vitamin D Supplementation Improves Adiponectin and Renin-Angiotension System Profiles in Obesity
Grant Amount: \$2,460

Name: Gregory Wanner
Institution: Philadelphia College of Osteopathic Medicine
Collingswood, NJ
Project Title: Teaching effective compression-only cardiopulmonary resuscitation (CPR) using a short internet-based video and homemade CPR tool
Grant Amount: \$1,003

HIV/AIDS

Name: Douglas Krakower, MD
Institution: Beth Israel Deaconess Medical Center
Boston, MA
Project Title: Implementing Antiretroviral Pre-Exposure Prophylaxis (PrEP) in Clinical Practice: Assessing and Enhancing Provider Intent to Prescribe and Frequency of HIV Risk Screening
Grant Amount: \$2,500

Name: Grace Marx, MD, MPH
Institution: University of Colorado School of Medicine
Denver, CO
Project Title: A Pilot for Tailored Reproductive Counseling for Heterosexual HIV-Serodiscordant Couples
Grant Amount: \$2,500

Name: Ellen Menocal
Institution: Stony Brook University Health Sciences Center School of Medicine
Stony Brook, NY
Project Title: HIV and EBV Act in Concert to Promote EBV-Associated Malignancies
Grant Amount: \$2,500

Name: Daria Szkwarko
Institution: UMDNJ - School of Osteopathic Medicine
Stratford, NJ
Project Title: Implementing a 'child tracker': improvement of contact tracing of TB exposed child household contacts in western Kenya
Grant Amount: \$2,487

Name: Jenni Weeks
Institution: Kansas University of Medicine & Biological Sciences, College of Osteopathic Medicine
Kansas City, MO
Project Title: Effects of HIV infection on the localization of the drug efflux pump P-glycoprotein in an enterocyte/lymphocyte co-culture system
Grant Amount: \$2,500

Leukemia

Name: Neeraj Agrawal
Institution: Baylor College of Medicine
Houston, TX
Project Title: Sequence dependent synergism of HDAC inhibitor SAHA and nucleoside analogue clofarabine in pediatric leukemia
Grant Amount: \$2,493.42

Name: Huy Ngo
Institution: University of California, Davis School of Medicine
Sacramento, CA
Project Title: Validation of a Human Leukemia Mouse Model Using Next Generation RNA Sequencing
Grant Amount: \$2,500

Neoplastic Diseases

Name: Ranjith Babu
Institution: Duke University School of Medicine
Durham, NC
Project Title: Evaluation of a Targeted Fluorophore for use in Fluorescence-Guided Glioblastoma Resection
Grant Amount: \$2,480

Name: Lindsey Burnett, PhD
Institution: University of Illinois College of Medicine, Urbana-Champaign
Urbana, IL
Project Title: Is EMMPRIN Released via Stimulation of the G Protein Coupled Estrogen Receptor GPR30 in Endometrial Epithelial Cells?
Grant Amount: \$2,338.31

Name: Elizabeth de la Garza
Institution: University of Texas Medical School at San Antonio
San Antonio, TX
Project Title: Investigating the potential role of RAF-1 in the pathogenesis of ovarian cancer
Grant Amount: \$2,500

Name: Robert Dood Jr., MSCE
Institution: University of Pennsylvania School of Medicine
Philadelphia, PA
Project Title: Endometrial Ablation and Endometrial Cancer Risk: A Population-Based Cohort Study
Grant Amount: \$2,500

Name: Daniel Ferraro, MD, PhD
Institution: Washington University in St. Louis School of Medicine
St. Louis, MO
Project Title: Targeting Radiation Inducible Antigens on Tumors with Peptides
Grant Amount: \$2,500

Name: Alejandro Garcia, MD
Institution: Columbia University College of Physicians and Surgeons
New York, NY
Project Title: The role of Notch1 in experimental neuroblastoma angiogenesis
Grant Amount: \$2,400

Name: Adele Haimovic
Institution: New York University School of Medicine
New York, NY
Project Title: Anti-glycan antibody profiles, a prognostic marker in primary melanoma
Grant Amount: \$2,500

Name: Jessica Naiditch, MD
Institution: Children's Memorial Hospital
Chicago, IL
Project Title: Exploring the role of the cancer stem cell in drug resistant neuroblastoma
Grant Amount: \$2,500

Name: Vivek Patel, MS
Institution: Albert Einstein College of Medicine
Bronx, NY
Project Title: Post-transcriptional Misregulation of RNAs by IMPs drives Malignant Transformation
Grant Amount: \$2,500

Name: Jack Rostas III, MD
Institution: University of South Alabama College of Medicine
Mobile, AL
Project Title: Determination of the Mechanisms and Clinical Relevance of the Loss of the Protein, N-Myc Interactor, in the Progression of Breast Cancer
Grant Amount: \$2,492

Name: Paul Simonson, PhD
Institution: University of Illinois College of Medicine, Urbana-Champaign
Urbana, IL
Project Title: Development of super-resolution imaging for chromosomal DNA
Grant Amount: \$2,500

Name: Laura Sonoda, MPH
Institution: Keck School of Medicine of the University of Southern California
Los Angeles, CA
Project Title: Metronomic chemotherapy in ovarian cancer: Alternative mechanisms of action and novel therapeutic opportunities
Grant Amount: \$2,500

Name: Rishi Surana
Institution: Georgetown University School of Medicine
Washington, DC
Project Title: Targeting the tumor microenvironment to boost antibody-initiated adaptive immunity
Grant Amount: \$2,492

Name: Allison Watson
Institution: Sanford School of Medicine of the University of South Dakota
Sioux Falls, SD
Project Title: Interaction of SUSD2 and Galectin-1: Characterizing their role in breast tumor immune escape
Grant Amount: \$2,500

Name: Cheng-Chia Wu
Institution: New York Medical College
Valhalla, NY
Project Title: 20-HETE in Prostate Cancer Growth and Metastasis
Grant Amount: \$2,500

2011 AMA Foundation Seed Grant Recipient Project Summaries

Cardiovascular/Pulmonary Diseases Recipients

Bonny Bardhan, MBBS

University of Tennessee Health Science Center
"Steroids for Pediatric Acute Lung Injury Trial"

Project Summary: Background: Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are devastating disorders associated with overwhelming pulmonary inflammation, severe hypoxemia and respiratory failure in children. Other than supportive management, there are no specific therapies directed against ARDS/ALI in children. In adult patients, use of corticosteroids early in the course of ARDS appears promising. There are no published clinical trials examining the use of steroids for treatment of ALI/ARDS in children. All clinical trials testing the use of steroids in ARDS have only studied ventilated adult patients. In the absence of any randomized controlled trials, the current use of steroids in pediatric patients has been extrapolated from adult data. Study Design: We hypothesize that administering low-dose steroids early in the course of ALI/ARDS will have a beneficial effect on lung function and lead to decreased duration of mechanical ventilation. 50 patients will be recruited for this double blind, randomized, placebo controlled study. Patients in the study group will receive a loading dose of steroid within 72hrs of diagnosis, followed by an infusion for 7 days and then it will be tapered over the next 7 days. Blood samples will be collected on Day 1, Day 7 and Day 14 for the measurement of plasma levels of C-reactive protein, serum cortisol, inflammatory cytokines and chemokines. Goals: To finish recruitment of patients by December 2011 and have manuscript ready for submission by Mar 2012. Need for Funding: I am a 2nd yr Fellow and if I get this Seed Grant it will help with the costs of this study such as the costs of the steroid, testing the blood samples and lab expenses and software needed for data entry and analysis.

Adrienne Barry

University of Illinois College of Medicine, Urbana-Champaign
"Tension Sensing at Vascular Endothelial Cell Adherens Junctions"

Project Summary: Maintaining vascular endothelial barrier integrity is crucial to human health. This barrier, comprised of a layer of endothelial cells that form the innermost lining of blood vessels, serves a critical role in the regulation of vascular smooth muscle tone, inflammatory responses, and angiogenesis. Disruption of the mechanisms that regulate barrier function is associated with numerous cardiovascular and pulmonary diseases, including atherosclerosis, acute respiratory distress syndrome (ARDS), and asthma. Forces applied by shear stress and ventilator-induced stretch play a fundamental role in the regulation of endothelial barrier function; however, alterations in the biomechanical properties of the tissue environment are pathophysiological factors associated with many of these diseases. Vascular endothelial (VE)-cadherin is the main structural protein at vascular endothelial cell junctions and is essential for maintaining barrier function. Indirect evidence suggests that cell contractility and global cell mechanics affect endothelial cell barrier function, but there is no clear demonstration that endogenous cell contractility or exogenous mechanical stress impact VE-cadherin function. In this proposal, I will examine the effect of matrix rigidity on basal endothelial adherens junctions using confocal imaging to visualize the localization of adhesion proteins at cell-cell junctions and the organization of the actomyosin cytoskeleton. Magnetic twisting cytometry experiments involving the application of mechanical stress to VE-cadherin receptors expressed on the cell surface will test whether VE-cadherin complexes modulate intercellular contractility in response to acute, exogenous mechanical force. Determining how vascular endothelial cells sense and respond to mechanical changes in the tissue environment could yield insights for therapeutic approaches used to treat vascular pathologies.

Katherine Berg, MD

Beth Israel Deaconess Medical Center; Massachusetts General Hospital
"The effect of thiamine on VO₂ in critical illness"

Project Summary: We propose to study the effect of a single dose of intravenous thiamine on oxygen utilization (VO₂) in critically-ill, mechanically ventilated patients. Thiamine is a co-factor for pyruvate dehydrogenase, an essential enzyme for aerobic metabolism. In the absence of thiamine, the conversion of pyruvate to acetyl-CoA is inhibited and pyruvate cannot enter the tricarboxylic acid cycle. This leads to a prevalence of anaerobic metabolism and a reduction in ATP production, leading to tissue hypoxia and lactic acid accumulation. In severe thiamine deficiency this process leads to shock and multi-organ dysfunction similar to septic shock. There is previous data indicating that 20% of ICU patients with sepsis are thiamine deficient within 72 hours of presentation, and there is animal data showing both increased VO₂ and faster shock reversal in dogs with septic shock who were given thiamine pyrophosphate, regardless of the dogs' baseline thiamine level. We therefore propose to administer a single dose of 200mg of IV thiamine to critically-ill patients who are on mechanical ventilators, measuring their VO₂ using indirect calorimetry both before and after thiamine administration. Our hypothesis is that thiamine will increase VO₂ in the critically-ill.

Kalkidan Bishu, MD

Mayo Clinic

"Renalase Regulation and Heart Failure"

Project Summary: The cardio-renal syndrome is a condition in which the heart and kidney interact such that acute or chronic dysfunction in one organ results in dysfunction of the other organ. The pathophysiologic nature of the underlying heart-kidney interaction is not well understood. One potential mediator of altered cardiorenal function is a recently discovered soluble monoamine oxidase enzyme, renalase, that is secreted in the kidney and heart and catabolizes catecholamines. Preclinical studies suggest that renalase is acutely activated by catecholamines. However the mechanism is not known. As the amino acid sequence of renalase suggests potential phosphorylation sites by cAMP dependent protein kinase (Protein Kinase A, PKA), the effector enzyme in sympathetic hyperactivity, in the first aim of my study I propose to evaluate if PKA phosphorylates renalase and alters its activity in cardiac muscle fibers treated with 8-Br-cAMP. Heart failure following chronic pressure overload may produce concentric or eccentric hypertrophy phenotypes which are both associated with increased sympathetic/beta-adrenergic signaling. To assess the contribution of alteration of renalase expression and activity in heart failure, in the second aim of my study, I will assess the expression level and phosphorylation state of renalase in plasma, cardiac and renal tissue from mice subjected to 9 weeks of pressure overload with transverse aortic constriction. This study of the mechanisms of regulation of renalase and its effects in downregulating sympathetic hyperactivity in heart failure, will assist in the future design of novel therapeutic strategies.

Katja Gist, DO

University of Colorado School of Medicine

"Evaluation of low cardiac output syndrome by Near Infrared Spectroscopy (NIRS) and organ specific biomarkers in children following cardiac surgery"

Project Summary: Near Infrared spectroscopy (NIRS) is a noninvasive technique used for continuous monitoring of regional tissue oxyhemoglobin saturation. Measurement of cerebral/somatic oximetry using NIRS allows for monitoring of venous-weighted regional hemoglobin oxygen saturation in the brain and other tissues beneath the sensors. The change in regional oxygen saturation reflects oxygen delivery and tissue viability. Changes in oxygen delivery are important in a wide array of clinical settings, in particular children following congenital heart surgery. Inadequate tissue oxygen delivery secondary to low cardiac output following cardiac surgery is a relatively common phenomenon. A diagnosis of low cardiac output syndrome (LCOS) is made in the presence of specific clinical signs (tachycardia, hypotension, oliguria and metabolic acidosis) as well as invasive measurements of mixed venous saturation where there is an increase in arterial oxygen venous saturation difference. Mean arterial pressures, measures of mixed venous saturation and serum lactate reflect global adequacy of perfusion, and are generally poor indicators of regional oxygen delivery and tissue viability. The impact of poor regional tissue perfusion may lead to decreased organ specific function, specifically in the kidney and gut. Animal studies have demonstrated that NIRS was able to detect flow-induced changes in regional saturation of the kidney and gut directly under the sensor. We propose that decreased renal and splanchnic NIRS may reflect decreased regional tissue oxygen delivery and tissue ischemia in children following cardiac surgery, and in conjunction with organ specific biomarkers may detect altered end organ function prior to changes in specific clinical signs and laboratory testing such as serum creatinine for renal function.

Yashar Kalani, MD, PhD

Barrow Neurological Institute

"Identification of novel molecular markers for vasospasm from the cerebrospinal fluid of patients with subarachnoid hemorrhage"

Project Summary: Cerebral vasospasm is a recognized and poorly understood complication for many patients who have aneurysmal subarachnoid hemorrhage (SAH). Experimental evidence suggests that red-blood-cell hemolysis and subsequent release of reactive oxygen species, metabolites of hemoglobin and other inflammatory mediators are necessary for the development of vasospasm. The goal of this study is to use modern tools of genomics to identify novel molecular markers for the process of vasospasm by studying the release of micro ribonucleic acids that are secreted into the cerebrospinal fluid following the initiation of vasospastic cascades. MicroRNAs have recently been identified as important regulators of many cellular processes including cell cycle progression, proliferation, metabolic, and inflammatory cascades. We propose to study the levels of annotated microRNAs in the cerebrospinal fluid (CSF) of patients who present with SAH from their presentation through their hospital stay. It is well established that the process of vasospasm occurs over the course of many days. Long before vasospasm becomes clinically evident, cellular processes causing spasm are in action and we hope to identify microRNA mediators of these processes using high throughput screening methods. We will correlate the level of identified microRNAs with patient clinical presentation, including transcranial Doppler measurements, Glasgow Coma Score (GCS), vitals and angiographic studies. The identification of novel molecular markers of vasospasm will provide new means of identifying spasm before its onset and will facilitate early intervention.

Sarah Kim

Drexel University College of Medicine

"Identification and Characterization of Novel Inhibitors of Protein Disulfide Isomerase"

Project Summary: Thrombosis is the end stage of many disease processes, including myocardial infarction, stroke and cancer. Venous thromboembolism is a widespread concern in Western countries and currently affects approximately 1/1000 people. Currently available antithrombotic agents carry serious risks and side effects, and are often unsuited for long-term patient use. Through a series of thoughtful experiments, we propose to investigate a new potential therapeutic target for anticoagulation. Protein disulfide isomerase (PDI), an endoplasmic reticulum enzyme involved in disulfide bond formation, has been shown to be involved in coagulation. In vitro studies have demonstrated activated platelets to secrete PDI. Recently, in vivo studies have shown PDI to be required for thrombus formation. This critical finding was discovered using the model created by the Furie lab, where laser-induced thrombus formation can be studied in real time in the cremasteric arterioles of live mice. Importantly, inhibition of PDI with bacitracin or a PDI monoclonal antibody completely inhibits both platelet aggregation and fibrin generation. While the mechanism for the role of PDI in thrombus formation has yet to be elucidated, the importance of discovering inhibitors of PDI, which may serve as potential therapeutic treatment for patients requiring anticoagulation, is clear. We propose to identify and characterize known bioactive compounds capable of inhibiting PDI in a specific manner. We believe this will serve as an important contribution to not only the research dedicated to this subject, but to the advancement of clinical medicine and how we treat patients.

Donald Lynch, MD

Johns Hopkins Hospital

"Investigation of Cyclooxygenase-1 N-glycosylation as a Novel Mechanism of Platelet Function Regulation in Aspirin Treated Diabetic Patients"

Project Summary: Diabetic patients have an increased risk of cardiovascular events relative non-diabetic patients of similar cardiac risk. Aspirin (ASA), which has a well-established role in the secondary prevention of vascular events, has been found to be less effective for patients with diabetes. ASA exerts its antiplatelet effect by acetylation of the serine 529 (Ser 529) residue of cyclooxygenase-1 (COX-1) causing irreversible inhibition of the enzyme which leads to diminished thromboxane production. This in-turn decreases the ability of platelet to form thrombus, and thus minimizes ischemic events. Aspirin resistance (AR), as defined by persistent thromboxane production or platelet activity, has been associated with markers of poor glycemic control among ASA-treated diabetic patients. I will test the hypothesis that glycosylation of COX-1 leads to impaired ASA response among patients with diabetes by interfering with Ser 529 acetylation. Preliminary studies have shown that the Ser 529 residue can be isolated from serum samples using a novel orbitrap mass spectrometry-based approach. I have demonstrated the ability of this technique to reliably identify post-translation modifications within COX-1, including glycosylations. I will use additional novel proteomics-based techniques to identify and correlate patterns of COX-1 glycosylation with Ser 529 acetylation and platelet function as assessed by aggregation in a cohort of diabetic and non-diabetic patients. The results of this project will provide valuable insight into the regulation of platelet function and further explore mechanisms of variability in the antiplatelet effect of ASA therapy in diabetic patients.

Matthew Painschab

Washington University in St. Louis School of Medicine

"The Role of Hypoxic-Responsive Plasma Biomarkers in Chronic Mountain Sickness: EPO, VEGF, and Endothelin-1"

Project Summary: The study of altitude-related chronic illnesses is an important field of investigation relevant to the 140 million people worldwide who currently reside at altitudes > 2500 meters above sea level. The most commonly fatal altitude-related illnesses are chronic mountain sickness (CMS) and high-altitude pulmonary hypertension, characterized by excessive erythrocytosis and pulmonary hypertension respectively. Each of these diseases is increasingly thought to be due to an overly sensitive response to hypoxia. The prevalence of CMS is higher in Andean populations than Tibetan and recent genetic evidence points to mutations in the Hypoxia Inducible Factor (HIF) pathway as protective in native Tibetans and correlated with decreased hemoglobin levels. Erythropoietin, vascular endothelial growth factor and endothelin-1 are potential pathologic effector proteins in the HIF pathway that can be measured in blood and each have been shown to contribute to excessive erythrocytosis or pulmonary hypertension in animal models. We anticipate that endothelin-1 and EPO will be elevated in CMS patients but that VEGF will be decreased due to binding by VEGFR1 when compared to healthy controls. We will conduct our study in Puno, Peru at an elevation of 3825 meters above sea level. Protein levels will be determined from plasma samples collected previously. This study has a number of important implications. First, this study has potential to shed light on a number of important molecular effectors of CMS. This will be the first study to measure endothelin-1 and VEGF in patients living chronically at altitude. Second, the results of this study could shed insight on therapeutic targets or biomarkers for any number of disease states marked by hypoxia or pulmonary hypertension. Finally, it has been recognized that patients living at altitude have a decreased incidence of atherosclerosis and this study may contribute valuable insights into cardioprotective mechanisms.

Vimal Ramjee, MD

Emory University School of Medicine

"Inflammatory and Lipid Markers Pre- and Post-LDL Apheresis: A Multimodal Experience (The INFLAME Study)"

Project Summary: This is a prospective case-series clinical research study assessing the effects of LDL apheresis on inflammatory and lipid markers in patients with familial hypercholesterolemia (FH). By using FH as a unique model of accelerated atherosclerosis in conjunction with an established procedure that resets our atherogenic burden, this study will enable us to understand the rebound kinetics of key inciting agents in the process of atherogenesis. We will evaluate the effects of LDL apheresis on an expanded panel of crucial biomarkers in this rare population. In carefully measuring changes at predetermined time intervals, we will gain a better understanding of the role of each pathway - inflammatory, lipid, and oxidative - in atherogenesis, as well as how these pathways relate to each other from a temporal standpoint. Furthermore, by assessing adjunctive novel parameters - endothelial progenitor cell (EPC) colonies and gene regulation - this study will help us relate biomarker changes in the blood to molecular and protein-directed events in the vascular system. Our findings in this pilot study will not only provide a unique perspective into the process of atherogenesis, but may act as a stepping stone to large clinical trials investigating the optimal LDL apheresis time interval based on rebound kinetics of atherogenic markers. This has the potential to directly impact patient care, improve the quality of life of patients with familial hypercholesterolemia, and provide a cost-savings in the healthcare system.

Casey Rebholz, MPH

Tulane University School of Medicine; Tulane University School of Public Health and Tropical Medicine

"The effect of soybean protein on novel cardiovascular disease risk factors"

Project Summary: Cardiovascular disease (CVD) is the leading cause of death in the US and the world. Clinical trials have suggested that soybean protein supplementation lowers serum lipids and blood pressure. However, the effect of soybean protein on novel CVD risk factors has not been well studied. The overall objective of the proposed study is to examine the effect of soybean protein supplementation on biomarkers of inflammation and endothelial dysfunction. We will test the following hypothesis in a randomized, placebo-controlled, double-blind, 3-phase crossover trial. Hypothesis 1: Soybean protein supplementation reduces plasma levels of systemic inflammatory markers. Hypothesis 2: Soybean protein supplementation reduces plasma biomarkers of endothelial dysfunction. The proposed study is very cost-effective because we will use data and plasma specimens from the completed NIH-sponsored soybean protein supplementation trial—Protein and Blood Pressure (ProBP) study. The ProBP study is designed to compare the effect of an 8-week intervention of 40 grams/day of soybean protein supplement (89.3 mg isoflavones), 40 grams/day of milk protein supplement, and 40 grams/day of complex carbohydrate placebo on blood pressure in 60 men and women aged 22 years and older with untreated prehypertension or stage-1 hypertension in New Orleans, Louisiana and Jackson, Mississippi. The effect of soybean protein supplementation will be compared to both milk protein and a complex carbohydrate control in order to separate the effect of soybean protein with other protein supplementation on CVD risk factors. In the proposed study, we will measure plasma levels of inflammatory markers (C-reactive protein, interleukin-6, and tumor necrosis factor- α) and biomarkers of endothelial dysfunction (plasma levels of E-selectin, intercellular adhesion molecule-1, vascular adhesion molecule-1, thrombomodulin, and endothelin-1) among all 60 study participants.

Monica Rodriguez, MD

Northwestern University, Feinberg School of Medicine

"Effect of Nitric Oxide on the Ubiquitination of Insulin Receptor Substrate-1 in Type 1 and Type 2 Diabetes"

Project Summary: Patients with diabetes suffer from higher failure rates following vascular interventions due to aggressive restenosis secondary to neointimal hyperplasia. While nitric oxide (NO) has been shown to effectively inhibit neointimal hyperplasia in animal models of arterial injury, we found that NO is more effective at inhibiting neointimal hyperplasia in type 2 diabetic rodents and less effective in type 1 diabetic rodents, compared to controls. These data suggest a role for insulin in mediating the effects of NO, given that the main difference between these animal models is hyperinsulinemia versus hypoinsulinemia. To investigate the etiology of the markedly different efficacy of NO in type 1 versus type 2 diabetes, we directed our attention to the ubiquitin-proteasome pathway which is responsible for the majority of protein degradation in our bodies, including proteins of the insulin signaling cascade. Specifically, insulin receptor substrate-1 (IRS-1) is responsible for activating the downstream MAPK or PI3K/Akt pathways, which propagate mitogenic or metabolic survival signals, respectively. Recent studies revealed that IRS-1 is regulated by protein ubiquitination through CUL7, a ubiquitin ligase. Given that our lab has shown that NO can mediate ubiquitination of proteins, and given the role of CUL7 in mediating ubiquitination of IRS-1, we hypothesize that NO differentially regulates ubiquitination and degradation of IRS-1 in type 1 versus type 2 diabetes by regulating CUL7 and that this accounts for the differential efficacy of NO in these metabolic environments. To investigate this hypothesis, our specific aim is to evaluate the effect of NO on the ubiquitination of IRS-1 in animal models of type 1 and 2 diabetes in vivo. By obtaining a deeper understanding of the effects of NO on the ubiquitin proteasome and insulin signaling pathways, we will be better equipped to develop innovative therapeutics to prevent restenosis in patients with diabetic vascular disease.

Theresa Tran, MD

Los Angeles Biomedical Research Institute at Harbor – UCLA Medical Center

“The Effect of Subclinical Hypothyroidism and Impact on Treatment with Levothyroxine on Exercise Capacity in Young and Elderly Patients”

Project Summary: Subclinical hypothyroidism, defined as an elevated serum thyrotropin (TSH) level in the presence of a normal serum free thyroxine (FT4) concentration, represents a common diagnosis that increases in prevalence with age. Recent studies have suggested that subclinical hypothyroidism may affect elderly patients differently than it affects younger patients. Patients with subclinical hypothyroidism have a higher frequency of muscular symptoms as well as objective evidence for impairment of muscle energy metabolism during incremental exercise, but it is unclear whether exercise capacity is affected in a clinically significant manner. The aim of this study is to determine whether patients with subclinical hypothyroidism have decreased exercise capacity compared to the general population, and whether treatment with levothyroxine has an effect of these changes. A secondary aim is to determine whether there is a difference among younger patients (<60 years) versus older patients (≥60 years). Patients with endogenous, untreated subclinical hypothyroidism will be recruited for this study. They will undergo cardiopulmonary exercise testing (CPET) with measurement of various exercise parameters including peak VO₂, the primary measure of exercise capacity. The exercise capacity of these participants will be compared to a control group consisting of healthy historical controls to establish whether baseline differences exist. The participants will be randomized into two groups, one group that will be treated with levothyroxine until they are euthyroid for six months, and another group that will remain untreated. The CPET will then be repeated in all study participants. The primary study outcome is peak VO₂ and its change after therapy between the treated versus untreated groups as a whole, and between older versus younger patients.

Anand Vaidya, MD

Harvard Medical School; Brigham and Women’s Hospital

“Vitamin D Supplementation Improves Adiponectin and Renin-Angiotension System Profiles in Obesity”

Project Summary: Obesity is strongly associated with cardiovascular diseases; excess activity of the renin-angiotensin system (RAS), hypoadiponectinemia, and vitamin D deficiency are all potential mechanisms for this increased risk. The specific reasons for the dysregulated RAS activity and adiponectin deficiency in obesity remain unresolved, however, preliminary data have implicated vitamin D as a potentially important regulator. Vitamin D has been shown to negatively regulate renin and has been positively associated with adiponectin. Whether vitamin D supplementation in obesity raises circulating adiponectin via reductions in RAS activity has not been studied. The demonstration that vitamin D improves RAS and adiponectin profiles would strongly support vitamin D supplementation as a cheap, natural, and physiologic intervention to potentially abrogate cardiovascular disease in obesity. This research study aims to study the effect of prospective vitamin D supplementation on circulating adiponectin and the RAS in obese individuals with vitamin D deficiency. Using a protocol designed to control for major confounders of the RAS and adiponectin, the results of this study may definitively answer whether vitamin D supplementation represents a favorable intervention to counter two major risks for cardiovascular disease: adiponectin deficiency and excess RAS activity.

Gregory Wanner

Philadelphia College of Osteopathic Medicine

“Teaching effective compression-only cardiopulmonary resuscitation (CPR) using a short internet-based video and homemade CPR tool.”

Project Summary: Each year hundreds of thousands of people die due to cardiac arrest outside of the hospital. Although cardiopulmonary resuscitation (CPR) has been shown to save lives and improve outcomes, less than 30% of cardiac arrest victims initially receive CPR from a bystander. Several studies have validated the effectiveness of compression-only CPR: The performance of chest compressions without the ventilation/breathing portion of CPR. In 2008 and again in 2010 the American Heart Association (AHA) recommended the use of compression-only CPR for bystanders who witness someone suddenly collapse. Despite the AHA recommendations and effectiveness of compression-only CPR, little research has focused on teaching compression-only CPR to potential bystanders. Our study aims to evaluate a method of teaching compression-only CPR using a short internet-based video and home CPR tool made from items commonly found around the house. We hope to determine if it is possible to teach the basics of compression-only CPR without the cost and time commitment required of traditional CPR training methods. While we do not foresee our training method as a replacement for traditional CPR courses, we do hope our method will provide a minimum competency in compression-only CPR for potential bystanders that would not otherwise receive any CPR training. Additionally, we hope this approach will re-familiarize individuals previously trained in CPR and encourage interest in a traditional CPR course for those individuals not previously trained.

HIV/AIDS Recipients

Douglas Krakower, MD

Beth Israel Deaconess Medical Center, Harvard Medical School

“Implementing Antiretroviral Pre-Exposure Prophylaxis (PrEP) in Clinical Practice: Assessing and Enhancing Provider Intent to Prescribe and Frequency of HIV Risk Screening”

Project Summary: In 2010, groundbreaking clinical trials demonstrated that antiretroviral pre-exposure prophylaxis (“PrEP”), a novel HIV prevention strategy, can reduce the risk of HIV infection in high-risk individuals. As most potential PrEP consumers will be in the care of primary care providers, translating trial efficacy into real-world effectiveness will require providers to identify individuals who are likely to benefit from PrEP and prescribe PrEP to these individuals. However, most providers will have limited experience prescribing antiretrovirals, and may not be comfortable prescribing PrEP. Furthermore, providers will need to screen patients for HIV risk factors to identify high-risk individuals, but current screening rates are low. I hypothesize that provider intent to prescribe PrEP will be predicted most strongly by perceived ability to prescribe PrEP safely, and frequency of HIV risk screening will be predicted by reported comfort obtaining a history of high-risk behaviors. My goals are to: (1) understand predictors of intent to prescribe PrEP and frequency of HIV risk screening; (2) develop an educational intervention designed to increase intent to prescribe PrEP and frequency of risk screening; and (3) explore its acceptability and impact on prescribing and screening intentions. I will administer a survey to 500 primary care providers in New England to assess intent to prescribe PrEP, frequency of HIV risk screening, and perception of self-efficacy around PrEP prescribing. I will analyze the surveys to determine predictors of my outcomes of interest. I will develop and pilot an educational intervention among 50 providers and use pre-/post-intervention surveys and 20 qualitative key informant interviews to explore its acceptability and its impact on provider prescribing and screening intentions. Understanding ways to enhance PrEP prescribing could facilitate implementation of this promising prevention strategy.

Grace Marx, MD, MPH

University of Colorado Internal Medicine Residency Program

“A Pilot for Tailored Reproductive Counseling for Heterosexual HIV-Serodiscordant Couples”

Project Summary: HIV-serodiscordant couples are routinely encouraged to use condoms to reduce the risk of HIV transmission. However, several studies have demonstrated that reproductive desire is not diminished in couples when one partner is infected with HIV. Counseling in reproductive services for this population is exceedingly limited and serodiscordant couples are often left to their own means to conceive, resulting in unsafe sexual practices without condom use. In this study, we will develop a pilot survey of HIV-infected patients at the University of Colorado Hospital Infectious Disease Clinic in Denver to explore reproductive desires, contraception and condom use, sexual partnerships, and satisfaction with their routine reproductive counseling. The survey will first be given to a small subset of patients to evaluate its accuracy and reliability. The standardized survey will then be administered to all HIV-infected individuals of reproductive age at the clinic. Identified HIV-serodiscordant couples will then be invited to participate in a future study. Participants will be randomized to the intervention or standard of care groups. The intervention arm will consist of sessions in which the HIV-infected partner and non-infected partner participate in an individualized discussion of reproductive options, horizontal HIV transmission risks and contraception/condom use. The non-intervention group will receive standard reproductive counseling provided routinely in the clinic. Reproductive intentions, understanding of HIV transmission risk and frequency of condom and contraception use will be compared pre- and post-intervention. Findings demonstrating reductions in high-risk sexual behavior and HIV transmission in the intervention arm would provide strong incentives for HIV clinics to routinely provide tailored reproductive counseling to their patients.

Ellen Menocal

SUNY Upstate Medical University

“HIV and EBV Act in Concert to Promote EBV-Associated Malignancies”

Project Summary: Epstein-Barr Virus (EBV) is a well-characterized virus whose disease spectrum is clearly defined. Its relationship and involvement in HIV disease pathogenesis, however, remains elusive. Evidence suggests the existence of an important relationship between HIV and EBV, as EBV levels are elevated in HIV-positive patients relative to HIV-negative controls, and there is an higher incidence of more aggressive EBV-associated malignancies, such as diffuse large B cell lymphoma and Burkitt's Lymphoma, within the HIV positive population compared to uninfected people. While it may appear that EBV may flourish as a result of immune compromise secondary to HIV infection, there are likely additional factors contributing to higher EBV DNA loads and the EBV-associated malignancies. For example, evidence from various studies suggests that persistence of the EBV may be enhanced by a transcription factor within the HIV genome itself. Our lab will adapt a published protocol to determine whether the HIV transcription factor, Tat, can induce EBV replication,. This will be examined by looking at BZLF1 and gp350 mRNA levels and associated protein products. in cell lines Chromatin Immunoprecipitation will be utilized to establish whether the Tat protein is directly acting on the EBV replication origin. Finally, long-term trends in EBV DNA levels relative to HIV levels (and by extension Tat levels) will be examined using a cohort of HIV-infected patients treated with anti-retroviral therapy.

Daria Szkwarko

University of Medicine and Dentistry of New Jersey – School of Osteopathic Medicine

“Implementing a ‘child tracker’: improvement of contact tracing of TB exposed child household contacts in western Kenya”

Project Summary: Tuberculosis (TB) in children has been estimated to account for 11% of new cases of TB globally. However, childhood TB has remained a neglected aspect of TB control programs in low-resource settings. Previous research has demonstrated that in >60% of pediatric TB cases there is a history of a positive household contact, and that the risk of TB disease progression is increased if primary infection occurs at a young age (especially in children aged 0-4). The World Health Organization (WHO) recommends that all child household contacts be recorded in a separate child contact register and screened for TB disease. In Eldoret, Kenya, the local TB program has been managing TB diagnosis and treatment according to country guidelines for 20 years. At AMPATH Center (Eldoret) a child contact register was implemented to track and symptomatically screen all household child contacts. Presently, HIV infected child contacts from the register are not systematically referred to the HIV pediatric clinic for standard evaluation and diagnostic screening. Under the current system, it is unclear whether these exposed children receive TB evaluation at their subsequent pediatric visits. The primary aim will be to implement and evaluate the WHO’s recommendation for TB screening of all TB exposed children in the AMPATH clinics. This study will: 1) establish a child tracker (CT) to maintain a ‘just in time’ list of all HIV+ child contacts exposed to TB from the contact register, 2) create the communication system between the TB clinic and the pediatric office, and 3) evaluate program outcomes. This program will close the existing gap between the TB program and the pediatricians caring for HIV+ children (ages 0-5). This program may serve as a reproducible model for other TB/HIV care programs in resource constrained, high TB burden areas.

Jenni Weeks

Kansas City University of Medicine and Biosciences

“Effects of HIV infection on the localization of the drug efflux pump P-glycoprotein in an enterocyte/lymphocyte co-culture system”

Project Summary: Human Immunodeficiency Virus (HIV) infection has become a world-wide problem, killing millions of people each year. A patient who is infected with HIV will develop Acquired Immune Deficiency Syndrome (AIDS) within ten years if left untreated; this is primarily due to widespread destruction of CD4+ T-lymphocytes during HIV infection. The current treatment regimen for HIV infection includes use of long-term antiretroviral therapy and has proven to be very successful; however, complete eradication of the virus remains inefficient due to the presence of viral reservoirs. These viral reservoirs are known to be found in many areas including the gut-associated lymphoid tissue (GALT). While many mechanisms of viral reservoir maintenance have been proposed, the focus of this study is on a drug efflux pump in a model of the human GALT, an enterocyte/lymphocyte co-culture system. P-glycoprotein is a drug efflux pump with broad specificity for many different drugs and chemicals, including most antiretroviral pharmaceuticals used during therapy for HIV infection. P-glycoprotein has been suspected to prevent antiretroviral drugs from reaching and subsequently eradicating the virus by pumping the drugs out of the cell and away from the HIV. Within the small and large intestine, P-glycoprotein is found in cells at the apical surface. Studies have shown, that during certain disease states, P-glycoprotein cellular localization is modified with the protein shifting to other sites such as the golgi apparatus and within the nucleus. We hypothesize that HIV infection will induce an atypical localization of P-glycoprotein. This may play a role in the reduction of intracellular accumulation of antiretroviral drugs leading to inefficient eradication of the virus. The knowledge gained from these studies may lead to the development of new strategies to increase the penetration of antiretroviral drugs into reservoir sites subsequently enhancing HIV therapy.

Leukemia Recipients

Neeraj Agrawal

Baylor College of Medicine

“Sequence dependent synergism of HDAC inhibitor SAHA and nucleoside analogue clofarabine in pediatric leukemia”

Project Summary: Leukemia is the most common cancer of the pediatric population. While a majority of these patients are curable, nearly 20% of children with leukemia relapse. Salvage therapy for high risk and relapsed patients has been associated with high rates of acute and long-term toxicities. Current research has focused on finding new or alternative treatments for these patients. Recent research of novel therapies has focused on the potential of histone deacetylase inhibitors (HDACI) like SAHA and nucleoside analogues (NA) like clofarabine. Clofarabine, a novel nucleoside analogue, was recently approved for the treatment of high risk and relapsed pediatric acute lymphoblastic leukemia (ALL) patients. However, clofarabine has been found to be highly myelosuppressive. HDAC inhibitors are potent antiproliferative agents that were recently approved in the treatment of Cutaneous and Peripheral T-cell lymphoma (CTCL, PTCL). Preliminary studies suggest there is a synergistic effect using the combination of clofarabine and the HDAC inhibitor SAHA in leukemia. Using leukemia cell lines and patient leukemia samples, this project would provide pharmacological evidence that this drug combination is synergistic by mathematically modeling their interaction. It would also determine if this interaction is dependent on the sequence of drug addition. The combination of HDACI and clofarabine is particularly important in pediatric oncology because the combination would have non-overlapping toxicities and could increase the efficacy of clofarabine while reducing its toxicities (potentially by the ability to use a lower dose of clofarabine). This could provide physicians with better treatment options for acute leukemia patients.

Huy Ngo

University of California, Davis School of Medicine

“Validation of a Human Leukemia Mouse Model Using Next Generation RNA Sequencing”

Project Summary: Having a validated disease model to characterize hematological cancers provides a tool to study how human malignancies proliferate and a means to develop and test treatment therapies. Currently, the xenograft mouse model is one of the most successful models for these purposes since primary leukemia cells do not grow well in vitro. Also, leukemia is a group of heterogeneous diseases and there are a very limited number of established cell lines. Dr. Satake and her colleagues developed a childhood leukemia mouse model using immunodeficient mice and patients' leukemia samples. To develop a novel drug therapy for patients using a mouse model, we need to validate this model by demonstrating that it carries the same leukemia as the original leukemia from patients. Among many tools which are currently used to determine leukemia type, including flow cytometry, karyotyping, and FISH analysis, gene analysis provides the most detailed and accurate comparison of these two samples. The goal of this project is to compare the detailed gene expression panel between the engrafted leukemia cells in the mouse model and the original leukemia cells from patients using an advanced gene analysis method. We hypothesize that the gene expression pattern will be the same between engrafted and original leukemia. We will test our hypothesis by using Next-Generation Sequencing, specifically RNA-Sequencing (RNA-Seq), which is the most contemporary method of transcriptome analysis. This new sequencing technology provides not only basic expression profiling, but also quantitative detection of splice variants and point mutations, all of which cannot be accomplished by a single microarray. In this project, we will use RNA-Seq to validate the mouse model with precursor B acute lymphoblastic leukemia, the most common leukemia in children. We expect successful validation of the mouse model, which will be valuable for subsequent use of this model.

Neoplastic Diseases Recipients**Ranjith Babu**

Duke University School of Medicine

“Evaluation of a Targeted Fluorophore for use in Fluorescence-Guided Glioblastoma Resection”

Project Summary: Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and is one of the most deadly cancers in humans. Despite attempts to treat it with surgery, radiation, and chemotherapy, the median survival of patients with GBM is 14.6 months. In recent years, chemotherapy research has flourished due to the discovery of tumor specific targets using genomic profiling. However, progress has lacked in what is considered the first line treatment of GBMs – surgery. GBM resections are challenging due to their infiltrative nature. Tumor margins are unclear, forcing neurosurgeons to balance aggressive resection with the risk of removing normal brain. Fairly recently, investigation into the use of fluorescence for intra-operative tumor detection has increased. Previous studies using 5-aminolevulinic acid (5-ALA) and fluorescein have shown statistically significant increases in gross total resection, disease free survival, and overall survival. However one limitation of 5-ALA and fluorescein is that they passively accumulate within tumors, resulting in fluorescence of adjacent edematous non-tumor tissue. This may cause resection of healthy tissue, increasing surgical complications and long term side effects. To avoid this problem, we seek to use a fluorophore targeted to the epidermal growth factor receptor (EGFR) which is overexpressed in approximately half of all GBMs. We will compare the targeted fluorophore, EGF-fluorescein, to 5-ALA and untargeted fluorescein in in vitro and in vivo models to determine the most effective fluorophore for optimal GBM resection. We hope to make fluorescence-guided GBM resection more safe and effective, improving the lives of those afflicted with this devastating disease.

Lindsey Burnett, PhD

University of Illinois College of Medicine, Urbana-Champaign

“Is EMMPRIN Released Via Stimulation of the G Protein Coupled Estrogen Receptor GPR30 in Endometrial Epithelial Cells?”

Project Summary: Metastatic cancer cell invasion and normal tissue remodeling in the uterus are both highly dependent on matrix metalloproteinases (MMPs). Secretion of MMPs can be induced by the transmembrane, glycosylated protein known as Extracellular Matrix Metalloproteinase Inducer (EMMPRIN). EMMPRIN expression is highest in luminal and glandular epithelial cells during the late proliferative phase of the menstrual cycle suggesting that expression is estrogen dependent. Previous studies in our laboratory have shown that estrogen increases EMMPRIN protein expression and release by uterine epithelial cells in vitro and that EMMPRIN induces MMP production by uterine stromal cells. Estrogen can elicit cellular response by interacting with conventional nuclear estrogen receptors or alternatively by acting on the cell surface estrogen receptor GPR30. Clinically GPR30 overexpression is correlated with highly invasive endometrial adenocarcinomas and poor survival. Endometrial carcinomas with overexpression of GPR30 also more frequently exhibited deep myometrial invasion in clinical studies. These studies suggest that GPR30 is an estrogen-responsive receptor that is over-expressed and functionally relevant in uterine endometrial cells. I propose to examine the role of GPR30 signaling on EMMPRIN production and secretion in normal (EECs) uterine epithelial cells and Type I and Type II endometrial carcinoma cells (Ishikawa and Hec50cs) to provide insight into estrogen-mediated cell invasion and proliferation. These experiments will investigate a novel mechanism of estrogen-mediated EMMPRIN release and subsequent cell invasion via stimulation of the G protein coupled estrogen receptor GPR30. These experiments may have

implications for treatment of endometrial carcinomas as well as other estrogenic neoplastic cancers such as breast and prostate cancer.

Elizabeth de la Garza

University of Texas Medical School at San Antonio

“Investigating the potential role of Raf-1 in the pathogenesis of ovarian cancer”

Project Summary: As of now, the development and pathogenesis of ovarian cancer remains a great mystery. Each year, more than 14,000 women die due to ovarian cancer. While little by little, scientists are unveiling the various biochemical markers, cytokines, intracellular events involved in this fatal malignancy, there is still much work left to be done. The goal of my research is to help participate in this great endeavor by identifying the role that the intracellular signaling protein Raf-1 plays in the processes involved in advanced malignant disease. My preliminary data has unveiled a crucial role of Raf-1 in mediating TGF-beta actions in endometrial cells. It is likely that cytokines elevated in the peritoneal fluid of women with ovarian cancer, specifically TGF-beta, EGF, and CXCL1, may also utilize Raf-1 to activate the MEK/ERK cascade in ovarian cancer cell invasiveness and proliferation. I hypothesize that Raf-1 mediates the actions of TGF-beta, EGF and/or CXCL1 in malignant progression of ovarian cancer. Through the use of in vitro trans-membrane cell invasion models and proliferation assays, I plan to examine the effects that the Raf-1 molecular inhibitor, GW5074, and Raf-1 siRNA have on the invasiveness and proliferative potential of ovarian cancer cells treated with physiologic concentrations of TGF-beta, EGF, and CXCL1. Western blot experiments will also be used to examine whether CXCL1 directly activates Raf-1 and downstream MEK/ERK since both TGF-beta and EGF have already been shown to do this by previous studies and according to my preliminary data. Identifying Raf-1's involvement in ovarian cancer will not only help us better understand the pathogenesis of ovarian cancer, but it could also potentially serve to unveil novel therapeutic targets in the treatment of ovarian cancer and one day help us to save lives.

Robert Dood, Jr.

University of Pennsylvania School of Medicine

“Endometrial Ablation and Endometrial Cancer Risk: A Population-Based Cohort Study

Project Summary: Dysfunctional Uterine Bleeding (DUB) and its similar diagnoses are the most common presenting gynecologic complaint (Jamieson 1996). Endometrial ablation is increasing in use to treat DUB, yet there are insufficient data on endometrial cancer risk and long-term patient safety and cancer outcomes following this procedure. Objective: To determine if undergoing endometrial ablation for DUB carries an increased risk of endometrial cancer, mortality, or poor endometrial cancer outcomes. Methods: A cohort study will be performed in the U.K. The Health Improvement Network (THIN) comparing almost 1 million women with a diagnosis of DUB, who elect endometrial ablation versus other treatments for DUB. The study will examine the relative risk of endometrial cancer, overall mortality, age and stage at diagnosis, and endometrial cancer mortality between those who elected endometrial ablation versus those who elected other treatment modalities for DUB.

Daniel Ferraro, MD, PhD

Washington University in St. Louis School of Medicine

Project Summary: Radiation therapy plays a role in the treatment of many solid tumors. There have been many advances in the technology of radiation delivery to tumors, including intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and ion therapy. These have all allowed for lower normal tissue radiation doses in hopes of fewer cases of significant radiation therapy side effects. The limitation of these techniques is that they are only able to control the biological effect of the radiation on a macroscopic level (i.e. area irradiated). A more precise approach to reduction of radiation therapy sequelae would be the modulation of radiation effect in tumor cells compared to normal tissue through targeted drug delivery. Tip-1, a protein expressed on the surface of irradiated cancer cells, has been found to bind the small peptide HVGSSV. This peptide can be conjugated to drug delivery vehicles and imaging agents to target these compounds to the cancer cells. The hypothesis for this proposed research is that modification of the amino acid sequence HVGSSV using rational protein engineering techniques will result in a peptide with higher affinity and more specificity to Tip-1. We will approach this problem using both in silico protein modeling methods and in vitro biophysical measurements. The long-term goal of this project is to develop a peptide that can be brought into animal studies as part of a novel targeted drug or imaging agent.

Alejandro Garcia, MD

Columbia University College of Physicians and Surgeons

“The role of Notch 1 in experimental neuroblastoma angiogenesis”

Project Summary: Neuroblastoma (NB) is the most common extracranial solid tumor in children. Most children present after 18 months of age with metastatic disease. Survival rates remain below 35% despite intensive therapy. Current trials demonstrate that children tolerate anti-VEGF treatment well, yet the emergence of resistance suggests that alternative mechanisms rescue tumors. Notch proteins are expressed in NB, and Notch signaling in vessels increases when VEGF is blocked. This suggests that Notch may partly compensate for lack of VEGF. Our lab previously engineered NGP NB cells to express a novel Notch-1 decoy (N1D) construct, which blocks Notch activation in tumors and vessels. N1D impaired angiogenesis but did not affect NGP cell proliferation or survival, suggesting that N1D primarily acted by disrupting

vessels. Knockdown of Notch1 in NGP tumors did not affect tumor growth or perfusion. Thus, I hypothesize that Notch functions primarily in the vasculature of NB. To test this hypothesis, I will cross Notch1-/+ heterozygote mice, which display impaired angiogenesis but are viable and fertile, to Rag2-/-gammaC-/- immunodeficient mice. Homozygote Notch1-null mice die early in embryogenesis with defective vasculature, supporting the critical role of Notch in physiologic angiogenesis. To determine whether Notch is required in NB host vessels, we will study the effect of xenografting NGP cells into Notch1-/+ mice. Next, we will determine how altered host Notch1 status influences responses to VEGF blockade.

Adele Haimovic

New York Medical College

“Anti-glycan antibody profiles, a prognostic marker in primary melanoma”

Project Summary: The prognosis of melanoma varies according to the stage of disease at the time of diagnosis. Patients with stage II disease have a variable prognosis, with an intermediate-risk for recurrence. The standard of care for stage II melanoma is controversial. For some patients with stage II disease surgical therapy is curative while others may develop metastatic diseases and require adjuvant therapy. A prognostic test that can help better stratify stage II patients according to recurrence groups would enable clinicians to select those melanoma patients whom the benefits of adjuvant therapy outweigh the morbidity of the side effects. This project will assess if antibodies against cell-surface antigens, specifically glycans, can be used as a risk assessment tool for recurrence in melanoma. Glycans displayed on the surface of cancer cells are modified versions of those found on healthy cells. These abnormal glycans are immunogenic, and antibodies against them can be detected in patients' sera. The sera of patients with stage II melanoma, half of who experienced recurrence, will be examined to create a melanoma anti-glycan antibody “recurrence signature”. We will conduct this study in 2 phases: Phase I, the training set, will test 70 patients diagnosed with localized melanoma, 35 of whom recurred, with minimum 2.5 years follow up. Anti-glycan antibody levels in the sera will be measured to create an anti-glycan antibody immunoprofile for patients at high risk of recurrence. Phase II, the validation study, will perform sera analysis of 50 independent patients with stage II melanoma to determine the validity of the “recurrence signature”. In phase II the investigators will be blind to the recurrence status of the patient. We hypothesize that this “recurrence signature” will be a clinically useful prognostic signature to determine the chance of recurrence in newly diagnosed cases.

Jessica Naiditch, MD

Children's Memorial Hospital, Chicago

“Exploring the role of the cancer stem cell in drug resistant neuroblastoma”

Project Summary: Neuroblastoma (NB) is one of the most common solid tumors in children. NB can have an excellent prognosis with over 90% survival when localized, but may also portend poor prognosis with 20-35% survival in late-stages. While most high-risk NB patients have an initial response to chemotherapy, the majority of such patients eventually develop progressive disease that is refractory to chemotherapy. Therefore, drug resistance poses a major obstacle in the treatment of NB. There is increasing evidence that a unique population of cancer stem cells (CSCs) exists that has the ability to lead to the heterogenous cell populations that make up a tumor, and their persistence through chemotherapy treatment may lead to relapse. The goal of this research is to identify the cancer stem cell in NB and determine its role in drug resistance. We will evaluate for the expression of “stemness” genes in multiple wild type and drug resistant NB cell lines. We expect to find one or more markers upregulated in drug resistant lines. We will isolate cells expressing these markers and determine if they possess the properties of a cancer stem cell including the ability to self-propagate and to differentiate into the heterogenous cell lineages that make up a tumor. Finally, we will assess for cells expressing these putative stem cell markers in human neuroblastoma tumor samples collected before and after treatment with chemotherapy to determine if the CSC subpopulation is upregulated in residual, drug resistant tumor. Resistance to chemotherapeutic agents is a problem that affects many patients with a variety of cancers and often is the cause for their ultimate demise. Given that CSC are thought to exist in numerous cancers, understanding how cancer stem cells mediate drug resistance may lead to therapies targeted against cancer stem cells in many malignancies with broad implications for cancer care.

Vivek Patel, MS

Albert Einstein College of Medicine

“Post-transcriptional Misregulation of RNAs by IMPs drives Malignant Transformation”

Project Summary: Insulin-like growth factor II messenger RNA binding proteins (IMPs) are a family of developmentally essential oncofetal RNA-binding proteins. IMPs have proven to be reliable prognostic and diagnostic biomarkers for multiple neoplastic conditions, emphasizing their fundamental role in the mechanism of malignant transformation. IMPs are capable of sequence specific RNA recognition and regulation, as originally shown by the interaction of IMP1 with a 54-nucleotide cis-acting element in the 3' untranslated region (UTR) of the β -actin mRNA, the “zipcode.” IMPs are required for localization, stability, and translational control of multiple mRNAs; altered regulation of these processes by IMPs may explain their role in tumor progression. It is our hypothesis that elucidating the complete array of RNA ligands of IMP proteins will reveal the specific cellular functions and pathways subject to post-transcriptional misregulation by IMPs during tumorigenesis. These mechanistic studies may provide insight into novel therapeutic strategies for the broad array of cancers reliant on IMP oncoproteins.

Jack Rostas, III, MD

University of South Alabama College of Medicine

“Determination of the Mechanisms and Clinical Relevance of the Loss of the Protein, N-Myc Interactor, in the Progression of Breast Cancer”

Project Summary: The Wnt/beta-catenin pathway is well described for its importance in cell growth and proliferation. The role of increased signaling of this pathway has recently been demonstrated in breast cancer. My project focuses on N-Myc Interactor (Nmi), a protein that has been found to inhibit the Wnt/beta-catenin pathway. Furthermore, the presence of Nmi reduces tumor invasion and contact-independent growth. Preliminary work has shown that Nmi mRNA levels attenuate in aggressive breast cancer. However, the reason for reduced expression of Nmi in breast cancer is unknown. Although many potential regulatory mechanisms could exist, I will initiate my investigation with two promising lines of study: epigenetic regulation and the presence of an aberrant microRNA. I will also explore the clinical application of Nmi in breast cancer, as a predictor of tumor aggressiveness. A biopsy specimen of invasive cancer with sufficiently depressed Nmi levels could contribute to a molecular profile of the tumor, thus impacting the treatment strategy. Finally, correctly identifying the molecular mechanisms involved in Nmi regulation may hold promise as a therapeutic target. Normalizing Nmi levels would provide a mechanism to inhibit the proliferative effects of the Wnt/beta-catenin pathway. This project will provide the foundation for the development of a novel therapy that would serve to reduce the aggressive nature of breast tumors.

Paul Simonson, PhD

University of Illinois College of Medicine, Urbana-Champaign

“Development of super-resolution imaging for chromosomal DNA”

Project Summary: Recent developments in single-molecule-based, super-resolution fluorescence microscopy are revolutionizing optical microscopy and opening doors for studying biology at levels of 20 nm or less. Yet, developments have been slow in reaching chromosomal DNA. This proposal seeks to develop super-resolution imaging for DNA, which can then be used for investigating important questions concerning chromosome structure, repair, mitotic chromatin condensation, transcription regulation, etc., all of which are important for neoplastic diseases. As a starting point, chromosomes will be prepared using established techniques for obtaining karyotypes and observing banding patterns. Chromosomes will then be imaged with ~20 nm resolution, and the resulting structure and banding patterns will be compared to standard images (where normal resolution is ~250 nm). It is expected that super-resolution will provide new, interesting insights into chromosome structure as well as giving more detailed information in patient karyotyping. Next, chromosomes in fixed cells will be imaged (some preliminary results are shown). This is important for understanding chromosome structure at super-resolution in the context of a cell. Since chromosomes might be oriented in any direction in the cell, three-dimensional imaging will be done using cylindrical lens techniques. Once it is shown that reliable, reproducible chromosome imaging can be achieved, DNA and proteins will be simultaneously imaged. This is important for understanding the interplay between DNA and proteins. Microtubules will be used as a starting point because they are easily identified, and I have already imaged microtubules at super-resolution. Assuming all goes well, some specific neoplastic disease questions will then be addressed. This will lay the groundwork for enabling me to establish collaborations with others in the field and answer interesting questions of my own relevant to neoplastic diseases.

Laura Sonoda, MPH

Keck School of Medicine of the University of Southern California

“Metronomic chemotherapy in ovarian cancer: Alternative mechanisms of action and novel therapeutic opportunities”

Project Summary: Metronomic dosing of chemotherapeutic agents, defined as a more frequent low dosing regimen without break periods, has shown efficacy in the treatment of cancers commensurate with traditional maximal tolerated dosing (MTD). Metronomic administration of topotecan has been shown to have favorable effects in the killing of tumor cells in ovarian cancer. One mechanism in which metronomic dosing has been hypothesized to elicit its antitumor effects is via inhibition of angiogenesis. However, since metronomic therapy has not been proven to result in complete elimination of angiogenesis, other mechanisms for cancer progression are likely involved. The chemopreventive molecule, epigallocatechin-3-gallate (EGCG), a natural polyphenol in green tea, has been shown to prolong survival among ovarian cancer patients, and may do so by inhibiting the cell's metabolic activity, abrogating endoplasmic reticulum (ER) stress, and decreasing vascular endothelial growth factor (VEGF) expression. This study aims to examine the effects of EGCG and metronomic topotecan on human ovarian cancer cell lines, as well as the effects of combination therapy. Platinum-sensitive (A2780) and platinum-resistant (A2780-CP70) human ovarian carcinoma cells will be treated with combinations of metronomically dosed topotecan (MTD topotecan) and EGCG, and evaluated for ER stress factors by Western blotting. I hypothesize that combination treatment with EGCG and metronomic topotecan in ovarian cancer cell lines will have greater effects in decreasing ER-stress, decreasing angiogenesis, and increasing tumor cell kill, compared to either treatment alone.

Rishi Surana

Georgetown University School of Medicine

“Targeting the tumor microenvironment to boost antibody-initiated adaptive immunity”

Project Summary: Monoclonal antibody therapy has revolutionized the treatment of cancer by reducing cancer related morbidity and mortality. Therapeutic antibodies work in part by activating host immune responses such as antibody dependent cell mediated cytotoxicity (DCC). Recently, antibodies have been shown to stimulate the development of adaptive immunity. This observation may be of clinical importance as the generation of adaptive immunity, specifically tumor infiltrating lymphocytes, is associated with a more favorable prognosis in many cancers. However, despite the success of antibody therapy, many patients fail to respond to therapy or develop resistance shortly after the initiation of treatment. Tumors actively suppress host anti-tumor immune responses, which serve to limit the efficacy of immunotherapy and promote failure of therapy. Here, I propose that targeting tumor derived immunosuppression will enhance the development of antibody initiated, protective adaptive immunity. Our group has developed a human Her2 transgenic mouse model (hmHer2Tg) that is immunologically tolerant to growth of a syngenic tumor expressing the human Her2 transgene. These tumors are sensitive to treatment with trastuzumab, which is a clinically useful antibody that binds to human Her2. I have also identified IL-4, a Th2 cytokine reported to suppress generation of protective anti-tumor adaptive immunity, in the tumor microenvironment in our model. Thus, I will test the hypothesis that combination therapy of IL-4 neutralization and trastuzumab will be more efficacious than each agent alone in our model system. Additionally, I will test the hypothesis that combination therapy will enhance the development of protective adaptive immunity. Finally, I will test the hypothesis that combination therapy will shift the balance of the anti-tumor immune response from a TH2 to a TH1 dominated response. These studies could form the basis for new antibody based combination therapies.

Allison Watson

Sanford School of Medicine of the University of South Dakota

“Interaction of the SUSD2 and Galectin-1: Characterizing their role in breast tumor immune escape”

Project Summary: Breast cancer is a heterogeneous disease. There are variations and subsets that are best diagnosed and treated with targeted therapies. Breakthrough immunotherapies, like Herceptin, provide personalized treatment while reducing side effects and shortening treatment regimens. Herceptin is targeted toward breast cancers that over-express ErbB2. However, ErbB2 is only over-expressed in 25-30% of breast cancers, so additional targets are desperately needed. To identify novel immunotherapy targets, a cDNA library enriched for breast cancer genes that encode membrane proteins was generated. From this library we identified a new breast cancer gene, SUSD2 (Sushi Domain Containing 2), which encodes an 820 amino acid protein containing a transmembrane domain and several domains inherent to adhesion molecules. Previous studies describe the mouse homolog, mSVS-1, but there are no studies on the human gene associated with breast cancer. The goal of my thesis is to characterize the role of SUSD2 in breast cancer. Recently, I showed that SUSD2 was expressed in 19 of 24 breast tumors, and localized to the plasma membrane of breast cancer cells. Immunohistochemistry analysis using an anti-SUSD2 antibody showed strong staining in lobular and ductal carcinomas, but weak or no expression in normal breast epithelial cells. Also, SUSD2 interacts with Galectin-1, a 14-kDa protein that is synthesized by carcinoma cells and secreted into the stroma. Galectin-1 has been shown to contribute to tumor evasion of immune responses by inducing apoptosis of activated T cells. Our hypothesis is that SUSD2, a membrane protein found on breast cancer cells, plays a role in immune evasion through its interaction with Galectin-1. The objectives are to define the direct interactions between SUSD2 and Galectin-1 and determine the role of SUSD2 in tumor immune evasion. Targeting SUSD2 could directly kill tumor cells, while simultaneously increasing the patient's T cell response against the cancer cells.

Cheng-Chia Wu

New York Medical College

“20-HETE in Prostate Cancer Growth and Metastasis”

Project Summary: 20-HETE is an ω -hydroxylated metabolite of arachidonic acid formed by cytochrome P450 enzymes of the CYP4 family (primarily, CYP4A and CYP4F). It is mainly found in the kidney, liver and brain and is a major constituent of the microcirculation. In addition to being a potent vasoconstrictor, 20-HETE is also known to induce angiogenesis, cell proliferation, and inflammation. 20-HETE has been implicated in cancer cell and tumor growth in glioma and renal adenocarcinoma. Administration of 20-HETE or overexpression of CYP4A induces glioma cancer cells to shift from G0/G1-phase to S-phase in the cell cycle; it increases the levels of Cyclin D1/2 and phospho-ERK suggesting that 20-HETE promotes cancer growth through activation of the MAPK signaling pathway. Our laboratory focuses on the role of 20-HETE in the renal microvasculature where it promotes vasoconstriction, endothelial dysfunction and activation. We demonstrated that in rats treated with 5 α -dihydrotestosterone, 30-HETE production is markedly increased, and that androgen-induced endothelial dysfunction, activation and hypertension are largely mediated by 20-HETE. Given that prostate cancer is highly regulated by androgen, these findings raised the possibility that 20-HETE may play an important role in the pathogenesis of this disease. Preliminary results indicated that 20-HETE is present in prostate cancer cells and its levels may be regulated by androgen. These findings are the basis for the working hypothesis: 20-HETE, an androgen-regulated eicosanoid, is a key lipid mediator of prostate cancer growth and metastasis. This hypothesis will be tested by assessing growth, cell cycle, migration and invasion of prostate cancer cells (androgen-sensitive and insensitive) in response to 20-HETE synthesis inhibitors, agonists and antagonists. Results will be the basis for a research project to identify the 20-HETE-producing gene in prostate cancer and to evaluate its presence in prostate tumors with the prospect of discovering novel therapeutic targets.