Health Research Formula Grants – State Fiscal year 2014-15

Twenty-six organizations received health research formula grants totaling $30,179,100 for the state fiscal year 2014-15. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2015 and have 1-48 months to complete the proposed research. The following list of grants provides the name of the grantee, amount of the grant award and a list of the research project(s) supported by the grant including the title of the research project, type of research (biomedical, clinical or health services research), focus of the project and purpose.

Albert Einstein Healthcare Network ($68,170)
Research Projects:

- Title: Therapeutic Tablet Application for Post-Stroke Motor Rehabilitation
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: One of the most devastating long-term post-stroke disabilities is impairment in movement production. Recent innovations in computer tablet application-based therapies ("therapeutic apps") are notable because they offer expanded rehabilitation opportunities due to their low cost, ease of dissemination, and widespread availability. The project will first complete a single-session analysis of usability of a previously-developed tablet-based motor app, and then test the app in the home setting with a chronic stroke population to collect pilot data on efficacy. If effective, app therapy would be a novel and significant advance in the cost-effectiveness of stroke rehabilitation.
- Title: Thromboelastography (TEG) Validation in Liver Disease Patients
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: The purpose of this project is (1) to establish intra-subject variability of TEG with platelet mapping and functional fibrinogen in liver disease without cirrhosis, cirrhotic patients, and stable post-orthotropic liver transplant (OLT) patients and (2) to evaluate complex coagulation in liver disease patients, cirrhotic patients, and stable post-OLT patients utilizing TEG with platelet mapping and functional fibrinogen.

Allegheny-Singer Research Institute ($42,788)
Research Project:

- Title: Promotion of Bacteriotherapy Adhesion in Chronic Wound Treatment
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Bacteriotherapy treatment in chronic wounds has the potential to change current wound management. However, a technique to reliably attach the individual bacteria to wound dressings has yet to be developed. Recently, a bacteria coating polymer which should promote adhesion of the bacteriotherapy to the synthetic mesh has been developed. We propose to investigate the polymer's ability to promote adherence of individual bacteria to the mesh fibers and to determine whether the polymer alters the bacteriotherapy's efficacy. By developing a reproducible application method we can expand the research into an in vivo model with the long term goal being the application of bacteriotherapy in the treatment of chronic wounds.

American College of Radiology ($1,268,999)
Research Projects:

- Title: Using the RTOG Legacy Clinical Trials Database to Investigate Non Protocol-Specified Research Questions
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: For over 40 years, the Radiation Therapy Oncology Group (RTOG) was funded by the National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. RTOG's research has been incorporated into a newly funded NCI clinical trials program, NRG Oncology, which is a member of the NCI National Clinical Trials Network. Drawing upon this vast resource of demographic, treatment, biospecimen, and outcome data from RTOG trials, the researchers will develop hypotheses and explore associations that were not defined in the treatment protocols for patients with brain tumors, head and neck, lung, pancreas, and prostate cancers, which may inform and/or lead to future protocols.
- Title: Improving Quantitative Imaging Biomarker Methods to Accelerate the Development of Effective Cancer Therapies
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: This project will leverage the unique and extensive biomarker trial data sets that the American College of Radiology Imaging Network (ACRIN), based in Philadelphia, has collected from clinical trials evaluating cancer therapies. Using the ACRIN expertise in cancer biomarkers, as well as image analysis, we will test and develop improved methods of image analysis and quantification for cancer imaging biomarkers. The project will leverage the functionality of ACR's Data Archive and Research Toolkit (DART) to access, share, and analyze data more efficiently. Successful completion of the project will be improved imaging biomarkers that will improve the efficiency and quality of therapeutic cancer trials and help direct individualized cancer therapy.

Carnegie Mellon University ($669,247)
Research Projects:

- Title: Spatiotemporal Codes Underlying Face Recognition
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Considerable progress has been made in mapping the cortical basis of object processing (including faces, words and common objects), yet much less is known about the representational and computational underpinnings of this complex visual ability. In this project, we aim to examine the structure of objects representations as reflected by patterns of data in the human cortex obtained from magnetoencephalography (MEG). To this end, we will start by using faces as a model set of stimuli and will have participants make judgments about the similarity of faces while we collect MEG data. We will then map the brain regions underlying face identification, examine the representation of facial identity within these regions in terms of their spatial and temporal properties, and provide an account of face encoding relying on image-based features.
- Title: The Role of Lhx6-GPe Neurons in Basal Ganglia Function in Health and Disease
  Type of Research: Biomedical
  Focus: Neurosciences

Purpose: Motor symptoms of Parkinson's disease, a neurodegenerative disorder affecting nearly 1 million Americans, are attributed to hyperactivity of motor suppressing circuits in the basal ganglia. Focus of this project is plasticity of a subset of neurons, called Lhx6-GPe neurons, that critically regulate neuronal activity in this motor suppressing pathway and may represent novel targets to restore basal ganglia activity and motor control after dopamine depletion.

- Title: Technology to Support Life-logging
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: An emerging paradigm in healthcare is the use of mobile and wearable technologies for monitoring a person's health status remotely and in real time. In particular, there is an opportunity to understand a person's health-related events and functional ability to perform daily life activities. To succeed, there is a need to correlate data from body-worn sensors with the actions that the wearer is actually engaged in. That can be accomplished with machine learning algorithms trained on labeled data sets. This research will advance capabilities for people to collect "life-logs" that serve as the basis for such labeled data, i.e., ground truth data to train the algorithms. As such, this project supports future population-based applications.

Children's Hospital of Philadelphia ($3,695,893)
Research Project:

- Title: The Human Microbiome in Pediatric Health and Disease
  Type of Research: Clinical
  Focus: Digestive Sciences
  Purpose: Our purpose is to study the pediatric microbiome with the goal of improving diagnosis and treatment of disease. Humans live in association with myriad microbes that strongly influence health and disease. Proper microbial populations are a key component of health. Dysbiotic microbes are associated with diseases such as pediatric inflammatory bowel disease (IBD). This project will support research efforts to better understand the microbiome in healthy pediatric patients and pediatric patients with IBD. It will further investigate the effects of antibiotic exposure, *Clostridia difficile* (*C. difficile)* infection, the metabolome, and human genetic variations on microbial populations in these children.

Drexel University ($1,079,197)
Research Projects:

- Title: Population Pharmacokinetics of Cefazolin on Cardiopulmonary Bypass in Neonatal and Pediatric Patients
  Type of Research: Clinical
  Focus: Infectious Diseases and Microbiology
  Purpose: The purpose of this study is to determine the pharmacokinetics of cefazolin used in cardiopulmonary bypass (CPB) circuits to characterize the pharmacokinetic changes related to the CPB circuit. The pharmacokinetics will be evaluated to determine whether a dosing equation or constant can be derived to apply to initial dosing regimens to account for the pharmacokinetic alterations with CPB circuits. Population pharmacokinetic estimates will also be derived and contemporary pharmacokinetic/pharmacodynamics analysis will be conducted to determine an optimal dosing regimen for patients on CPB.
- Title: Early Exercise Intervention Prevents Spinal Cord Injury-induced Neuropathic Pain Development by Modulating the Levels of Pro- and Anti-inflammatory Cytokines
  Type of Research: Biomedical

Focus: Neurosciences
Purpose: The purpose of this experiment is to determine whether exercise prevents pain development after spinal cord injury (SCI) by modulating the post-injury inflammatory response throughout the spinal cord and brain as well as systemically. By examining the inflammatory response in the brain and spinal cord, we will understand how inflammation affects pain signaling. Detection of changes in systemic inflammatory response after SCI and/or exercise over time will identify potential biomarkers or predictors of pain development that could be directly translated to clinical SCI. These biomarkers would also inform on potential pharmacologic targets, as well as the effectiveness of the exercise, and lead to refinement of the rehabilitation protocol.

- Title: Targeting Microtubule-severing ATPases in Glioblastoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The research study will be undertaken to discover new knowledge leading to new treatment approaches in glioblastoma (GBM), a highly aggressive brain tumor that does not have a cure. High spastin expression correlates with increasing grade of malignancy and aggressive tumor behavior. The outlined approach will allow us to determine the therapeutic relevance of spastin in glioblastoma in vivo and investigate the mechanistic basis of spastin in drug chemosensitivity in vitro. This study has the potential of revealing a new drug target to improve the long-term survival of patients diagnosed with GBM.
- Title: Non-Thermal Plasma as an Effective DNA Vaccine Adjuvant
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Dielectric barrier discharge (DBD) plasma, which is a form of non-thermal plasma (NTP), is generated by applying high voltage to an electrode encased in a dielectric material. This project will test the hypothesis that DBD plasma can be used to augment the delivery of a DNA-based vaccine. The project will provide proof-of-concept results and a solid basis for a more comprehensive research plan to be submitted as an NIH grant application. The ultimate goal of this work will be the development of a novel and non-invasive method for improving the delivery and increasing the efficacy of DNA-based vaccines effective against important human pathogens.
- Title: Impaired Immune Priming and Diminished B cell Repertoires in Aging Models of *Clostridium difficile* Infection and Vaccination
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: There is a significant correlation between advanced age and risk of severe and recurrent *Clostridium difficile* infection (CDI). Aged individuals have a reduced ability to produce high affinity anti-toxin antibodies, but it has yet to be determined whether the defect in the elderly is due to lack of host immune priming to CDI and/or a decrease in B cell repertoire diversity making individuals more susceptible to severe disease. The purpose of this project is to identify age related functional changes in the B cell populations in the context of Clostridium difficile infection using a novel aging mouse model of CDI developed in our laboratory.
- Title: Neuroprotective Effects of Inhaled Carbon Monoxide in a Piglet Model of Hypoxia
  Type of Research: Biomedical
  Focus: Neurosciences

Purpose: In a newborn piglet model of hypoxic cerebral injury, increased activation of the enzyme Ca++/calmodulin kinase (CaM Kinase) IV localized in the nucleus is seen within one hour of exposure to hypoxia. The focus of this project is to build on these observations and test whether carbon monoxide (CO) inhalation given therapeutically at low safe doses after hypoxic cerebral injury improves functional disability scores, attenuates brain pathology, and/or inhibits caspase-9 /caspase-3 activation in a neonatal piglet model of hypoxic cerebral injury. We envision CO being present in neonatal intensive care units, akin to inhaled nitric oxide, to be administered at the bedside via nasal cannulas or ventilator if needed.

- Title: Non-invasive Monitoring of Cerebral Edema in Real-Time Using a Novel Near Infrared Spectroscopy Monitoring System.
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The development of cerebral edema following a hypoxic ischemic (HI) event in newborn infants carries high risk for brain damage and death. Currently, edema is detected by CT/MRI scan. However, these infants are often critically ill and cannot tolerate transport to undergo imaging. We developed an alternative portable and non-invasive NIRS-based neuroimaging device to monitor changes in the blood and water content of the brain. We will perform pre-clinical studies in piglets to demonstrate the ability of the device to detect the evolution of edema in real time in a well-characterized animal model of HI and neuroprotection. This novel cerebral edema monitoring system can then be used to assess patient status in a safe, accurate and timely manner.
- Title: Metabolic Control of Neurogenesis Via Histone Acetyltransferase Tip60
  Type of Research: Health Services
  Focus: Neurosciences
  Purpose: The purpose of this research is to elucidate the metabolic control of a process called neurogenesis critical to a therapeutic intervention for a number of neurodevelopmental and neurological diseases such as autism spectrum disorder and Alzheimer's disease.
- Title: *In Vivo* Targeting of ERK1/2 Map Kinase Signaling in Dopaminergic Neurons
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Psychostimulants such as cocaine and amphetamine trigger their rewarding and addictive effects by an acute elevation of extrasynaptic levels of dopamine (DA). Current treatments for psychostimulant use disorders are acknowledged to be ineffective and therefore finding better treatment options is imperative. The research outlined in this project is designed to characterize mediators of adaptive dopaminergic changes that occur during psychostimulant exposure that will permit the identification of novel therapeutic treatment opportunities. The goal of this project is to determine the role of ERK1/2 Map kinase signaling in dopaminergic neurons *in vivo* in the regulation of cocaine-associated DA homeostasis.
- Title: Mechanical Circulatory Assistance for Congenital Heart Disease: Biologically-Inspired Heart Pumps
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The treatment of congenital cardiac Fontan anomalies is a formidable and costly challenge for clinical teams caring for patients with congenital heart disease. Surgical and pharmacologic treatment only slows the progression of premature heart failure in these patients. The availability of donor organs is limited given the number of patients in need, and no mechanical blood pump has been specifically developed

for Fontan patients. The purpose of this project is to establish the ideal biofluid dynamic mechanical circulatory support conditions for Fontan patients. The goal of this project is to inform the new development of a novel, biologically inspired, axial flow blood pump for these patients as a viable treatment option in their clinical management.

- Title: Direct Role and Mechanism of Activation and Expression of BKCa Channel in Cardioprotection from Ischemia-Reperfusion Injury
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Large conductance Ca2+ and voltage-activated potassium channels (BK_{Ca}) were discovered in cardiac mitochondria where they were shown to be involved in cardioprotection from ischemia-reperfusion (IR) injury by activation with pharmacological agents (NS1619). Outstanding questions are, does BK_{Ca} play a direct role in cardioprotection or is it via non-specific effect of pharmacological agents used? And, what is the mechanism of BK_{Ca}-mediated in cardioprotection? The proposed project will facilitate establishment of the direct role of BK_{Ca} in cardioprotection from IR injury and provide a possible mechanism involved in BK_{Ca} - mediated cardioprotection.
- Title: Designing an Information System to Support Data-driven Decision-making in RTI
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Response to intervention (RTI) is a framework used by schools to adhere to the Individuals with Disabilities Education Improvement Act (IDEA) and provide children the support they need to learn. RTI involves academic and behavioral intervention, tracking a student's progress, and frequently adjusting interventions as needed. The process of RTI should be data-driven, but schools lack the appropriate technology to manage and analyze data. The proposed work will design and validate an information system for real-time data collection, visualizations of aggregated data, and automatic identification of trends. The purpose of this work is to address health and educational disparities by ensuring RTI decisions are data-driven.
- Title: Screening for Autism Spectrum Disorder in Child Care Settings
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Early detection of Autism Spectrum Disorder (ASD) facilitates early intervention, which improves lifelong prognosis. Efforts focusing on universal screening in the medical home overlook an important setting with regular access to young children: childcare settings. The current project will used a mixed-method design to pilot ASD-specific screening in five childcare centers in the Promise Zone, an underserved neighborhood in West Philadelphia to (1) demonstrate feasibility and acceptability of screening in childcare centers, and (2) gather empirical data on the validity of ASD screening in childcare.

Duquesne University ($65,557)
Research Projects:

- Title: Project for Cognitive Advancement in infants with Neuromotor Disorders: The CAN-DO project
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Bio-behavioral Processes
  Purpose: The purpose of this longitudinal study is to examine the ongoing interaction between the domains of cognitive and motor development in infants with neuromotor

disability, and to compare outcomes of two groups of infants receiving two different types of home-based, parent-delivered intervention, in order to determine which intervention is more effective in advancing cognitive as well as motor development. Knowledge of the effectiveness of two types of intervention will lead to improved early intervention for children with developmental disabilities, as well as future studies to examine ongoing outcomes.

- Title: RNA-protein Interactions: G quadruplex RNA Structure Involvement in Neurodegeneration
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The goal of this project, which will employ a novel combined biochemical/biophysical experimental and computational biophysics approach, is to investigate the detailed mechanisms of RNA G quadruplex structure interactions with specific proteins and their involvement in neurodegeneration, in the context of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The results of the project will contribute to our understanding of the molecular mechanisms that cause ALS/FTD, potentially providing the basis for drug design.

Geisinger Clinic ($137,129)
Research Project:

- Title: Identification of Genetic Variants that Contribute to Biological Functions and Disease States
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Using genomic information to improve the health of Pennsylvanians is an enormous undertaking that will require novel strategies to separate the pathogenic variants from the $>10^6$ unique variants identified in the Geisinger cohort thus far. Offering an innovative approach, this project will combine a clinic based algorithm with a comprehensive experimental platform to rapidly identify new gene functions and suspected genetic variants that compromise protein function and contribute to disease pathology or treatment response. Maximizing the potential for therapeutic benefit, this strategy will focus on the G-protein coupled receptor (GPCR) family whose members represent proven targets for the majority of prescribed medications. The successful implementation of this strategy will advance the discovery and understanding of this important family of drug targets.

Hepatitis B Foundation ($324)
Research Project:

- Title: Ecosocial Determinants of Hepatitis B Screening and Linkage to Care in High Risk Philadelphia Populations
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to assess the economic, cultural, social, environmental and systemic barriers to hepatitis B screening and linkage to care among high-risk Asian and Pacific Islander (API) communities in Southeastern Pennsylvania. These communities have disproportionately high rates of chronic HBV infection. Results from this study will allow us to tailor future interventions to best meet the needs of our target audiences, and to more successfully improve hepatitis B screening rates among high-risk APIs in Southeastern PA.

Institute for Cancer Research ($1,246,366)
Research Projects:

- Title: Targeted Therapy for Ovarian Carcinoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project will determine the utility of avatar models of human ovarian carcinoma (OC) to predict the efficacy of single agent and combined targeted therapeutic agents. Using novel, patient-derived xenograft (PDX) mouse models of OC, we will: 1) Determine molecular and gene expression alterations present in primary ovarian carcinomas and matching PDXs; 2) Determine the efficacy of targeted inhibition of heat shock protein 90 (HSP90) alone or combined with targeted inhibition of key pathways or proteins that contribute to OC progression; 3) Determine if low-level inhibition of HSP90 durably sensitizes tumors to drug inhibition.
- Title: Hedgehog Pathway Components in Pancreatic Tumor Initiation
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project aims to define the role of a novel cell surface molecule in the initiation of pancreatic adenocarcinoma, an extremely lethal form of cancer. Preliminary results suggest that this protein creates an environment that enables cells bearing K-Ras mutations to develop from benign precursor lesions into frank adenocarcinoma. Our goal is to delineate the signaling pathways that promote development of this environment with the future aim of identifying potential therapeutic interventions for treatment of patients with early pancreatic lesions and strategies for targeting this pathway in adenocarcinoma.
- Title: Ack Function in T cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The study will shed light on how a druggable kinase regulates a fundamental immune response with relevance to cancer, pathogen clearance, and transplant rejection.
- Title: Regulatory Mechanisms of Talin by RIAM in Integrin Signaling
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Traditional anti-integrin inhibitors have proven ineffective for cancer treatment, mainly owing to unexpected integrin-activating effects that are poorly understood but involve tumor cell feedback mechanisms. We hypothesize that targeting an alternative integrin activation pathway, either independently or in conjunction with the existing extracellular inhibitors of integrins, will achieve greater potency by limiting feedback. The purpose for this research is to understand how integrin activity is regulated by interaction between talin and RIAM (Rap1-interacting adaptor molecule). The results will provide a novel cancer therapeutic strategy that inhibits integrin activity by blocking this specific interaction.
- Title: Identification of Neuronal Progenitors with Regenerative Potentials in Developing Cerebellum
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Medulloblastoma (MB) is the most common pediatric brain tumor. Radiation therapy has been very effective at killing tumor cells, but it also causes significant

long-term losses in motor and cognitive function. There is still no successful treatment for these side effects. The goal of our studies is to understand the effects of radiation on cells in developing cerebellum, from where MB originates. In particular, we hope to learn why some cells are killed by radiation, while others not only survive but are subsequently able to expand and repair the damaged cerebellum. Identifying these progenitors with repairing capacity after radiation and studying their properties could help us develop approaches to preventing or mitigating the side effects of radiotherapy.

- Title: Biosample Repository Facility Freezer Storage Research Infrastructure Renovation
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to renovate the laboratory space in R157 to accommodate the Biosample Repository Facility's (BRF) -80°C mechanical freezers. The BRF coordinates in the ethical collection, storage, annotation and distribution of tissue and peripheral blood samples to support translational research at Fox Chase Cancer Center. The current BRF sample storage space is spread across multiple buildings, lacks a centralized monitoring system and has reached its maximum capacity. The renovation will modernize the monitoring of storage units, consolidate sample storage into a centralized location, and allow the BRF to expand its storage capacity to keep pace with continued accrual of specimens.

Lankenau Institute for Medical Research ($80,638)
Research Project:

- Title: Investigating the role of IDO1 in neovascularization using a mouse model of oxygen-induced retinopathy
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The tryptophan catabolizing enzyme IDO1 is emerging as a promising immunotherapy target that promotes tumoral immune escape in the context of chronic inflammation where it may represent one of the earliest determinants for directing the immune response towards supporting rather than eliminating tumors. We recently made the unexpected discovery that the loss of IDO1 can negatively impact vascularization. The current proposal aims to elaborate on the novel hypothesis that one of the key biological roles for IDO1 is to mitigate immune-based angiostasis, informing not only the clinical development of IDO1 inhibitors for the treatment of cancer but also suggesting a completely new use for such agents in the treatment of ocular diseases.

Lehigh University ($68,785)
Research Project:

- Title: On Mental Illness Underpinnings: Neural Circuits on a Chip
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Neural circuits in a brain that is afflicted by mental illness or a neurological disorder are different than circuits in a healthy brain. Returning neural circuits to their healthy state is a desirable therapeutic endpoint. However, the function of neural microcircuits and its dependence on genetic control remain poorly understood. We will take a novel approach to the analysis of neural circuits. Instead of analyzing neural circuits in brain tissue, we will dissociate the brain tissue into individual neurons, and then use these neurons to construct semi-artificial, but living, circuits. We will use neurons from normal and genetically altered animals to determine how

genes influence neural circuit development and function.

Magee-Womens Research Institute and Foundation ($837,715)
Research Projects:

- Title: Molecular Basis of LCoR Action in Placental Fuel Metabolism
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The transcriptional cofactor LCoR (Ligand-dependent nuclear receptor Co-Repressor) functions as a coactivator on select placental target genes of the nuclear receptor PPARγ (Peroxisome Proliferator-Activated Receptor γ), including *Muc1* (Mucin-1) and *Gcgr* (Glucagon Receptor). LCoR deficiency causes retention of placental glycogen, resulting in placentomegaly accompanied by fetal growth restriction. The purpose of this project is to determine the fine molecular details of LCoR action, including its mechanisms of interaction with PPARγ and RXRα (Retinoid-X Receptor α), a systematic screen for its collective target genes in the placenta, and its potential interaction with the transcriptional cofactor TLE3 (Transducin-Like Enhancer of Split 3) in mediation of these processes.
- Title: Microvascular Endothelial Dysfunction Following Vascular-mediated Preterm Birth
  Type of Research: Clinical
  Focus: Cardiovascular Sciences
  Purpose: Cardiovascular disease (CVD) is the leading cause of death among women in the U.S. Guidelines for CVD prevention in women indicate that a history of preterm birth (PTB) may identify women in whom risk factor screening and management is warranted, although mechanisms linking these conditions are not known. We hypothesize that placental evidence of maternal malperfusion is a common feature of PTB that may identify women with higher CVD risk. We will enroll 80 women (40 with PTB and placental malperfusion, 40 with term uncomplicated births) to evaluate carotid intima-medial thickness and microvascular endothelial function of the finger arterioles via pulse amplitude tonometry 15 years after pregnancy.
- Title: Angiogenic Factors in Pregnancy and Preeclampsia: Obesity and Race
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The purpose of this project is to more thoroughly investigate the dysregulation of soluble vascular endothelial growth factor receptor 1 (sFLT1) and placental growth factor (PlGF) in women who develop preeclampsia, and to investigate the potential role of these factors in contributing to the risk of preeclampsia among obese and Black women. Preeclampsia is more common among Black (African American) women, and obesity significantly increases the risk of preeclampsia; however the biological mechanism(s) underlying these relationships are not understood. This project directly relates to the state's research priorities including population-based investigations that address disparities in health status given the significant prevalence of obesity among reproductive aged women including African American women.
- Title: Enabling Technologies for the Non-Invasive Prenatal Detection of Monogenic Disease
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: The purpose of this study is to develop tools for the rapid and cost-effective non-invasive prenatal detection of monogenic disease. The proposed experiments will focus on common mutations in the cystic fibrosis transmembrane receptor (CFTR) gene but they are applicable to any mutation with similar inheritance patterns. Eventual clinical deployment of such tests would improve our ability to detect deleterious mutations *in utero* and could potentially reduce the number of risky and stressful invasive procedures that are performed, such as chorionic villus sampling and amniocentesis.

- Title: Regulation of Genome Integrity by Chromatin
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Errors in repair of DNA damage are a major determinant of cancer and infertility. Histone post-translational modifications can influence the access to and repair of DNA, but our understanding of how particular chromatin modifications influence DNA repair processes is still quite rudimentary. Our studies using the nematode *C. elegans* will use genetic and biochemical approaches to attain new knowledge about how germline chromatin structure influences DNA repair during the critical process of germ cell formation. These studies have the potential to identify genes and pathways that lead to human aneuploidy and therefore may identify targets for therapeutic purposes.
- Title: Expression of Long Non-coding RNAs in Primary Human Trophoblast Cells under Hypoxic Condition
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: In this project we will examine the regulation of long noncoding RNAs in human primary trophoblast cells cultured in normoxic or hypoxic conditions. Specifically, we will apply our newly developed machine learning algorithms to a comprehensive historic dataset about miRNAs, mRNAs, lncRNAs, and proteins in primary human trophoblasts (PHT cells) to explore regulatory relations between lncRNAs and other types of molecular species. We will also use next generation sequencing technologies to comprehensively define the expression of lncRNAs and other RNAs in the PHT cells, and interrogate their response to hypoxic condition. The results from this study will enhance our understanding of human placenta epigenomics, and suggest new tools for diagnosis and prevention of placenta diseases.
- Title: Understanding Perinatal Marijuana Use: Attitudes, Use, Screening, Disclosure and Counseling Among Pregnant Patients in Pittsburgh
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Marijuana is the most commonly used recreational drug during pregnancy. The purpose of this project is to expand the analyses of our existing data from prior studies to understand patients' and obstetric providers' attitudes, beliefs and concerns regarding perinatal marijuana use and how to address this use during obstetric visits. We will also explore how women who use marijuana at the start of their pregnancy change their use, beliefs, attitudes and plans over the course of their pregnancy and their perceptions on how their obstetric care influences their decisions to stop or continue using marijuana while pregnant. Our findings will inform future policies and practices on perinatal marijuana use.

Monell Chemical Senses Center ($187,425)
Research Projects:

- Title: Taste Signaling Pathways in the Regulation of Gut Inflammation and Gut Microbiota
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The intestinal tract contains trillions of microbes that comprise a unique microbiota for each individual. Gut microbes help food digestion, produce nutrients, and regulate immune responses. However, disturbance of this microbial community can lead to serious health challenges such as diabetes, obesity, and inflammatory bowel disease. Recent studies indicate that the taste system is involved in multiple physiological roles. One of the functions of taste receptors is to sense and respond to microbes, and to modulate immune reaction. The purpose of this project is to investigate the roles of taste signaling pathways in regulating the gut microbiota and inflammation using animal model for human inflammatory bowel disease.
- Title: Olfaction as a Biomarker for Health and Cognitive Decline
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The goals of this project are to study the associations between olfactory performance, cognitive function and health status in a large cohort of adults. We will recruit from individuals who have recently joined an internet-based registry and provided health, medical history and lifestyle information along with cognitive function assessments. The study will target 1000 participants in the registry who will self-administer the NIH Odor Identification Test and record their responses on the registry website. Once completed, performance on the odor ID test can be compared not only with cognitive performance, but health status, occupational history and lifestyle factors.

National Disease Research Interchange ($41,096)
Research Project:

- Title: Susceptibility Genes for Microvascular Complications in Patients with Type 1 Diabetes
  Type of Research: Health Services
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The overall goal of this project is to identify loci contributing to the susceptibility of microvascular complications of Type 1 Diabetes (T1D). We are specifically searching for loci that predispose to T1D complications but that are not necessarily related to T1D susceptibility. Identifying such loci will allow us to predict which patients are at greatest risk for the blindness, kidney failure and nerve disease caused by diabetic microvascular disease.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation ($606,228)
Research Project:

- Title: Development of Tools for Colon Cancer Molecular Subtyping and Treatment Selection
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to improve colorectal cancer (CRC) treatment by developing a CRC-specific mutation panel and a gene expression signature that will identify clinically meaningful biomarkers and CRC subtypes. We propose to

develop a gene expression signature to distinguish patients who will respond to standard chemotherapy from those who have a poor prognosis and do not receive benefit from chemotherapy. Tumors from the latter patients are referred to here as stem-like. We will test new agents or agent combinations in pre-clinical models to identify drugs effective against the stem-like tumors. The development of a CRC mutation panel has the potential to identify patients who would be responsive to new, targeted agents.

Pennsylvania State University ($4,608,037)
Research Projects:

- Title: Research Infrastructure – Biospecimen Processing Core
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of the Biospecimen Processing Core (BPC) is to provide a centralized service for the collection, processing and distribution of human subject research samples for all of the clinical research activity at the Penn State Hershey campus.
- Title: Functional Studies of Herpesvirus Tegument Protein UL21
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: This study will examine the molecular mechanisms of virus replication using the human herpes virus type 1 (also known as HSV-1 or herpes simplex virus) as a model to understand all herpesviruses. The specific goals are to gather new knowledge concerning the functional role of a particular viral protein (UL21) in virus replication and, more specifically, to identify what other viral and cellular proteins it interacts with in the virus replication process. This type of information will not only improve our overall understanding of the virus but will provide new leads that may be translated into advancements in antiviral therapies.
- Title: Identification of Genetic Predictors of Response to the Clinical Management of Bladder Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Bacillus Calmette-Guerin (BCG) is the treatment of choice for non-invasive bladder cancer, while cisplatin-based chemotherapy followed by radical cystectomy is the gold standard treatment for muscle-invasive bladder cancer[1]. BCG reduces tumor recurrence, while ~40% of patients experience a complete pathologic response following neoadjuvant chemotherapy. The tumor-specific molecular mechanism(s) responsible for response to BCG and cisplatin-based chemotherapy remain unclear. This research seeks to develop the research stream to perform whole exome sequencing on bladder cancer patients, and to identify specific genetic predictors associated with treatment response in patients with bladder cancer.
- Title: Inhibitors of the Farnesoid X Receptor for the Treatment of Obesity and Non-Alcoholic Fatty Liver Disease
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Obesity has reached epidemic proportions worldwide and is associated with chronic diseases such as type 2 diabetes mellitus, cardiovascular diseases, hepatosteatosis, and cancer. Obesity is also linked to hepatosteatosis, which can lead to hepatocarcinogenesis and liver failure. We and others recently established intestinal farnesoid X receptor (FXR) as a major regulator of diet-induced obesity. We have identified a potent FXR antagonist that improves insulin resistance, glucose

tolerance, and reverses and/or prevents the development of fat. We propose a study to better understand Absorption, Distribution, Metabolism, and Elimination (ADME) of this agent before starting a phase 1 trial in humans.

- Title: Definition of Somatic Variants Corresponding to Immune Targets in Metastatic Melanoma
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: This project seeks to identify single nucleotide differences among genes expressed in healthy tissues and primary melanomas and/or their metastases from individual patients that develop recurrent metastatic melanoma. From these identified mutations, we will determine the number and type of potential targets created that can be recognized by T lymphocytes capable of destroying the cancer cells. This knowledge will be used to identify predictors associated with clinical response to immune-based and standard cancer therapies in order to improve success rates and reduce treatment costs associated with therapies that are unlikely to benefit individual patients.
- Title: Altered Ghrelin Modulation of the Reward System after Gastric Bypass
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: At present, Roux-en-Y gastric bypass (RYGB) surgery is one of the most effective methods of achieving significant, long-term weight loss and treating comorbidities associated with obesity. However, there is growing evidence suggesting that RYGB may lead to increased alcohol use whereas the underlying mechanism remains unknown. Our preliminary data in a rat model of RYGB suggests a key role for the gut-brain peptide ghrelin. This project will use rats and molecular, electrophysiological, behavioral methods, which cannot be used in human subjects, to test the role of ghrelin as potential pharmacological target for the development of effective treatment for alcoholism in general, and to reduce risk of alcohol use disorder after RYGB.
- Title: Diabetes-Induced Alterations in Translational Control Mechanisms in the Liver
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The purpose of the project is to characterize translational control mechanisms and protein expression patterns that undergo acute variation in response to Type 1 diabetes. Contrary to the view that gene expression is primarily regulated at the level of transcription, we now know that this accounts for only about 40% of variation in protein expression. Instead, control of mRNA translation is now known to contribute more than 50% to variation in protein expression. Our preliminary studies show that diabetes-induced hyperglycemia leads to alterations in key components of the translational machinery. By characterizing these alterations, the project will yield insight into identifying targets for preventing diabetes-induced defects in liver function.
- Title: Hormonal Effects on Human Humoral Immunity
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this study is to explore the molecular basis for the well-known sex differences in humoral immune responses of humans. This project will explore the influence of male and female sex hormones on a key process in the initiation of antibody response and on the molecular affinity of antibodies produced by women vs. men. We seek to identify hormonally-regulated processes that could serve as therapeutic targets to augment vaccine responses or to attenuate

pathologic autoantibody production.

- Title: Molecular Mechanisms Underlying Infertility in Men: an *in vivo* Model of Spermatogenesis.
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Elucidating the molecular mechanisms underlying spermatogenesis and sperm function will contribute to the search for treatments and prevention of male infertility and subfertility, and may also help to develop a new approach for contraception in human and other mammals. As such, the purpose of this project is to generate and characterize an *in vivo* model of a conditional Pramel1-knockout (KO). This will provide a valuable new tool for the advanced study of PRAME in spermatogenesis, particularly the stage-specific deletion of PRAME will provide novel insights into molecular mechanisms that regulate acrosome formation and sperm morphogenesis, two key steps in the formation of viable and productive sperm.
- Title: FXR and the Gut Microbiota as Modulators of Obesity
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: Recently published data from our group and others strongly suggests that not only is farnesoid X receptor (FXR) antagonism important for the anti-obesity effects observed with tempol treatment or bariatric surgery but it also likely serves as a conduit by which the gut microbiome regulates and manipulates the host environment. These signals are likely through modification of bile acid pools and in particular through the deconjugation of bile acids such as tauro β muricholic acid and glycine β muricholic acid. However, how these compounds impact the microbiome and alter its metabolism and that of the host remains to be determined. Harnessing these changes to promote health is the focus of this project.
- Title: Intestinal Muscularis Macrophages and Intestinal Homeostasis
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: The overall goal of this project is to define the role of muscularis macrophages (MMs) in enteric neuroplasticity during and post mucosal inflammation. The project will substantially advance our understanding of the pathophysiology of post-inflammatory irritable bowel syndrome (IBS), and will provide novel strategies to prevent and treat post-inflammatory IBS by selective targeting of muscularis macrophages and muscularis macrophage-produced factors.
- Title: Does Human Cytomegalovirus Require an ESCRT for Cytoplasmic Envelopment?
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Human cytomegalovirus (HCMV) is a virus found throughout all geographic regions and socioeconomic groups. Infection can cause serious disease and death in individuals with compromised immune systems. HCMV can also cause severe congenital disease if a fetus becomes infected. Current therapeutics, although effective at dramatically improving clinical outcomes, are plagued with limitations. Developing better therapeutics requires a better understanding of viral replication. In this project, we will investigate an essential step in replication called cytoplasmic envelopment. Understanding this process in greater detail will provide vital information for future attempts to fight infection.
- Title: Coronary and Skeletal Muscle Vascular Control During Exercise in Patients with Peripheral Arterial Disease (PAD)

Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: Peripheral arterial disease (PAD) is a progressive and debilitating condition characterized by impaired leg blood flow and pain during walking. PAD affects ~10 million Americans and is a tremendous burden to the healthcare system. However, a basic understanding of leg blood flow regulation at the microcirculatory level in PAD is limited. In this study we will use ultrasound and magnetic resonance imaging to understand how the leg skeletal muscle (Aim 1) and heart (Aim 2) respond to exercise in patients with PAD. With these data in hand we will propose a clinical trial using a dietary or lifestyle modification.

Salus University ($23,918)
Research Project:

- Title: Evaluating The Role Of Domain Structure Of Retinal Guanylyl Cyclase In Pathogenesis Of Inherited Blinding Diseases
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Retinal membrane guanylyl cyclase 1 (RetGC1) imparts to the retina the ability to respond to light. Mutated RetGC1 alters interaction with its regulatory proteins and causes congenital blindness. Molecular mechanisms defining the interaction of RetGC1 with its regulatory proteins remain obscure and the data on how they cause blindness are limited. The purpose of this short-term pilot project is to collect data to expand the knowledge on how different parts of the RetGC1 primary structure define the specificity of its binding with regulatory proteins and how mutations in the various RetGC1 domains functionally relate to blindness.

Swarthmore College ($11,956)
Research Project:

- Title: Understanding of Interactions Between Porphyrin Ligands and G-Quadruplex DNA
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The project will contribute to our fundamental understanding of porphyrin interactions with G- Quadruplex (GQ) DNA, shed light on the origin of ligand selectivity for a specific DNA target, and provide guidance in preparation of GQ ligands with desired medicinal properties. In a broader sense, given the importance of telomeres and oncogenes to the biology of cancer and aging, the project will contribute to our understanding of these areas that have a major impact on human health and wellbeing. Additionally, it will serve as a teaching tool to inspire, excite, and motivate Swarthmore undergraduates.

Temple University ($1,656,950)
Research Projects:

- Title: Improved Health Outcomes through Minority Recruitment and Clinical Trials
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of the project is to systematically investigate the factors contributing to poor accrual of urban populations into therapeutic clinical research studies. Many past and present social circumstances, knowledge gaps and health restrictions have been identified as contributing to longstanding and disturbingly low

participation rates of minority patients in clinical trials, resulting in both a medically AND scientifically underserved population. Improvement in health outcomes can only be expected when new therapies are based on evidence emanating from inclusion of racially and ethnically diverse populations in clinical trials.

- Title: Temple Genomics and Analytics Collaborative (TGAC) Research Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The newly formed Department of Medical Genetics and Molecular Biochemistry and the Institute for Genomics and Evolutionary Medicine in the College of Science and Technology at Temple University are partnering to create the Temple Genomics and Analytics Collaborative (TGAC) to address an urgent need for a new capacity to conduct state-of-the-art Next Generation Sequencing (NGS) and bioinformatics for life sciences, medical, and health disparities research. In support of the TGAC, an outdated 1500 square foot laboratory will be renovated to provide the necessary physical and computational infrastructure to support the use of NGS to fill a critical institutional gap in an essential biomedical research capacity.

Thomas Jefferson University ($1,695,434)
Research Projects:

- Title: Response to Targeted Therapies in Uveal Melanoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Uveal melanoma is the most common intraocular malignant tumor in adults. No targeted inhibitor treatment has been FDA-approved for metastatic uveal melanoma and patient survival is poor. Hence, there is an urgent need to identify mechanisms leading to therapeutic strategies in uveal melanoma. RAF-MEK-ERK1/2 signaling is activated frequently in uveal melanoma. While the MEK inhibitor trametinib is FDA-approved for the treatment of advanced stage mutant BRAF cutaneous melanoma, the response rate to MEK inhibitors in metastatic uveal melanoma is low. Our objective is to identify mechanisms that underlie the high degree of resistance to MEK inhibitors in uveal melanoma and to identify biomarkers that are predictive for therapeutic response.
- Title: Mechanisms of Resistance to Therapy of Prostate Cancer Mediated by the Tumor Microenvironment
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The hypothesis behind this proposal is that exosomes released by endothelial cells modulate prostate cancer resistance to therapies, specifically to enzalutamide.
- Title: Using Mobile Technology to Engage Hispanics in CRC Screening
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to determine the impact of mobile technology in conjunction with a Decision Support and Navigation Intervention on colon cancer screening adherence.
- Title: Autophagy Restraint in Cancer Onset and Progression
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: We hypothesize that endogenous *Akt1*, and *cyclin D1* restrain mammary tumor autophagy. Therefore, we propose that the induction of autophagy by inactivation of these targets (through targeted therapies) may contribute to tumor

maintenance. The proof of this hypothesis herein will provide the rational basis for the addition of autophagy inhibitors to targeted therapies of Akt1/cyclinD1. Testing this hypothesis is important to provide relevant preclinical evidence that autophagy inhibitors may be valuable in disrupting the maintenance and progression of human breast cancer and to substratify genetic subtypes based on pathway activity in an individual patient's tumor.

- Title: Pharmacologic Treatment of Pulmonary Fibrosis
  Type of Research: Biomedical
  Focus: Respiratory Sciences
  Purpose: The major purpose of this project is to identify drugs capable of modifying the abnormal fibrotic response in the lung found in several human diseases. This will be attempted through the use of a mouse model of pulmonary fibrosis.
- Title: Inflammation as a Novel Target in Early Diabetic Cardiomyopathy
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Diabetic cardiomyopathy (DCM) is characterized by ventricular remodeling and dysfunction independent of atherosclerosis, coronary heart disease, or hypertension, suggesting that other mechanisms associated with diabetes underlie the development of cardiomyopathy. We hypothesize that cytokines derived from inflammation associated with DCM, whose identify remains poorly understood, are critical of DCM pathogenesis, and once the specific cytokines induced during DCM are identified using our mouse model of DCM, the pathogenic role of specific cytokines can be characterized and anti-cytokine treatment strategies can be developed and tested as therapeutics in preclinical models.
- Title: Molecular Mechanisms of Slitrk Signaling in Brain Development and Disorder
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Slitrk is a family of transmembrane proteins that have been implicated in neuropsychiatric disorders, but their functions in normal brain development and their contributions to disease pathogenesis are not well understood. A key missing link is the knowledge of both extracellular and intracellular binding partners of Slitrk proteins. The proposed research attempts to identify these factors by employing 1) a well-established expression cloning strategy; and 2) a newly developed mouse line with affinity purification/mass spectrometry. Results from these studies will not only help understand the function, mechanism, and specificity of Slitrk proteins, but also provide potential diagnostic markers and therapeutic targets.

Treatment Research Institute ($125,033)
Research Project:

- Title: Addiction Treatment for Adults: Developing Quality Measures for Consumers
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Progress has been made in defining the principles of effective addiction treatment but these have not translated into standard and operationalized indicators of quality that can be measured to provide consumers and other stakeholders with information on treatment quality. Such well-defined indicators and ways to measure them will be developed in this study. These are important because addiction treatment programs vary in content and presumably quality. Additionally, consumer-oriented information is fundamental to improving individual healthcare choices, and

more generally the quality of healthcare services, including addiction treatment for adults.

University of Pennsylvania ($5,421,220)
Research Projects:

- Title: Mechanisms of Kras- and p53-induced Metabolic and Epigenetic Remodeling in PDA
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project is based on recent findings showing that cancer cells have distinct metabolic behaviors compared to normal cells. The project leverages the background of the principal investigator in pancreatic ductal adenocarcinoma (PDA), who will work with a team of co-investigators with expertise in cancer metabolism. The goal is to dissect the molecular mechanisms underlying altered cancer metabolism and testing the therapeutic potential of specific inhibitors in preclinical models.
- Title: Hypoxia Benefits or Impedes on PDA Growth
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project is based on the finding that pancreatic tumors have a relative paucity of blood vessels and as a consequence are hypoxic. A major question, however, is whether hypoxia impedes tumor growth, by creating an environment in which only a limited amount of oxygen can be delivered and utilized, or whether it results in a more aggressive tumor phenotype as the result of growth pathways stimulated by the induction of HIF1a. This project aims to delineate the role of HIF1a in pancreatic tumorigenesis using genetic models.
- Title: Targeting the Metabolic Vulnerabilities of PDA
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project will build on progress from advances in the metabolism research field which suggest that targeting the "rewired" metabolism of a cancer cell may provide a therapeutic opportunity for the development of agents that selectively kill cancers while sparing normal cells. In this Project, we will test the impact of inhibiting key metabolic enzymes on pancreatic tumor cell growth in vitro and in vivo, assess the impact of losing ACL, a major source of acetyl CoA, on tumor growth, and testing the impact on tumor growth of pharmacologic agents that act by altering cell metabolism in the KPC model of pancreas cancer.
- Title: Research Infrastructure: Renovation of Laboratory Space for Biophysical Chemistry
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to upgrade and renovate 2097 square feet of laboratory space to standards appropriate for a 21st century laboratory performing research at the interface between physical chemistry and biology. The renovations include outfitting the laboratory space with modern fume hoods, electric, and case work as well as the creation of two rooms controlled to +-.2deg C to accommodate highly sensitive laser-based evaluation of biological samples. The renovated space will be occupied by researchers from the Chemistry Department whose research work includes studying the conversion of certain monomeric, soluble IDPs into toxic oligomers and mature fibrils, with the ultimate goal of developing therapies to modulate the disease processes of Alzheimer's, Parkinson's, and Type II Diabetes.

- Title: Research Infrastructure: Laboratory Space Renovation for Computational Neuroscience Initiative
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to upgrade and renovate 5020 square feet of laboratory space to standards appropriate for a 21st century laboratory performing research at the interface between life sciences, the physical sciences and engineering to spearhead development and use of quantitative approaches to the study of the brain and the mind. The renovations include fully renovating 1960's era space to modern standards of air-handling, temperature control, layout, and equipment to accommodate the new collaborative research efforts in the area of neuroscience.

University of Pittsburgh ($5,421,220)
Research Projects:

- Title: Research Infrastructure: Starzl Biomedical Science Tower 10th Floor West Lab Renovations Disease
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to renovate approximately 19,000 gross-square-feet of laboratory space on the west side of the 10th floor of the Thomas E. Starzl Biomedical Science Tower (BST). This biomedical research facility in the center of the University of Pittsburgh's campus provides nine floors of laboratory facilities for various research programs. The renovated space will support critical research activities in the growing Department of Immunology. Improvements to this space will also aid in the recruitment of top-tier new faculty to this department.
- Title: Determining Mechanisms of Disease Progression Using Quantitative Systems Pharmacology
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: An overarching challenge for translational research, especially for personalized medicine, is to determine the mechanistic relationships between gene variants and complex disease phenotypes. Such detailed knowledge of disease progression can inform both precise diagnostic, prognostic, and predictive biomarkers and novel therapeutic strategies. Our purpose is to address this challenge by demonstrating the broad applicability of quantitative systems pharmacology (QSP), a comprehensive, unbiased, physiologically relevant systems approach. As examples, we will elucidate critical aspects of disease progression for metastatic breast cancer and Huntington's disease that, in turn, will inform novel therapies and companion biomarkers.
- Title: Protein Kinase D as a Potential Target for the Treatment of Colorectal Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Colorectal cancer (CRC) remains a major public health problem in the U.S. and Pennsylvania. When metastatic disease is diagnosed, CRC is usually associated with poor prognosis, with five-year survival rates around 10 percent. Thus, there is an urgent need to identify and develop more effective therapies. This project seeks to characterize protein kinase D (PKD) as a key signaling pathway in CRC and then develop novel therapies that target this pathway. PKD plays an important role in the regulation of cell proliferation and survival. A clearer understanding of the PKD isoform that is critical for CRC growth and the downstream pathways regulated by

this isoform will enable development of targeted nano-encapsulated nucleic acid therapies.

- Title: Molecular Phenotyping of Lung Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Lung cancer is not one disease, but consists of multiple subtypes driven by different molecular changes. These phenotypes define patient outcomes and responses to specific therapies. Previous efforts have focused on oncogenic drivers. However, limiting the analysis to only these molecules reduces the utility of molecular analyses to a small percentage of lung cancer patients. By comprehensively analyzing lung cancers for mutational, epigenetic, and expression changes, we will define molecular subtypes that can be used to direct targeted therapies and conventional chemotherapy. These alterations may also be useful as disease biomarkers and for improving early detection and therapeutic monitoring.
- Title: p16/p53-Independent Induction of Senescence by Disruption of Anti-Silencing Function 1
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Our long-term goal is to address the consequences of dysfunctional DNA replication-coupled chromatin assembly with respect to aging and cancer. The overall objective of this research project, which is the next step toward attainment of our long-term goal, is to define the consequences of deregulated chromatin assembly during senescence.
- Title: Intestinal Protection against Chemotherapy by a Novel PUMA Inhibitor
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Radiation and chemotherapy remain the most widely used cancer treatments, yet dose limiting and long-term gastrointestinal (GI) toxicities impair treatment efficacy and quality of life for cancer patients and survivors. Normal tissue protection is expected to have a major public health impact. Our work aims to provide a better mechanistic understanding of intestinal stem cell injury and regeneration after chemotherapy and explore p53-dependent apoptosis, which is disabled in most cancers, as a selective and safe target that will improve the therapeutic index of chemotherapy by protecting intestinal stem cells. These studies may provide a novel strategy to potentially help many cancer patients and survivors.

University of the Sciences in Philadelphia ($6,940)
Research Project:

- Title: Identifying Critical Barriers to Cervical Cancer Screening Among Hispanic Women Living in Norristown, PA
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Cervical cancer represents one of the starkest health disparities facing U.S. Hispanic women. Community health workers (CHWs) provide novel and culturally congruent strategies to address such health disparities. Planned Parenthood of Southeastern PA (PPSP) implemented a CHW program in 2011 to meet the urgent health needs of this growing population. The purpose of this research is to conduct focus groups with both CHWs and Hispanic women living in Norristown, PA to identify key factors that motivate Hispanic women to receive recommended screening and to identify critical barriers to cervical cancer screening. The findings from this project

will inform future health disparities research and health education outreach with PA Hispanics.

Wistar Institute ($1,112,835)
Research Projects:

- Title: Thymic Development of Autoreactive and Regulatory T cells in Response to Self-Peptide
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Autoreactive thymocyte deletion and CD4+Foxp3+ regulatory T cells (Tregs) are required to prevent autoimmunity and maintain immune system homeostasis. Failure to effectively eliminate autoreactive CD4+ T cells can lead to a wide variety of autoimmune diseases, including rheumatoid arthritis, diabetes and multiple sclerosis. The studies in this project will define the processes by which CD4+ T cells that can potentially recognize self-antigens are either eliminated, differentiate into Tregs, or persist as potentially autoaggressive lymphocytes, and will aid in the application of Tregs to therapeutic settings.
- Title: Specific Immunotherapeutic Targeting of Ovarian Carcinoma
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Epithelial ovarian cancer kills ~15,000 Americans per year. The accomplishment of the proposed aims will define the potential and mechanisms of therapeutic activity of targeting the follicle-stimulating hormone receptor (FSHR), expressed on up to 70% of ovarian cancers and not on any nucleated cell outside the ovary in healthy tissues. For that purpose, we have generated chimeric antigen receptor (CAR) T cell constructs that use the endogenous FSH hormone as an effective and selective targeting motif. This project will define a new, selective and effective treatment of this devastating disease, which may be applicable to other lethal epithelial tumors.
- Title: Regulation of Multiple Myeloma by Myeloid cells
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: Multiple myeloma is a common and devastating blood cancer. Despite the emergence of novel therapeutics, myeloma remains an incurable disease. The bone marrow microenvironment plays a critical role in myeloma cells survival and progression; however molecular mechanisms responsible for interactions between host and cancer cells are poorly understood. The proposed study not only will contribute to our understanding of these mechanisms but also will test a novel therapy that targets myeloma cell interaction with its microenvironment. These studies, therefore, will address a significant clinical gap existing in the management of this disease.

Updated 6/10/2015