Health Research Formula Grants - State Fiscal Year 2009-10

Thirty-one organizations received health research formula grants totaling $53,415,200 for the state fiscal year 2009-10. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2010 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 ($119,376)

- Title: A Feasibility Study of Fruit and Vegetable Consumption in Low Income Communities
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to collect preliminary data from supermarket shoppers in a low income community about their purchasing of fruits and vegetables and to assess the feasibility of our methods. The results will provide us with preliminary data that will be used in designing a larger intervention study on the use of incentives to promote healthier eating, particularly in low income populations.
- Title: The Role of Left Inferior Frontal Cortex in Sequencing and Language
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: The project purpose is to explore an important component of language - the sequencing of words in a sentence - that is commonly impaired in non-fluent aphasia. Non-fluent aphasia is a stroke-related disability that features poor grammatical structure, effortful speech and impaired comprehension under some conditions. It is a complex syndrome that may consist of dissociable components. Understanding the cognitive and neuroanatomical bases of these components is critical for the accurate categorization of aphasic impairments and their subsequent treatment. A preliminary study suggested a key role for the left inferior frontal cortex (LIFC) of the brain in sequencing. This project aims to reproduce those results, clarify the relationship between the sequencing of words and sentence production, and test whether the sequencing deficit is specific to language.
- Title: Longitudinal Multi-modal Neuroimaging of Natural Recovery after Traumatic Brain Injury: A Pilot Study
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: This project will provide pilot data for a large-scale future study whose aims include 1) determining the pattern of longitudinal changes in structural and functional neuroimaging indices associated with traumatic brain injury (TBI) and their relationship with behavioral improvements and 2) developing a "recovery potential" index, based on the difference between structural and functional imaging measures obtained at different points of post-injury, and collect data on its relationship with behavioral recovery. This project will demonstrate our capability to collect and analyze longitudinal multi-modal neuroimaging data and to estimate the appropriate sample size for the larger study to be proposed for NIH funding.

Allegheny-Singer Research Institute ($186,525)

- Title: 16S FISH-based FACS Purification of Unculturable Bacteria for Whole Genome Amplification and Sequencing
  Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: It has recently become evident that most bioactive secondary metabolites isolated from marine invertebrates such as sponges, bryozoans, and tunicates are actually produced by their bacterial symbionts as part of mutual defense systems. The purpose of the planned research is to obtain pure populations of target unculturable microbial symbionts that will then be used for the generation of species-specific whole genome sequences. From these we can clone the biosynthetic pathways into genetically tractable organisms for the inexpensive engineered production of these medically important compounds. To obtain the single species bacterial cell populations, we will use a combination of metagenomics, deep 16S sequencing, 16S fluorescent in situ hybridization, fluorescence-activated cell sorting, whole genome amplification, and whole genome sequencing.

American College of Radiology ($2,043,960)

- Title: Novel Methods for Cancer Clinical Trial Design and Analysis
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: Clinical trials provide the critical evidence necessary to advance treatment for cancer. With the ever growing number of promising interventions, there is a need for improvements in trial design in order to a) obtain answers more quickly, b) conserve and optimize resources, and c) make better choices of what treatments to pursue in further evaluation. In addition, as treatment regimens become more complex and multimodal, the ability to accurately characterize whether anticipated benefits with respect to specific disease event reduction have occurred requires extensions of standard analytic methods. To address these needs, we propose a series of methodological projects aimed at addressing current questions in clinical trial design and analysis. These projects encompass a range of needs that apply broadly to cancer clinical trials and research in general.
- Title: Exploration of the RTOG Clinical Trial Database – Beyond Protocol-Specified Endpoints
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: For over 40 years, the Radiation Therapy Oncology Group (RTOG) has been funded by the National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. Drawing upon this vast resource of demographic, treatment, outcome, and patient-reported data, the researchers will develop hypotheses and explore correlations that were not defined in the treatment protocols for patients with brain, cervix, gastrointestinal, head and neck, lung, and prostate cancer. These analyses may lead to future protocols and/or better ways to identify high-risk subgroups and screen patients for specific treatment regimens.
- Title: Emerging Imaging Technology Clinical Trials in PA: Comparison of Full Field Digital Mammography with Digital Breast Tomosynthesis Imaging: Comparison of Recall Rates
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this multi-center study, to be conducted as part of the American College of Radiology Imaging Network – Pennsylvania, is to evaluate the digital breast tomosynthesis screening recall rates compared to routine 2D projection digital mammography. The goal is to understand if a hybrid combination of 3D tomosynthesis and low dose 2D digital mammography can significantly reduce the

recall rate of women from screening mammography without a concomitant reduction of sensitivity of cancer detection.

- Title: Investigation and Analyses of Patient Co-Morbidities in a Survey of Radiation Oncology Facilities in the USA and their Association with Treatment Decisions in Radiation Oncology
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to describe the distribution of co-morbidities by socio-demographic characteristics such as age, race, geographic region, insurance status and socio-economic status in patients diagnosed with cancer of the breast, cervix, stomach, lung and prostate, to investigate the association of the prevalence of co-morbidities with treatment decisions and variations in compliance with recommended disease management guidelines for such patients, and to examine the interaction of co-morbidities by site and stage of disease with gender, race, and age.

Carnegie Mellon University ($910,547)

- Title: Mid-Level Feature Representation in Human Visual Cortex
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Despite five decades of research, remarkably little is known about the representation of objects in "high-level" human visual cortex. Although both neurophysiology and neuroimaging have informed us about the spatio-temporal properties of early visual cortex (V1->V4), the subsequent encoding of objects within the ventral pathway is largely an unknown. Advances in neuroimaging technologies, including functional Magnetic Resonance Imaging (fMRI), Diffusion Tensor Imaging (DTI), Magnetoencephalography (MEG), and Electroencephalography (EEG) have altered the way vision scientists are able to study object representation. To that end, this project will develop a variety of novel, real-time neuroimaging paradigms and analysis methods designed to study and decode the representation of objects in terms of visual features.
- Title: Understanding Schizophrenia through Logical and Empirical Analysis
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Schizophrenics have persistent experiences of hearing voices (auditory hallucinations) and thoughts that are paradoxically taken to belong to another (inserted thoughts). To explain these symptoms, a common model postulates a mechanism whereby a person's thoughts or actions are "marked" as self-generated. Under this theory, trouble arises when this mechanism fails: a person's thoughts appear "alien" because they are not marked as self-generated. This project suggests an alternative hypothesis: a central problem in patients who hear voices or have alien (inserted) thoughts is not the misattribution of central thoughts, but rather that thinking and imagining are abnormal because they automatically generate thoughts and images. This project develops and tests this new hypothesis regarding the origins of these specific symptoms of schizophrenia.
- Title: Computational Immunology for Toleragenic Composite Tissue and Solid-Organ Transplantation
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: We propose to elucidate the tissue specific biological and informational principles of complex immunological mechanisms and systems that drive rejection and inflammation in solid or composite tissue transplants. Through advanced computational methods, machine learning and other high dimensional analytic

techniques, a new understanding of the patterns and governing principles of the immune system will be formulated, and will pave the way for novel clinically relevant toleragenic transplant protocols, therapeutics and long term patient care strategies. The longer term objective is to improve transplant tolerance and reduce side effects from indiscriminant immunosuppression.

Children's Hospital of Philadelphia ($4,034,902)

- Title: Pediatric Hospital Quality, Safety, and Cost Project
  Type of Research: Clinical and Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The project will inform the research agenda for pediatric hospital medicine and provide answers to key questions about how we can best organize and deliver hospital care to children in order to improve quality, safety, and outcomes, and reduce costs.
- Title: Methods to Evaluate the Content and Dissemination of Internet-Based Interventions to Prevent Injury
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Decades after the National Academies emphasized the importance of injury prevention for our nation's health, injury prevention science remains an underdeveloped field. As a result, in Pennsylvania, injury remains the leading cause of death for ages 1-44, and 135,334 hospitalizations for injury cost $4.6 billion per year. Children, youths and young adults are the primary victims of injury. With an established highly successful and integrated 50-member multidisciplinary team, the mission of Children's Hospital's injury research program is to reduce the burden of injury through evidence-based prevention. This study aims to leverage this expertise to fill the crucial gap for advancing injury prevention by generating new methods to inform injury prevention interventions that are (1) developed systematically and evaluated and (2) disseminated widely and adopted.

Children's Hospital of Pittsburgh ($1,039,905)

- Title: New Reporters of Protein Conformation and Compartment Composition
  Type of Research: Biomedical
  Focus: Respiratory Sciences
  Purpose: The purpose of this project is to develop new methods for the assessment of protein location and compartment composition that are necessary to determine the mechanism of human diseases and to develop therapeutic options for their treatment. These methods will be developed initially for the common genetic disease, cystic fibrosis (CF). These expressible reporters permit the detection of expressed proteins at exceptional signal-to-noise. Expressed tags that recognize a variety of fluorogens will permit also the determination of compartment composition, permitting functional anomalies attributed to CF can be assessed in primary airway cell cultures. These methods will be valuable for mechanistic evaluation and drug discovery opportunities for CF and a variety of other human diseases that affect cellular protein handling or localization.
- Title: Therapeutic Targeting of Breast Cancer Stem Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We have identified a means of inhibiting the differentiation of breast cancer stem cells (CSCs), thus allowing the expansion of this otherwise exceedingly rare and difficult to study population. Characterization of CSCs from 4 different

breast cancer cell lines shows them to possess common properties, including a >100-fold increased tumor initiating capacity relative to non-CSCs and resistance to traditional chemotherapeutic drugs. We have identified a number of novel small molecules and siRNAs which selectively inhibit CSC proliferation. We propose to expand these studies to CSCs from primary tumors, to screen for additional small molecule inhibitors, and to better characterize the siRNA-targeted pathways that are necessary for CSC viability. These studies could point the way to new rationally designed strategies for improving breast cancer treatments.

Drexel University ($1,431,165)

- Title: Effect of Antiretroviral Therapy on Surrogate Markers of Cardiovascular Disease and Inflammation in HIV-infected Patients
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: Numerous studies have demonstrated that HIV infected patients are at an increased risk of developing cardiovascular disease (CVD) and myocardial infarction (MI). There is evidence to suggest that HIV infected patients have unique risk factors related to their infection and its treatment that interact with traditional cardiac risk factors to put them at increased risk of CVD. The purpose of this study is to prospectively evaluate measures of endothelial function and subclinical atherosclerosis as well as markers of inflammation in HIV patients in order to elucidate the nature of HIV specific risk factors for cardiovascular disease. This knowledge will allow more effective risk stratification and treatment in this population which is disproportionally affected by cardiovascular disease.
- Title: Modulation of Capsid Stability as an Antiviral Strategy
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: The project purpose is to identify anti-HIV compounds that work by antagonizing the functions of the viral capsid protein.
- Title: sPLA2 Inhibition Therapy for Epilepsy
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: This project will test the efficacy of new secreted phospholipase A2 (sPLA2) inhibitors as therapy for both the excitability disturbances and inflammatory consequences of epilepsy. These inhibitors, called CHECs, consist of 7mer and 9mer peptides with demonstrated systemic efficacy in traumatic and autoimmune disease models. They are part of a portfolio of intellectual property (composition of matter, applications, diagnostic) held by Drexel University. The goal of this application is to expedite the clinical development of these peptides by expanding potential clinical applications. These compounds are especially suited for commercial development since it has been unequivocally demonstrated that they are active when taken by mouth. The present experiments are proof-of concept studies for treatment of epilepsy, where the inflammatory consequences of the disease have been largely overlooked. Interestingly, there is also evidence, including our own preliminary studies, that excitability changes during epilepsy are closely related to inflammation, raising the possibility that the CHEC peptides represent a unique monotherapy for this disease.
- Title: Role of Septins in Growth Cone Guidance
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: This project will investigate the roles of three members of the septin family of GTPase (septin 2,6,7) in the guidance of growth cones by extracellular signaling

molecules. The correct guidance of axons is crucial to nervous system development and regeneration following injury. The project will determine if septins are involved in growth cone guidance and the extension of axons, and thus whether they may be targets for therapeutics aimed at promoting or regulating axon extension and regeneration.

- Title: Development of the Cardiac Ultrasound Pacemaker
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: There is an unmet need for a technology to reliably and painlessly pace the heart without any surgical implantation or intravascular catheter placement. Our objective is to develop a technology that would provide noninvasive, low infection risk, and reliable pacing for minutes to weeks in conscious patients requiring temporary or emergency pacing. We envision an ultrasound device that could be placed directly on the skin of the chest wall that would function as a pacemaker for the heart.
- Title: Human Lung Progenitor Cells for Pulmonary Tissue Engineering and Regenerative Medicine
  Type of Research: Biomedical
  Focus: Respiratory Sciences
  Purpose: The purpose of this interdisciplinary research is to isolate and study human lung-specific somatic progenitor cells. These cells can be used to engineer high-fidelity distal pulmonary constructs (alveolar forming units, AFUs) for studying basic mechanisms of lung development and ultimately, for treating currently incurable lung diseases, such as in newborns (e.g., pulmonary hypoplasias) and/or in adults , e.g., chronic obstructive pulmonary disease (COPD), such as emphysema. Moreover these AFUs can also lead to a commercializable tissue-engineered product for use as models in accelerated drug discovery (e.g., improved anti-asthmatics), in understanding common lung infections (e.g., pneumonia/tuberculosis), or in toxicity studies (e.g., asbestos/vapor inhalation).
- Title: Novel Oligomers Targeting AMPA Receptors as Therapeutics for ALS
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: In this project we will evaluate the efficacy of compounds we have developed called splice modulating oligomers (SMOs), which dramatically decrease flip/flop levels of targeted GluR AMPA subunits, to improve motor function and prolong lifespan in transgenic ALS mice. SMOs are compounds that function by binding to their target pre-mRNA, and redirecting pre-mRNA splicing by the spiceosomal complex in a predictable fashion. Due to recent improvements in chemistry, SMOs show extraordinary specificity, potency, and resistance to degradation. We propose that our SMOs could ultimately be used clinically as neuroprotective agents for treating amyotrophic lateral sclerosis (ALS), by reducing calcium influx in motor neurons (MNs) and breaking the feedback cycle involved in glutamate-mediated excitotoxicity.
- Title: Neuronal Substrates of Cognitive Flexibility
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Cognitive flexibility is the capacity to alter behavior to meet unexpected challenges, and is an essential aspect of adaptive behavior. Unfortunately, deficits in this capacity are hallmarks of various psychological and neurodevelopmental disorders including schizophrenia, obsessive compulsive disorder, and autism. Furthering the development of effective treatments for individuals with these disorders requires a more comprehensive understanding of the physiological

processes mediating behavioral adaptability. The overarching aim of this project is to develop a novel experimental paradigm to explore the detailed neurophysiological substrates of cognitive flexibility using the laboratory rat as an experimental model.

- Title: Microfabricated QLISA Biosensor with Embedded Heating and Mixing Elements
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this project is to develop a novel, low cost microfabricated poly (methyl methacrylate) (PMMA) Quantum-dot-Linked-ImmunoSorbent-Assay (QLISA) biosensor with embedded mixing elements. The significant advantages of this microfluidic platform with integrated electrokinetic mixing are: a) Higher optical detection sensitivity b) Improved detection limit c) Higher signal to noise ratio d) Reduction of assay e) Multiuse system - repeated use of the sensor is possible, and f) Platform technology – can be used to detect any biomarker. The bioassay platform developed will use only 1-2 microliters of sample and achieve detection sensitivity of picomolar quantities of antigen.
- Title: The Role of miRNAs in Modulating Alzheimer's Disease Risk
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: We will test the hypothesis that genetic variation in the 3' untranslated region (3'UTR) of the human amyloid precursor protein (APP) gene may modulate the risk of developing Alzheimer's disease by disrupting miRNA mediated regulation APP levels. The genetic basis of Alzheimer's disease (AD) is not fully understood. Identifying polymorphisms that increase risk will allow for early prediction of who may develop disease. This knowledge may also lead to a novel therapeutic approach to treating AD with molecules that act like miRNAs to decrease APP levels.
- Title: Suppression of Monocyte Migration by Inducible CCR2 Silencing
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: The purpose of this work is to develop a new method to intervene in the progression of neurologic disease that often occurs in HIV-1 infected individuals. We will investigate a method designed to reduce the ability of HIV-1 infected immune cells to migrate into the brain. This migration is enhanced by signals released from brain-resident infected cells in a positive feedback loop that we will disrupt using a strategy based on RNA interference. Certain receptors that are present on the surface of immune cells, and that allow these cells to respond to the migratory signals, will be down-regulated specifically in HIV-1 infected cells. If successful, this will lead to therapies designed to reduce the overall inflammatory immune response to infection in the brain and help to curb the progression of neurologic disorders.

Duquesne University ($121,663)

- Title: Implementation of an Asthma Program to Improve Asthma Identification and Education in Children
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of the Asthma Program is to develop and implement a method to increase the identification of children with undiagnosed or uncontrolled asthma; to develop and evaluate educational interventions that teach caregivers and children with asthma how to properly control their disease state; and to encourage active healthy lives. The goal of the Asthma Program is to improve health outcomes and quality of life for children suffering from asthma.
- Title: Engineering Aβ-selective Enzymes for Treatment of Alzheimer's Disease
  Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This project involves approaches aimed at engineering metalloendoproteinases to specifically cleave and clear Aβ peptide as a potential therapeutic approach for treatment of Alzheimer's Disease (AD). Dysfunctional metabolism leading to excess quantities of Aβ that is produced at normal levels throughout life may be the causative agent in many, if not most, cases of AD. Neprilysin, neprilysin-2 and insulin degrading enzyme have been shown to cleave Aβ *in vivo* or *in situ.* However, these enzymes are promiscuous with respect to substrate specificity and proteolyze other (neuro)peptides involved in critical physiological responses. The nano-engineering studies proposed here offer the opportunity to produce Aβ-selective enzymes that may be safely employed in subsequent gene transfer studies aimed at treating AD.

Fox Chase Cancer Center ($3,477,323)

- Title: Regulation of Genomic and Epigenomic Stability at CpG Sites
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to understand how two base excision repair enzymes, thymine DNA glycosylase (TDG) and methyl-CpG-binding endonuclease 1(MED1)/ methyl binding domain 4 (MBD4), not only protect CpG sequences from transition mutations and ward off against endogenous deamination events, but also mediate DNA demethylation and modulate DNA methylation states, chromatin structure and gene transcription. This dual role in genomic and epigenomic stability of CpG sites is likely to be important for cancer formation, given the frequent occurrence of CpG to CpA (or TpG) point mutations and hypermethylation of tumor suppressor genes in cancer. Thus, knowledge accumulated in this project may lead to novel strategies for cancer prevention.
- Title: Estrogen Receptor-Mediated Gene Silencing in Tumorigenesis
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The role of estrogen in contributing to women's cancers, especially those of the breast and uterus, is well established at the epidemiologic level. The molecular mechanism through which inappropriate timing and/or excessive levels of estrogen exposure initiate or promote human tumorigenesis remains largely unknown, however. The purpose of this study is to test the hypothesis that the activated estrogen receptor, which functions as a transcription factor, is also capable of silencing genes, through promoter hypermethylation, that normally function to suppress tumorigenesis in human cells subject to regulation by estrogen. In addition, we will explore the molecular mechanism of this methylation-dependent gene silencing.
- Title: Markers of Adult Epithelial Stem Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to identify novel stem cell markers in adult epithelial tissues. Currently, no markers are available that consistently and robustly enable the in vivo identification and purification of adult stem cells from normal tissues or tumors. Moreover, the difficulty associated with in vivo identification of stem cells has hampered attempts to conduct functional analyses of genes thought to regulate stem cell function or contribute to the formation of tumor cells with self-

renewing properties. We aim to determine the molecular identity and function of a new epithelial stem cell marker in the fly and assess its functional conservation in mammalian epithelial tissues. The information provided in this study will be a foundation for the development of agents that promote or target stem cell function for use in replacement therapies and anti-cancer treatment.

- Title: Role of a Novel Zinc Finger Factor in Hematopoietic Development
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: The purpose of this project is to understand the role of a novel erythroid factor (G4) in hematopoietic development using the zebrafish model system. Since the molecular basis for G4 function in controlling erythropoiesis is completely unknown, we will determine where g4 fits in the hierarchy of transcription factors controlling hematopoietic development, identify its human ortholog, and perform structure/function analysis to identify the domains of g4 that are essential for its function. Results from these studies will provide insights into how normal blood cell development is controlled and how those processes are perturbed in cancer.
- Title: Reducing the Burden of Hepatocellular Carcinoma: Identification of New Targets against Hepatitis B virus (HBV) for Drug Development
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: A reduction in the burden of liver cancer depends on the development of effective therapies that prevent or arrest the growth of hepatocellular carcinomas. The purpose of the project is i) to develop rapid screening assays for primary cultures derived from hepatocellular carcinoma for drugs and drug combinations that induce cell death and to identify serine and tyrosine kinases that are required for the survival of tumor cells in the presence and absence of already available anticancer drugs and ii) to identify novel targets for antiviral therapy against hepatitis B virus.

Geisinger Clinic - Weis Center for Research ($104,117)

- Title: Genetic Factors Associated with Aneurysms
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The goal of this project is to identify genetic variants associated with abdominal aortic aneurysms (AAA). This will provide new insights into the disease mechanism, leading to new non-surgical therapies. Knowledge of AAA-associated genetic variants could also be used to identify individuals with increased genetic risk so that they could be diagnosed and treated before their aneurysm ruptures, which would reduce their chance of dying from a ruptured AAA.

Hepatitis B Foundation ($1,073)

- Title: Identifying Novel Antiviral Agents against Hepatitis B Virus
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The purpose of this project is to identify new viral targets for development of antiviral agents against hepatitis B virus. Identified targets will be tested for antiviral activity. This will lead to potential future antiviral development, necessary to augment the short-comings of existing antiviral therapies, including the development of resistance.

Lankenau Institute for Medical Research ($241,281)

- Title: Tirapazamine and a Novel Drug in the Control of Hypoxic Human Colon Cancer Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Low oxygen (hypoxia) is prevalent in most solid tumors. These types of hypoxic cells are up to three times less responsive to cancer therapy that involves radiation and chemotherapeutic agents. Previously several approaches have been tested to target hypoxic cancer cells in vitro. These approaches used drugs such as tirapazamine that produced "damages" in low oxygen tumors. However, these damages are easily repairable by repair molecules since tirapazamine does not target cancer cell's repair capacity, which play a major role in the survival of cancer cells. Our recent studies have shown that a novel drug studied in our lab inhibits repair molecules in human colon cancer cells. In this project, we will test whether this drug increases hypoxic cancer cell response to tirapazamine under conditions found in solid tumors.
- Title: The Role of IDO in B Cell Activation and Memory
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Patients with the autoimmune disease rheumatoid arthritis have an elevation in the level of activity of the immunoregulatory enzyme IDO. IDO elevation correlates with disease activity, suggesting that IDO may contribute to the disease process. In support of this, we have evidence that inhibiting IDO activity interferes with arthritis development in mice. This alleviation of arthritis resulted from a diminished autoreactive B cell response, suggesting for the first time an important role for IDO in directing B cell responses. In this project, we will use model systems of B cell activation to explore the importance of IDO in driving B cell activation. The overall goal of this project is to define the mechanism by which IDO modulates B cell responses and provide new insights into strategies that can be used to manipulate this pathway to reduce or prevent disease.

Lehigh University ($119,007)

- Title: Development of a Point-of-Care Opto-Fluidic HIV Viral Load Detector
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The intended result of this work is the design and construction of a hybrid platform that uses a combination of filtration and concentration methods in order to quantify the number of circulating HIV virons directly from patient blood samples. The purpose of this project is to perform fundamental studies to gauge the feasibility and performance of the device. After primary feasibility studies, we expect that the device will address the challenges associated with a point of care diagnostic platform that is both portable and easy to use in both resource-limited and general settings.

Lincoln University ($23,171)

- Title: Polymorphisms in the 1,25D_3-MARRS Receptor: Characterization and Association with Serum Vitamin D Levels
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to expand the scope of current research activities to include investigations on existing tissue and blood samples to determine

the prevalence of polymorphisms in the 1, $25D_3$-MARRS receptor., which is a membrane receptor for vitamin D. Lower incidences of cancer have been correlated with increasing levels of vitamin D, but the mechanism of action is not well understood. It is possible that different forms of both vitamin D receptors cause vitamin D to have different effects. Therefore, we will examine the occurrence of polymorphisms (different forms) in three different genes associated with activity of 1α, 25 $(OH)_2$-vitamin D.

Magee Womens Research Institute ($1,541,095)

- Title: Refinement of the Appropriate Animal Model for Respiratory Infection with Influenza in Pregnancy
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The purpose of the project is to develop and test a ferret model for respiratory challenge with influenza virus infection during pregnancy. This is critical given the disproportionate morbidity and mortality seen among pregnant women during previous influenza pandemics, seasonal epidemics and the current novel 2009 H1N1 influenza pandemic. Development of a pregnant animal model for respiratory challenge will also allow for future investigations to delineate more effectively the susceptibility to infection noted among pregnant women and their immunological response mechanisms. In addition, with the growing threat of bioterrorism and the fact that most category a bioterror agents would be targeted for inhalational spread, development of pregnant animal models allows for ongoing countermeasures' research against these agents in this unique population.
- Title: Relationships among PPAR gamma Activity, Hypoxia, and Differentiation in Human Placenta
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The main purpose of this study is to understand the relations among four important biological processes occurring in human placenta: placental hypoxia, normal trophoblast differentiation, peroxisome proliferator-activated receptors (PPAR) gamma activity, and fetal growth restriction. By applying various statistical procedures to both historic and recently generated data sets, the results of this study could deepen our understanding of these placental processes from the genomic point of view, shed light on the mechanism behind the fetal growth restriction caused by hypoxic injury, and eventually facilitate the development of prevention and treatment methods for fetal growth restriction.
- Title: Hypoxia Inducible miR-210 as a Potential Therapeutic Target in Renal Cell Carcinoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: We plan to illustrate the mechanism of apoptosis in clear cell renal cell carcinoma cells (ccRCC) harboring VHL mutation caused by inhibition of a hypoxia inducible microRNA (miRNA), miR-210. By identifying the genes responsible for this phenotype, we will discover potential novel therapeutic targets for ccRCC, which is refractory to current chemo- and radiation-therapies.
- Title: Role of miR-424 in the Differentiation and Function of Placental Trophoblasts
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Our ultimate goal is to understand how hypoxic stress impacts placental function. Feto-placental hypoxia is associated with pregnancy complications but the molecular mechanisms remain poorly understood. We recently found that hypoxia

induces major changes in the expression levels of several microRNAs (miRNAs), a family of small regulatory RNAs that are increasingly found linked to disease. One of them, mir-424, is normally abundant in placental trophoblasts but is significantly decreased when cells are exposed to hypoxia. The downregulation of miR-424 could lead to the de-repression of a number of target genes and have profound consequences on the trophoblast biology. This research will focus on the expression and the role of miR-424 in the differentiation of placental trophoblasts.

- Title: Epigenetic Analysis of Human Aneuploidy
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Common chromosomal disorders resulting in live births include Down, Turner, Edwards and Klinefelter Syndromes. Although our knowledge of human aneuploidy has improved, there are still many gaps in our understanding of the mechanisms by which an altered number of chromosomes can lead to a specific disease phenotype. One area that has not been previously explored is the effect of aneuploidy on DNA methylation patterns. This is significant because appropriate DNA methylation is known to play a central role in gene regulation and normal homeostasis. This pilot project will therefore characterize genome-wide DNA methylation patterns in normal pregnancies and compare these to aneuploid pregnancies. A practical outcome of this work will be the identification of potential diagnostic biomarkers of human aneuploidy.
- Title: Antigen Expression and Adaptive Immunity in Human Endometriosis and Endometriosis-Related Ovarian Cancers
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Ovarian cancer most often presents as advanced disease and survival at 5 years is very low. We postulate that identification of precursor lesions would allow for timely detection of early ovarian cancer and will ultimately improve survival. To date, the only precursor lesion reported in ovarian cancer is endometriosis, a common disease which can affect up to 10% of reproductive-age women. However, the major pathogenesis mechanisms are not well understood in either ovarian cancer or endometriosis. One common denominator of these two clinical entities is chronic inflammation, given by the interaction of cancer cell-intrinsic factors and the host immune system. We postulate that a better understanding of the role of the adaptive immune system in endometriosis could potentially contribute to the design of vaccines used for ovarian cancer prevention rather than therapy.
- Title: The Impact of Age on the Nematode Germline
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: In human oocytes, defects in meiotic crossover exchanges are the most significant age related abnormality. Nevertheless, our understanding of the processes that control where and how many crossovers occur is not well understood. Furthermore, it is unclear how aging impinges on different crossover configurations to increase missegregation at increased maternal age. Our studies in the nematode *C. elegans* will use high resolution confocal imaging to identify changes in the germline chromatin structure during normal aging and will analyze how aging pathways influence these processes. These studies have the potential to identify genes and pathways that lead human aneuploidy and therefore may identify targets for therapeutic purposes.

Monell Chemical Senses Center ($240,428)

- Title: Relationship between Parental Smoking, Dietary Habits, Salt and Sweet Preferences and Blood Pressure among Children
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Children whose parents smoke eat a poorer quality diet (e.g., high in sodium) than children of nonsmokers, thus further increasing their future risk for chronic disease. Because primary hypertension, an important risk factor for cardiovascular disease, is rooted early in life and because taste and flavor preferences are important determinants of food choice, this project will evaluate for the first time the relationships among preferences and sensitivity for salty and sweet foods, dietary intake of these nutrients, and blood pressure among children, half of whom have mothers who smoke. This project will also consider recent advances in genetics to genotype all participants for selected genes related to taste perception, blood pressure and addiction. The information gleaned will set the stage for developing strategies to reduce salt and sugar intake in children.

National Disease Research Interchange ($73,679)

- Title: Fine Mapping of Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes
  Type of Research: Health Services
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The Human Biological Data Interchange (HBDI) database is a vast repository of family and medical information focused on the study of type 1 diabetes and its complications. A previous project confirmed that genetic factors likely influence susceptibility to microvascular complications of diabetes, including retinopathy, kidney disease and neuropathy. In this project we will test for associations between specific genes and the presence or absence of complications by using HBDI samples newly typed by the T1DGC (Type 1 Diabetes Genetic Consortium). To enhance our analyses and maintain the scientific value of our dataset, we will continue our ongoing program of administering follow-up questionnaires. Finally, we will begin a SNP saturation study of statistically important genes. The additional information we collect will better define the genetic contribution to diabetes complications.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation ($1,255,581)

- Title: Discovery and Validation of MicroRNAs as Biomarkers in Breast and Colon Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Messenger RNA (mRNA) expression profiling has yielded useful prognostic tests for breast cancer (e.g., Oncotype DX® and MammaPrint®), but has not been very useful in identifying definitive treatment targets. This is because mRNA expression profiling does not necessarily provide insight about which changes may be susceptible to therapies. For colon cancer, no clinically useful gene-expression-based prognostic tests exist yet. MicroRNAs (miRNAs) are a subset of RNAs which have regulatory functions and, so, could be viewed as master switches for many coordinately regulated genes. This project's purpose is to identify miRNAs that are prognostic or predictive of benefit from systemic therapies for breast and colon cancers, using archived tumor tissues from completed NSABP clinical trials. Identified markers may point us to new treatment strategies.

Pennsylvania State University ($8,412,824)

- Title: Modifications of Histone H3 in Diabetic Retinopathy
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The overall purposes of this project are twofold. First we plan to define some of the changes in chromatin structure that occur in the retinas of an animal model of Type I diabetes. This will give us fundamental information about the range of retinal changes seen in this disease and will offer new insights into the types of change that need to be treated. The second objective is to monitor how treatment with insulin can reverse these changes and restore the retina to its normal state. This set of experiments will test the hypothesis that some of the retinal changes in diabetes become irreversible with time.
- Title: Brain and Behavior in Early Iron Deficiency
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Aggressive iron repletion following iron deficiency in infancy will result in excessive accumulation of this potential neurotoxin in the brain and is associated with alteration in brain genomic level and myelin composition. The purpose of this project is to determine if aggressive dietary iron intervention to replenish brain iron concentrations in formerly iron deficient animals is neurotoxic.
- Title: Cell Signaling Mechanisms Necessary for High-Fidelity Replication of Repetitive Sequences
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The integrity of an organism depends on faithful replication of the genome with every cell division. The human genome contains six billion bases, many of which can be present in structures that make it difficult for replicative enzymes to work efficiently and accurately. Human cells have 15 different DNA polymerases that function to copy the genome. Mutations caused by polymerase errors within repetitive microsatellite sequences pose a significant threat to genome integrity, as is evident in colorectal cancers. The goal of this project is to elucidate the polymerases and cell signaling mechanisms that are necessary for high-fidelity replication of microsatellites. Understanding the dynamics of microsatellite replication will lead to new approaches for detecting and treating colorectal cancer, one of the most common cancers in the United States and Pennsylvania.
- Title: Impact of the Penn State Diabetes Patient Registry
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Disease registries (or electronic patient databases) are being implemented extensively by health care systems with the goals of improved records management, individualized patient care, and population-based disease management. They are a central feature of improving quality care for chronic illnesses and feature prominently in the national effort towards redesigning primary care as the Patient Centered Medical Home (PCMH). Although used extensively, little data are available on the overall impact of registries on care. The Penn State Diabetes Registry (PSDR) was first implemented in the Penn State Hershey system in 2002 to achieve the aforementioned goals and to simultaneously provide a research network for patient recruitment for diabetes research. The purpose of this project is to identify the value of this chronic illness registry for quality improvement of clinical outcomes, to examine its effectiveness in promoting high quality clinical research and to identify opportunities for PSDR refinements through assessments of the impact of the PSDR.

- Title: Epigenetic Changes in Myeloid Differentiation and Acute Myeloid Leukemia
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: The purpose of this project is to identify changes in epigenetic mechanisms controlling myeloid differentiation and transcription in order to predict and prevent the progression of acute myeloid leukemia (AML), a highly malignant blood cancer. Recent development of high-throughput "next-generation" genomic sequencing technologies such as ChIP-sequencing provided a dramatic breakthrough in whole-genomic mapping of epigenetic markers such as histone methylation and acetylation and their abnormalities. Here we propose to conduct a detailed whole-genomic characterization of the localization and expression of one such marker, histone H3 methylation, which is altered in AML cells, and to identify clusters of genes involved in epigenetic changes marked by this histone modification and transcriptionally deregulated in leukemia.
- Title: Bridging the Gap between Label-Retention and Mammary Stem Cell Properties
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Breast cancer patients frequently suffer relapse after prolonged periods of clinically undetectable disease. Whether dormant breast cancer is comprised of quiescent cells versus cycling cells, whose proliferation is offset by cell death, remains unknown. When modeling dormant breast cancer by reversing Wnt1-initiated mammary tumorigenesis in transgenic mice, we found that minimal residual disease (MRD) lesions harbor both latent malignant potential and mammary gland reconstitution capacity. Moreover, our preliminary data demonstrate that MRD lesions harbor a slow-cycling mammary epithelial cell (MEC) population. We propose to demonstrate that these quiescent cells are enriched for expression of validated mammary stem cell markers.
- Title: Neural Control of Breathing by a Signal Encoding Venous Pressure: Implication in Heart Failure
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Respiratory symptoms such as chronic hyperventilation are dominant expressions of cardiac insufficiency. Hyperventilation induced hypocapnia also has the potential to disrupt sleep architecture and to provoke central sleep apnea, further limiting quality of life in these patients. Distension of the venous system, a common feature of cardiac failure, leads to the activation of neural afferent fibers located in the adventitia of the post capillary bed, which in turn increases breathing. The proposed studies are intended to establish, in an animal model, the involvement of such a mechanism at rest and during muscle activity.
- Title: Influence of Brain Astrocyte Glutamate Concentrations on Neurotransmission
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The most abundant type of cell in the brain is the astrocyte. Astrocytes may control neurotransmitter traffic by lowering the concentration of neurotransmitter glutamate in synaptic spaces. Vesicular glutamate released from presynaptic neurons into the synaptic space stimulates depolarization and electrical signal transduction by post- synaptic neurons. The synaptic space barrier is composed of membranes from both presynaptic and post-synaptic neurons and astrocytes. Astrocytes rapidly remove glutamate from the synaptic space which would otherwise prolong signal transmission and cause excitotoxicity. The study examines the properties of the glutamate transporter in the astrocyte membrane to

evaluate the influence of the intracellular astrocyte glutamate on inward transport and examines how cytosolic concentrations of glutamate are regulated by astrocytic enzymes.

- Title: Identification and Function Study of Inflammatory Bowel Disease-associated DNA Methylation
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: Inflammatory bowel disease (IBD), with Crohn's disease (CD) and ulcerative colitis (UC) as its two major forms, is a complex human disease. In the US, about 1.4 million people are affected with IBD. Currently, there is no known specific cause and no medical cure for the disease. Although more than 32 genes have been identified as IBD-associated genes, the total number of genetic factors discovered so far can only account for less than 20% of the overall genetic risk. It is clear that other factors make a significant contribution to the disease process. In this project we will examine the role of DNA methylation in IBD. DNA methylation is a modification of DNA molecules and has emerged as an important player in human development and diseases.
- Title: Allogeneic CMV CTL for Refractory Glioblastoma Multiforme
  Type of Research: Biomedical, Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to determine the safety as well of the clinical and immunological effects of infusing allogeneic, cytomegalovirus (CMV) specific cytotoxic lymphocytes (CTL) in patients with refractory, CMV positive glioblastoma multiforme (GBM). Patient tumors will be tested for the presence of CMV pp65 and IE-1, and if the tumors are positive and the patients meet other eligibility criteria they will receive CMV CTL from an HLA partially matched donor. We will determine the duration and magnitude of CMV specific T cell function and donor cell microchimerism, the latter using PCR assays. We will also determine the incidence of clinical responses to this intervention, and correlate these clinical responses with donor cell chimerism and CMV specific immunity post-infusion.
- Title: Molecular Mechanisms of Olanzapine's Metabolic Side Effects in an Animal Model
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Understanding the mechanism of the metabolic side effects of atypical antipsychotics is very important to the patients taking these drugs and their families. This research will focus on how atypical antipsychotics lower free fatty acids and will provide data supporting our hypothesis that it both impairs lipolysis leading to increased adiposity and simultaneously increases lipid oxidation leading through substrate competition to hyperglycemia and apparent insulin resistance.
- Title: Genetic Analysis of Papillomavirus Virion Morphogenesis
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The central hypothesis of this project is that the capsid proteins of human papillomavirus (HPV) have specific functional domains for morphogenesis of infectious viral particles in a differentiation-dependent manner. When completed, this project will provide new insight into the molecular mechanisms of virion morphogenesis in a system capable of reproducing the natural complex process and differentiating environment of native HPV virion (NV) morphogenesis and infection.
- Title: Epidermal Stem Cell Properties in Mice with Altered Polyamines
  Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Our research studies the role of the polyamine pathway in early skin cancer development. Since skin cancers are the most common form of malignancies world-wide, identification of possible targets for prevention is highly relevant to public health. Understanding the role of the polyamine pathway is also of great importance because the polyamine biosynthesis inhibitor difluoromethylornithine (DFMO) is a promising chemopreventive agent of human skin cancer.

- Title: Topical Application of Isoselenocyanates for the Prevention of Melanoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Malignant melanoma is the most fatal and invasive form of skin cancer. The cause of 60% of melanomas is yet to be determined, making development of effective targeted chemopreventive agents especially important. In spite of the widely appreciated magnitude of the problem, there is still a critical gap in knowledge regarding key deregulated signaling pathways causing melanoma and chemopreventive agents targeting these gene defects to prevent this disease. Therefore, the purpose of this project is to develop *a rationally designed chemopreventive agent targeting the Akt3 signaling pathway.* As a direct outcome of the investigation, we expect to validate the effectiveness of novel synthetic agents derived from naturally occurring chemopreventive agents as a topical agent that prevents early melanocytic lesion development.
- Title: Activation of STAT3 Protects Liver from Ischemia Reperfusion Injury
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: Liver resection is the only curative option for liver tumors and liver transplantation is the only viable treatment for end stage liver disease. Warm ischemia/reperfusion (I/R) is a common clinical problem during both types of surgeries. Warm ischemia also occurs in trauma and shock. The liver is the most commonly injured abdominal organ in blunt and penetrating abdominal trauma. The management of trauma and shock frequently involves exposing the liver to varying periods of warm ischemia followed by reperfusion. I/R injury is significantly associated with morbidity and mortality in such conditions. Prevention or minimization of liver I/R injury is the clinical priority for our study, because there is still no safe and promising strategy to protect liver from I/R injury.
- Title: Multifunctional Nanoparticles for Melanoma and Brain
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Malignant melanoma and glioblastoma multiformi (GBM) are invasive and deadly forms of skin and brain cancer respectively with no effective therapy to treat advanced disease, leading to poor survival rates. A P01 Program Project Grant is proposed consisting of 5 projects using "Multifunctional Nanoparticles" to develop a new category of agents to treat these cancers. This project will focus on developing preliminary data to be used in supporting the Program Project application and to illustrate advanced integration and improved synergy between the 5 projects incorporated in the Program Project Grant (PPG).
- Title: Parathyroid Hormone and Prostate Cancer Colonization of Bone
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: There is a fundamental gap in understanding how osteosclerotic prostate cancer (PCa) metastases colonize bone, and the contribution of bone formation and parathyroid hormone (PTH) to this process. Our long term goal is to understand what

regulates PCa colonization and establishment in bone, and to aid development of treatments that prevent bone metastases. The objective of this project is to identify the requirement(s) for PTH-enhanced bone formation in osteosclerotic PCa colonization and establishment in murine bone. Our central hypothesis is that osteosclerotic PCa colonization of bone, from the vasculature, requires enhanced bone formation. The rationale for this project is that once we know how enhanced bone formation facilitates the favorable interaction(s) between osteosclerotic PCa cells and bone, novel treatments can be developed to prevent such interactions.

- Title: Perlecan Regulation of Synovial Hyperplasia
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: In patients with arthritis, synovial hyperplasia (SH) gives rise to pannus formation, invasion and erosion of articular cartilage, leading to joint destruction and chronic pain. There is a fundamental gap in understanding what regulates SH. The objective of this proposal is to identify a role for the HSPG, perlecan, in modulating SH.
- Title: A Multi-Center Randomized Single Blind Trial of Intravenous Fluids during Labor
  Type of Research: Clinical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: To determine if intrapartum use of a glucose-containing solution will improve the outcome of labor and reduce operative deliveries.
- Title: Identification and Characterization of Regulatory Factors of the Human Telomerase Gene
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Normal human somatic cells age, due to the fact that telomere is limiting and telomerase is stringently repressed in these cells. On the other hand, telomerase is activated in cancer cells. Our research is to reveal how telomerase is repressed during development and activated in cancer cells. Specifically, we have identified several candidate genes involved in telomerase regulation and plan to understand how telomerase is regulated by these genes. We have also generated a transgenic model of the human telomerase gene expression. The Department of Health approved a request in August 2010 to add aims 2 and 3 to this project. In the additional studies, we plan to characterize in detail the expression of the luciferase expression in somatic mouse cells to further validate this transgenic model for the human telomerase regulation. These studies will lead to a better understanding of cancer and age-related diseases, and ultimately better therapeutic strategies for these diseases.
- Title: Biomechanical Failure and Loosening Characteristics of a Novel Posteriorly Augmented Glenoid Component
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The objective of this study is to characterize the mechanics of novel and standard cemented Total Shoulder Arthroplasty glenoid implants subject to cyclic mechanical loading. We have developed a novel glenoid implant that includes a posterior augmentation to compensate for posterior bone loss often found in shoulder osteoarthritis. We seek to understand the loosening resistance and micro-mechanics of the bone-cement-implant interface in both this implant and standard glenoid implants. Micro-computed tomography will be used to image the implant fixation after various stages of controlled cyclic loading applied to simulate physiologic shoulder activity.

- Title: Delivery and Mechanism of Action of Novel Therapeutic Agents to Combat ALS
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Amyotrophic Lateral Sclerosis (ALS) is a progressive degenerative disease causing loss of spinal cord motor neurons and is almost always fatal within 3 -5 years of diagnosis. In this project we will use mutant SOD1 transgenic mice to test the actions of a well-established neuroprotective factor Pigment Epithelium Derived Factor (PEDF) that has a number of unique features about its structure and mode of action that strongly suggest it will succeed in treating ALS where studies of different growth factors or neurotrophic factors have failed. The outcome of this project will be new knowledge on ways of delivering drugs to combat ALS as well as an understanding of the molecular mechanisms by which PEDF can exert its protective action on spinal motor neurons.
- Title: Developing an Animal Model of Cognitive Bias to Study the Impact of Emotion on Health and Behavior
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Emotional states play a fundamental role in influencing health outcomes; individuals with a bias toward negative emotions, such as anger and depression, are more prone to health related problems. Furthermore, it has recently been shown that positive emotions help to protect against certain kinds of disease. Animal models provide a powerful tool to experimentally determine the processes involved in disease pathways. Such models are used to investigate the health consequences of states such as depression or anxiety, but current models of animal emotion are poor and incomplete because they take no account of the cognitive aspect of emotion - appraisal processes that bias an individual toward a more negative or positive outlook. This project aims to develop an improved animal model of emotion.
- Title: Structural Studies of Tight Junction Structure Function and Regulation
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Tight junctions (TJ) are supramolecular structures that form the cell-cell barriers required for tissue formation and in regulating the flow of solutes through paracellular spaces. Occludin (Occ) is a tetraspanning integral membrane protein in epithelial and endothelial tight junctions. This protein and its interacting extra- and intracellular partners are believed to be critical for regulating TJ properties. Specifically, Occ is proposed to act in signal transduction to adapt TJ properties to cellular and tissue need. Understanding the structure and function of Occ is critical for understanding its role in TJ biology. The results obtained from this project will lay the foundation for pursuing external grants, including one from the NIH membrane protein structure initiatives, where proposals that show purified, well behaved membrane proteins are generally well received.
- Title: Epigenetic Basis of Metabolic Memory in Diabetic Retinopathy
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Recent longitudinal studies demonstrate that despite achieving good control of blood glucose for ten years patients formerly under non-intensive insulin therapy continue to have a higher rate of developing diabetic retinopathy and other complications. With this background, we hypothesize that poor glucose control causes epigenomic changes that are not fully reversed with intensive insulin therapy. Demonstration of epigenetic changes in the retina, in response to diabetes, not reversible by insulin, would be an example of an innovative, high pay-off, paradigm-

shifting outcome. Such information would open new avenues for understanding diabetic complications and developing treatments that, used in conjunction with homeostatic insulin replacement, would be capable of restoring the pre-diabetes epigenetic state and reducing the risk of complication development.

- Title: Transplantation of Human Retinal Pigment Epithelial Cells (RPECs) in the Nucleus Accumbens of Rats
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
- Purpose: The purpose of this research project is to determine, preclinically, whether rats with a history of cocaine self-administration can be rescued from the grips of this disease with focal bilateral transplant of 20 or 30 K/side of L-dopa producing fetal human (fh) Retinal Pigment Epithelial Cells (RPECs) into the nucleus accumbens. The potential effectiveness of the transplant in preventing relapse will be examined following 14, 30, and 60 days of abstinence. Given that transplant of these cells already is in Phase II Clinical Trials as a potential treatment for Parkinson's Disease, the long-term objective is to determine whether such a transplant into the reward, rather than the motor, pathway is a viable option for the treatment of addiction in humans.
- Title: Interrogating the Role of Myoepithelial Cells in Mammary Carcinogenesis
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Breast cancers arise from mammary epithelial cells (MECs). Two distinct MEC compartments have been defined which occupy concentric layers in normal mammary ducts. An inner luminal MEC layer harbors milk-producing cells whereas an outer myoepithelial cell layer forms a contractile sheath that aids milk expulsion. The role of myoepithelial cells in breast carcinogenesis remains poorly defined. Some findings suggest that myoepithelial cells can themselves be transformed into cancer cells. Other findings suggest that normal myoepithelial cells protect against cancer by providing a barrier against luminal MEC invasion. By using novel transgenic mouse models, we will test whether myoepithelial cells promote or inhibit carcinogenesis. These studies will define whether prevention strategies ought to maximize or minimize myoepithelial cell number.
- Title: Outcomes for Recurrent Thyroid Cancer in the Elderly
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to identify factors associated with variation in treatment for thyroid cancers in the Medicare population, to estimate the impact of different treatments on cost of medical care for patients with recurrent thyroid carcinomas, controlling for tumor features, demographic characteristics, and co-morbid conditions, and to assess the impact of different treatments on overall and disease-free survival for patients with recurrent carcinomas. Results will inform and guide physicians as they consider treatment recommendations for individual patients and policy makers as they develop and refine treatment guidelines for Medicare patients. In addition, while these aims deal with recurrent thyroid cancer, the broader issues of treatment specific costs and effectiveness are also relevant for other cancers.
- Title: Body Weight- and Nutrition-Sensitive Regulation of Skeletal Muscle Composition in Health and Obesity
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The purpose of this project is to extend preliminary findings showing that experimental manipulation of body weight results in precise adjustments to skeletal

muscle Troponin T (Tnt) expression, and that this response is impaired in a genetic model of obesity. This response is mediated by alternative splicing and is sufficiently accurate that a unit of externally attached load has the same effect on the Tnt mRNA splice form profile as does a unit of actual body weight. The project will more firmly establish body weight- and nutrition-dependent causes of variation in mammalian skeletal muscle Tnt expression, and the generality of a mismatch between body weight, Tnt splicing, and skeletal muscle performance and energy expenditure during obesity.

- Title: Role of Olfactory Cues in Addictive Behavior
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: In this pilot study we will be studying altered brain activity related to the reward value of eating/smoking in smokers, binge-eaters, smokers who binge-eat, and healthy controls. This project will test the following hypotheses concerning the human brain's response to food/smoking cues. We predict that responses will be 1) lowest for pictures, larger for odorants, and maximal for combined congruent pictures with odorants; 2) larger for smokers for smoking cues and larger for binge-eaters for food cues. These responses may have implications for treatments designed to change smoking or eating patterns.
- Title: MRI Marker(s) for Neuropsychological Outcomes in Adolescents with Mild Concussion
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this study is to identify MRI markers that correlate with neuropsychological outcomes in adolescents who have suffered a mild concussion. Recent imaging results in adults with concussions have demonstrated alterations in imaging parameters that are associated with outcome measures. The current project will extend these results to adolescents with mild concussions to test the central hypothesis that axonal injuries, microbleeding, and/or functional interruption occurring during concussion may be responsible for the observed neuropsychological dysfunction and predictive of recovery patterns in adolescents.
- Title: Epigenetic Changes in Gene Expression Associated with an Anxious Depressive like Phenotype
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this study to discover gene expression changes that could serve as diagnostic biomarkers of anxious depressive disorders. Such biomarkers hold the promise of 1) improving the speed and accuracy of diagnosis, thereby reducing the time consuming and often futile guesswork involved in finding an efficacious therapy for anxious depressive disorders, and 2) finding novel therapies for currently drug resistant forms of the syndrome.
- Title: Tumor Associated Receptor Targeted Neuroimaging for Effective Diagnosis of HGA
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Our major intention in this project is to develop tumor targeted gadolinium loaded nanovesicles which will allow us to visualize tumor initiation and growth non-invasively in a much more efficient manner compared to free gadolinium. We will also study the ability of the gadolinium loaded IL-13 receptor targeted nanoliposomes to differentiate the radiation induced necrosis and tumor recurrence which is one of the common phenomenon observed among patients undergoing radiation therapy for brain tumors. Diagnosis of radionecrosis is a challenging issue

because of the resemblance of radiological pattern with tumor recurrence. In our second aim we will focus more on differentiating the normal and tumor tissues using an IL-13 conjugated nanoconjugate known as quantum dots.

- Title: Viral RNA Trafficking in Living Cells
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Mouse mammary tumor virus (MMTV) is a retrovirus that causes adenocarcinoma in mice, and MMTV-like elements have been detected in human breast cancers. This project focuses on how MMTV commandeers cellular machinery to facilitate capsid assembly with the ultimate goal of identifying targets for the treatment of retrovirus-induced cancers.
- Title: Social Networking for Activity Promotion with Cell Phones (SNAP-C)
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Programs designed to help sedentary adults increase their physical activity are often effective in the short-term, but these effects are rarely maintained. Technology-based physical activity programs, such as those using cell phones, may help expand social networks that could support maintenance of physical activity. This project aims to explore the efficacy of using cell phones to engineer social networks that could provide long-term support for active lifestyles. We plan to conduct a randomized controlled trial that compares an intervention group (Social Networking for Activity Promotion with Cell Phones: SNAP-C) to a minimal treatment control group (Usual Care).
- Title: Cerebral Malaria as a Cause of Epilepsy
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Malaria is a widespread problem in much of the world. In malaria endemic regions, there is a high rate of childhood epilepsy, approaching a 2-10 fold higher incidence (5-10% prevalence) over developed countries with temperate climates. Clinical studies have clearly linked malarial infection with future chronic seizure disorders in children. There is no animal model for post-malarial epilepsy. The purpose of this project is to develop a mouse model of post-malarial epilepsy that will permit us to explore the feasibility of using modulation of the immune response, in addition to antimalarial medication, to reduce post-malarial epilepsy.
- Title: Mechanisms of Excess Dietary Salt on Sympathetic-Cardiovascular Function
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Both preliminary and recently published data in our laboratory demonstrate the ingestion of excess dietary salt enhances sympathetic-cardiovascular reflexes and increases blood pressure variability in laboratory animals – blood pressure variability is a major risk factor for end-organ damage and cardiovascular disease including hypertension. The purpose of this project is to determine whether excess dietary salt intake alters sympathetic-cardiovascular regulation in humans.
- Title: Chemokines and Immune Cells in Diabetic Nephropathy
  Type of Research: Biomedical
  Focus: Renal and Urological Sciences
  Purpose: Inflammation and endothelial cell dysfunction are central pathophysiologic mechanisms that contribute to diabetes and diabetic nephropathy (DN). CCR2 chemokine receptors are required for monocyte emigration from the bone-marrow and play pivotal roles in the pathogenesis of inflammatory disorders, endothelial dysfunction and fibrosis. We hypothesize that inhibition of CCR2 receptors expressed

on kidney derived cells, such as endothelial cells or podocytes will ameliorate renal injury associated with DN. An understanding of the interaction between diabetes, CCR2 signaling, inflammation, and specific cell types in the kidney may help to better elucidate the pathologic mechanisms involved in diabetic renal disease and lead to the development of new therapeutic strategies to manage the disease process.

- Title: Spectroscopic Studies of Cardiac Myosin Structure Function
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of these studies is to investigate how mutations in the cardiac myosin heavy chain associated with inherited cardiomyopathies alter cardiomyocyte contraction and the development of specific disease phenotypes. Our approach will be to express and purify a motor fragment of human beta cardiac myosin in the muscle derived C2C12 cells that can be fluorescently labeled at strategic sites. We will examine key structural changes in the enzymatic cycle of cardiac myosin using fluorescence spectroscopy, kinetic analysis, and fluorescence resonance energy transfer. Our analysis of the impact of mutations on structural transitions and contractile function will provide insight into disease pathogenesis and potential therapies.
- Title: Oncogenic Mutations/Rearrangements in Patients with Advanced Adenocarcinoma Lung
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Most patients present after non-small-cell lung carcinoma (NSCLC) has spread to regional or distant sites. Patients presenting with advanced, unresectable disease (stage IIIB or IV) and patients who develop recurrent or metastatic disease following surgical resection are candidates for systemic therapy. There is an urgent need to develop novel and effective regimens as the current therapies do not offer a curative potential. Testing for mutations/gene rearrangements as predictive biomarkers of efficacy to both chemotherapy and targeted approaches with integration of molecular diagnostics in tumor samples and circulating tumor cells will be key to personalized treatments. The current project is designed to pave the way for individualizing therapy for patients with lung cancer.
- Title: Development of a Nanotechnology Platform for Delivery of siRNA to Cancer Cells
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to develop a nanotechnology platform that will deliver an effective dose of siRNA to a cancer cell thereby increasing the vulnerability of the cancer cells to therapeutic intervention. We have selected glioblastoma multiforme (GBM) as our initial target for this research. We will build on our established and successful liposomal formulation that selectively targets GBMs and delivers effective doses of chemotherapeutic agents to the cancer cells. Specifically, we have developed an innovative approach taking advantage of the selective expression of interleukin 13 receptors on glioma cells to selectively target drug and contrast enhancing agents in liposomes to cancer cells. We will modify these liposomes to carry siRNA for ferritin, an intracellular iron storage and cytoprotective protein to the cancer cells. We have shown that decreasing expression of ferritin through siRNA therapy will increase the vulnerability of the cancer cells to chemotoxins and radiation thus allowing more efficient killing of cancer cells while limiting side effects to normal tissue. We have developed liposomes to carry the siRNA for ferritin and the efficacy data have been published.

This project will focus on optimizing the technology for targeted delivery of the siRNA carrying liposomes to tumors and showing efficacy in an orthotopic tumor model.

- Title: Molecular Analysis of Breast Cancer CTC Heterogeneity and Drug Sensitivity in Preclinical Models and Patients
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Circulating tumor cells (CTCs) in patients with metastatic breast cancer are shed into the blood circulation and provide valuable information about a patient's prognosis as well as their response to therapy. We believe that a molecular analysis (gene mutations and proteins) of CTCs and a study of our ability to kill living recovered tumor cells from a patient's blood sample (drug sensitivity) will provide important information to the treating physician to guide therapy decisions. Because cancer cells even within a given patient are heterogeneous and may require combination therapy to target all the different kinds of malignant cells, we believe that a 'liquid biopsy' of the circulating cells in patients with advanced aggressive breast cancer will allow us to personalize therapy by testing treatments on the patient's own tumor cells before treatments are given to patients.
- Title: UGT Genetic Variants and Colorectal Cancer Risk
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We aim to identify genetic variants in the UDP-glucuronosyltransferase (UGT) genes associated with carcinogen metabolism and risk. The findings will result in a significant advance in our understanding of colorectal cancer (CRC) and help to identify high-risk individuals for the development of colorectal cancer screening and prevention strategies.
- Title: Determining the Neurochemical Profile of Addiction in Near Real Time
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: As we see it, drug addiction is a two-part problem involving drug-induced devaluation of essential natural rewards and cue-induced craving and relapse. Our paradigm models both of these key features, allowing for us to begin to discern the underlying neurocircuitry. *Specific Aim 1* of the project will test whether a non-gustatory cue can elicit the onset of the conditioned aversive state known to contribute to drug-seeking and 'relapse'. *Specific Aim 2* seeks to block the onset of this conditioned aversive state with the infusion of a known anxiolytic 5-HT1A agonist, 8-OH-DPAT, into the pariacqueductal gray. Finally, *Specific Aim 3* will adopt a new technique to allow for a minute by minute simultaneous assessment of all major neurotransmitters in the nucleus accumbens during the onset of the conditioned aversive state and subsequent drug-seeking and taking. This new methodology offers a very powerful, cutting edge technique that will revolutionize our understanding of the neurochemical basis of cue-induced craving, withdrawal, and relapse.
- Title: Mechanisms for km23-1 Control of Ras/TGFß Signaling in Human Colon Cancer and Noncancer Cells
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: km23-1 was only recently identified as a novel Ras adaptor and critical target for regulating Ras and transforming growth factor-beta (TGFß) signaling. Further, km23-1 knock-down (KD) can reduce TGFß-mediated mitogen-activated protein kinase (MAPK) signaling events and TGFß production in noncancer/untransformed epithelial cells (UECs), as well as in human colon

carcinoma cells (HCCCs). This project will address the precise nature of the intracellular (IC) regulation of TGFß receptor (TßR)/km23-1/Ras signaling complexes, as well as how these pathways (PWs) are altered in human colon carcinoma cells (HCCCs). This research will also provide a better understanding of how inhibition of km23-1 can diminish major Ras/Raf-regulated events, particularly in HCCCs harboring mutations in KRas or BRaf.

- Title: Risk Profiling in Lupus
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: These studies will develop an approach to profiling risk for development of systemic lupus erythematosus (SLE) and evaluate whether hydroxychloroquine (HCQ) might have properties that could decrease this risk. Our preliminary data indicate that measures of autoantibodies and genes that are expressed in peripheral blood cells of patients with incomplete lupus (ILE) syndromes can detect changes that look like those seen in SLE. We hypothesize that when these markers are expressed in ILE, risk for disease progression is increased. The markers that are identified will be used to develop a risk profiler for prediction of lupus onset and to assess the impact of treatment with HCQ on the risk profile components. The long term goal is to develop strategies that can be used to identify patients in early preclinical stages and then to design appropriate preventive treatments.
- Title: Basal Ganglia Neurophysiology During Drug Induced Dyskinesia
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Parkinson's disease (PD) is characterized by a disabling complication called drug induced dyskinesia (DID). Our previous studies suggest that dopaminergic grafts into the brain can possibly normalize the abnormal electrophysiology and thus prevent DID. This project will examine the feasibility of using a rodent model of PD to understand the pathophysiology and electrophysiology of DID using variety of techniques including tetrode recordings that have never been attempted previously. These studies, to be performed in collaboration with tetrode recording experts, will potentially open new avenues of research in PD.
- Title: Targeting Survival Pathways in Treatment of Large Granular Lymphocyte (LGL) Leukemia
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: The purpose of this project is to assess the potential therapeutic efficacy and the mechanisms of targeted drug therapy with HuMax-IL15, a human IgG1 anti–IL-15 monoclonal antibody, PDGF-RTK inhibitor (Nilotinib/Imatinib), NF-κB inhibitor (MLN9708/Bortezomib) and ERK/Survivin pathway inhibitors (LCL161 and MY155) in treatment of LGL leukemia of both T and NK subtypes.
- Title: Research Infrastructure: Penn State Center for Computational and Integrative Biomedical Research
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: We propose to renovate facilities to house the Center for Excellence in Computational and Integrative Biomedical Research at Penn State. The renovated facility will create critical infrastructure and the support of key shared resources that are needed to catalyze the discovery of new knowledge and the development of novel methods to detect, prevent and treat disease. This will be accomplished by the development of current open and unfinished space on the 3rd floor of MSC into high quality collaborative workspaces that will house computational scientists and scholars engaged in interdisciplinary research in biomedical, life, materials, bioengineering

and information sciences. The newly developed space will be able to house more than 20 research scientists, including bioinformaticians, cyberscientists, postdoctoral fellows and graduate students. In addition, we propose to enhance infrastructure in the West wing of MSC to enable the safe and secure conduct of biomedically relevant research, especially in the areas of infectious diseases, genomics and bioinformatics, neurosciences, imaging, and biomedical (neural) engineering through the installation of keycard entries and upgrading of critical research infrastructure that will support the activities of an additional 20 faculty led laboratories involving over 100 research scientists within the MSC.

- Title: Characterizing a New Mouse Model to Study Diabetes and Stroke
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The immediate objective of this project is to obtain sufficient preliminary data on our new RCS10 mouse model of type II diabetes to justify our proposed R01 study into the role anti-diabetic agents have on stroke outcome. Diabetics are at a 3-fold higher risk of experiencing a stroke and have a greater incidence of mortality and morbidity following an ischemic stroke and currently there are no known therapies that are specifically targeted at diabetics to improve stroke recovery. This project will investigate: 1) the role a compromised inflammatory response plays in the stroke recovery in the diabetic RCS10 and how this might be modulated by anti-diabetic agents and 2) the behavioral consequences associated with stroke recovery in the diabetic RCS10 mice and the efficacy of the anti-diabetic agents in ameliorating behavioral outcomes.
- Title: Defining the Neonatal Septisome and Postinfectious Hydrocephalus
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Neonatal sepsis kills over 1 million newborn infants each year, with cases highly concentrated between sub-Saharan Africa and southern Asia, and in survivors accounts for most of the world's infant hydrocephalus. We have assembled a unique collection of samples for microbial genomic analysis from 80 mother-infant pairs with neonatal sepsis from Uganda, and a set of samples from matched cohorts of 25 patients with postinfectious and 25 with non-postinfectious hydrocephalus. This project will complete the metagenomic analysis on these infant samples in order to further delineate the microorganisms responsible for neonatal sepsis and its sequelae in this setting.
- Title: The Gastrointestinal Microbiome in Parasitic Infections - Towards Testing the "Hygiene Hypothesis"
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Diseases have been proposed to disrupt the composition and function of the commensal microbiota and to alter the homeostatic interactions between the microbial community and the host. How this happens and how the microbiota influences disease dynamics and severity is still unclear and largely based on correlation studies. This project seeks to identify how changes in the intensity of parasitic infections impact microbiome assembly and composition in the gastrointestinal tract. This study aims to provide fundamental knowledge for understanding disease development and pathogenicity and for developing targeted approaches to the prevention and treatment of the adverse health consequences of these common parasitic infections.
- Title: Targeting the Oncogenic Mutant p53 Signaling in Colorectal Cancer Therapy
  Type of Research: Biomedical
  Focus: Oncological Sciences

Purpose: Tumor suppressor p53 is a transcription factor that is frequently mutated or inactivated in colorectal cancer (CRC). Small molecules that can activate the p53 family member p73 in mutant (mt) p53 expressing tumors can elicit a p53-like tumor suppressive function. Utilizing a luciferase reporter based functional screen we have identified Prodigiosin and CB-7587351 (Chembridge library # 7587351) as potent p53-family transcriptional activators. Our goal is to evaluate these compounds as lead candidates to target mt p53 in therapy of CRC. We will test the efficacy and safety of p53 restoration in preclinical models of colorectal cancer harboring mt p53. Currently there are no FDA-approved drugs targeting activation of p73 for CRC therapy. Our project addresses this unmet need for safe and effective small molecules in this class.

- Title: Therapeutic Targeting of Malarial Placental Cytoadherence
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Infection by malaria parasites, particularly Plasmodium falciparum infection, during pregnancy leads to several pathological conditions, including low birth weight, spontaneous abortion, stillbirth, and a significant number of infant deaths and maternal morbidity and mortality. These conditions are collectively called placental malaria (PM) or pregnancy-associated malaria (PAM) and are caused by the sequestration of P. falciparum in the placenta via binding of parasite-infected red blood cells (IRBCs) to the placental chondroitin sulfate proteoglycan (CSPG) receptor. This results in the massive accumulation of IRBCs in the placenta, leading to infiltration of mononuclear cells, inflammation and placental dysfunction. Understanding the molecular details of parasite placental sequestration is expected to provide strategies for the development of a vaccine and/or small molecule inhibitor-based therapeutics for PM.
- Title: Genetic Determinants in Familial Diverticulitis
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to identify specific, measureable genetic determinants that can: 1) eventually be used as a clinical decision making tool for the identification of diverticulitis patients who will require surgery for their disease; and 2) be used as a basis for studying the pathophysiology of diverticulitis.
- Title: Posttranscriptional Mechanisms Regulating Epstein-Barr Virus Latent Infection
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The purpose of this project is to provide insight into the basic mechanisms of action of two families of Epstein-Barr virus (EBV) long non-coding RNAs (lncRNAs) that are expressed during EBV infections associated with several human cancers. Cellular lncRNAs are known to function in many ways and likely affect virtually all cell processes, e.g., differentiation and development, gene expression and immune responses. Viruses have no doubt conscripted lncRNAs for their own purposes, however very few viral lncRNAs have thus far been identified, and their functions in virus infections are unclear. Elucidation of the mechanisms of action of the two EBV lncRNAs we have identified should provide greater insight into the contribution of EBV to several human cancers, information that could ultimately be harnessed to inhibit EBV-dependent tumor development and growth.
- Title: Role of mTOR in Repair of UVB-Induced DNA Damage
  Type of Research: Biomedical
  Focus: Oncological Sciences

Purpose: The goal of this project is to investigate the role of the two mTOR complexes, mTORC1 and mTORC2, in the repair of DNA damage, specifically global-genome nucleotide excision repair (GG-NER), in keratinocytes exposed to UVB. UVB wavelengths account for the majority of the biologically damaging effects from sun exposure. UVB is a complete carcinogen, acting as a tumor initiator by inducing mutations in critical target genes, and a tumor promoter by inducing cell cycle progression and proliferation. Better understanding of the pathways activated by UVB in keratinocytes is essential for the effective prevention and treatment of skin cancer. If keratinocyte GG-NER is enhanced when mTOR activity is limited, this would provide a strong rationale for using mTOR inhibitors in skin cancer prevention.

- Title: Research Infrastructure - Central Research Sample Storage Facility
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: The purpose is to create a centralized facility to store biological specimens from both the new Institute for Personalized Medicine as well as the larger institutional research community. Biological specimens are important in clinical research because they make it possible to correlate laboratory science with clinical response. While researchers may store aliquots of specimens in their own labs, storing aliquots of non-commercial and unique cell-lines in these freezers will allow for samples to be protected by the safeguards built-in to protect them from possible power-outages, leaks, etc. This is also true for tissue samples that the labs would store in this facility. The cell-lines and tissue samples can be used for comprehensive projects ranging from genetic therapies to drug affinity protocols.
- Title: Small Peptide Eye Drops for Diabetic Retinopathy
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Although diabetic retinopathy (DR) is a leading cause of blindness with a projected incidence of ~350 million worldwide by 2020, there are no effective treatments for this condition. DR includes a spectrum of pathologies including cell death, inflammation, and vascular leakage. We have developed a 29-mer bioactive peptide (serpxA1), the first targeted DR drug that reduced both early and advanced DR pathologies in rodents when administered as an eye drop. Our goal in this proof-of-concept study is to improve this technology by designing a series of structurally novel and potentially patentable analogs that show equal or better activity as well as improved bioavailability, and metabolic stability in rodents. We will then confirm bioavailability of lead compounds in primates.
- Title: Research Infrastructure: Animal Biosafety Level-2 Facility
  Type of Research: Research Infrastructure
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: This project will renovate existing space to provide additional animal biosafety level-2 (ABSL-2) housing in the Central Animal Quarters (CAQ) of the Penn State College of Medicine. Modifications of the exit and entrance of the facility will also be part of this project and will greatly enhance the security and biocontainment of the facility. The overall goal of the renovations and equipment purchases is to provide housing for "humanized" mouse models, i.e., immunodeficient mice ingrafted with various human cells. These immunocompromised animals require special housing condition, including autoclaved cage setups and sterilized, autoclaved drinking water to minimize infection with adventitious pathogens.

Philadelphia College of Osteopathic Medicine ($25,305)

- Title: Psychological Functioning, Coping, and Factors Affecting Quality of Life in Persons with Long QT Syndrome

Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: This project is designed to identify and address the psychosocial needs of persons with Long QT Syndrome (LQTS) and distressed subsets of this population. Presently, little is known about the experience of anxiety, depression, quality of life or methods of coping in this population, despite the large numbers of people living with this life-threatening condition, significant lifelong medical treatments and restrictions on activity and diet, and the experience of cardiac arrest and revival in many of these persons. Information gained may inform medical and allied health professionals about the psychosocial aspects of living with LQTS. New knowledge expected will be used to develop clinical resources, interventions, and services for delivery on the internet, and in medical inpatient and outpatient settings.

Philadelphia Health Management Corporation ($21,969)

- Title: The Impact of Masculinity Ideals on HIV Risk among Black and White Bisexually-Active Men
  Type of Research: Health Services
  Focus: AIDS and Related Research
  Purpose: The overall purpose of this project is to increase the current understanding of how contextual factors such as ideals of masculinity may contribute to HIV risk among Black and White men who have sex with men and women (MSMW). This project will utilize existing data gathered from 346 Black and White MSMW in Philadelphia to examine the relationship between masculinity ideals and sexual behaviors that may increase risk for HIV infection or transmission among MSMW and their partners. This project will examine the differential impact of masculinity ideals for Black and White men and examine how other factors such as internalized homophobia and history of marriage may moderate the impact of masculinity ideals on HIV risk. These findings will help guide HIV prevention messages for these populations.

Pittsburgh Tissue Engineering Initiative ($12,224)

- Title: Novel Biofuel Cell Based on High Surface Area Enzymatic Microelectrodes
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this project is to continue our development of a miniaturized biofuel cell, a device that can turn available substances like sugars and oxygen to energy, by using an assembly of biocatalysts and a special gold fiber electrode. The device will be designed to utilize fructose as the fuel, and turn the sugar into energy by a series of enzymatic reactions, using commercial enzymes as the catalytic elements. The process will be carried out on the surface of a new type of gold microfiber electrode, which will be developed. In this project continuation we would like to expand the fuel sources and study a biofuel cell based on fructose conversion into electrical energy by fructose dehydrogenase.

Salus University ($59,678)

- Title: Mechanisms of Signal Transduction and Degenerative Diseases in the Retina
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The general long-term purpose of this high-risk pilot project is to obtain new knowledge for the subsequent in-depth study of the intricate mechanisms triggering photoreceptor death. Human congenital retinal diseases causing blindness often arise from deregulated signal transduction mechanisms in rods and cones. Our

main purpose is to evaluate how intracellular signal transduction messengers, cAMP and cGMP, contribute to retinal degeneration in a mammalian retina. The specific aim in the planned pilot study is to develop a new, presently unavailable, transgenic mouse model that would produce cAMP through a controlled light-sensitive mechanism in vivo. The outcome from this proof-of-concept project can then be used for leveraging funds to further expand the study on a larger scale.

Temple University ($2,375,033)

- Title: The Anabolic Role of Cannabinoid Receptors in Bone
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: The goal of the planned project is to define the anabolic role of cannabinoid receptors in bone. Recent studies have demonstrated the presence of endocannabinoids and their G protein-coupled cannabinoid receptors, CB1 and CB2, in the skeleton. Although it has become clear that this system is functional in bone, the precise mechanisms of action are only beginning to emerge. The planned studies will generate new information regarding the anabolic effects of cannabinoid receptors and mechanisms of action on osteoblast differentiation and function. Once we understand how cannabinoid receptors function to promote bone formation, this information will be helpful in developing new therapeutic strategies to selectively enhance bone formation in patients with clinically significant bone loss.
- Title: Effects of IL-19 on Endothelial Cell Activation and Angiogenesis
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Cardiovascular disease is the number one killer of Americans. Vascular diseases such as atherosclerosis, and hypertension are inflammatory in nature. Very little has been reported on the potential protective effects of anti-inflammatory cytokines on development of vascular disease. We have novel preliminary data which shows that the naturally occurring anti-inflammatory compound, Interleukin-19 (IL-19) can have stimulatory effects on endothelial cells grown in culture. The purpose of this project is to determine if IL-19 can have pro-angiogenic effect in vivo.
- Title: A Targeted Drug Delivery System for Preventing Cardiac Remodeling after MI
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Cardiac remodeling after myocardial infarction increases the stress on the surviving myocardium and predisposes viable myocardial cells to premature death leading to heart failure. Presence of an appropriate microvasculature is a prerequisite for preventing cardiac remodeling and improving cell survival resulting in maximal regeneration of a functional tissue after myocardial infarction. The goal of this project is to use targeted delivery of pro-angiogenic agents to enhance the morphology and function of post-infarct neovasculature, prior to scar formation, and to establish the optimal time post-myocardial infarction when pro-angiogenic interventional strategies could prevent cardiac remodeling and congestive heart failure.
- Title: Mechanism(s) of Vascular Damage in Obesity
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Cardiovascular disease accounts for much of the morbidity and mortality ultimately suffered by patients with diabetes mellitus. Adiponectin is a protein from fat cells that circulates in the bloodstream and has been shown to protect the blood vessels in diabetes. Interestingly, adiponectin opposes the adverse effects on blood

vessels of several factors including glucose that is known to be elevated in Type 1 and/or Type 2 diabetes. In this project, we seek to identify the cellular mechanisms by which adiponectin exerts its salutary effects in the endothelial cells that line the blood vessels. These results will advance our understanding of the role of adiponectin in vascular protection in diabetes and in obesity with insulin resistance, conditions with a high risk of life-threatening cardiovascular complications.

- Title: Targeted Multidrug Delivery System to Overcome Chemoresistance in Breast Cancer
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: In this project, the Principal Investigators propose to develop a novel multidrug delivery system for the treatment of breast cancer. This novel treatment strategy would provide a significantly more efficacious platform for breast cancer treatment than current treatments.
- Title: Nanoconjugates for Targeted Treatment of Acute Lung Injury
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The development of the acute respiratory distress syndrome (ARDS) following infection or injury is a major public health problem and one of the leading causes of death in Intensive Care Units (ICU). ARDS is characterized by excessive neutrophil infiltration of the lungs and neutrophil-mediated lung tissue damage. To date, there are no specific pharmacologic therapies available that protect the lung from neutrophil-mediated damage. We identified the enzyme delta-Protein Kinase C (δ-PKC) as a critical regulator of the inflammatory response. The goal of this project is to develop a specific δ-PKC peptide inhibitor into a viable therapeutic by the use of nanocarriers to transport the inhibitor directly to the lung. If successful, this approach could significantly decrease the morbidity and mortality associated with sepsis, burns, hemorrhagic shock and trauma.
- Title: Role of Dorsostriatal Glutamatergic Signaling in the Regulation of Cocaine-induced Synaptic and Behavioral Plasticity
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Chronic drug use leading to drug addiction is associated with impairments in reinforcement seeking behaviors. The pathological mechanisms associated with these maladaptive behaviors are not known. The primary goal of this project is to understand the role of dorsostriatal glutamatergic signaling in the regulation of drug (cocaine)-induced synaptic plasticity and behavioral sensitization. To accomplish this goal, we will utilize multidisciplinary approaches in neurosciences to gain an integrative perspective on the neurobiological basis of compulsive cocaine-seeking behaviors. Results from this project will provide important preclinical data on potential targets for treatment of cocaine addiction.
- Title: Genetic Variations in Inflammation-Related Genes in Patients with Chronic Pelvic Pain Syndrome
  Type of Research: Biomedical
  Focus: Renal and Urological Sciences
  Purpose: The etiology and pathogenesis of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) are unknown. The purpose of this study is to test the hypothesis that genetic polymorphisms of candidate genes *COMT, CGH1, IL10, TNF*, or *HMGB1* contribute to the development of CP/CPPS. We will also capture data on past medical history to assess whether specific medical conditions such as cardiovascular disease, hematologic disease and psychiatric conditions are associated with specific polymorphisms, and if these conditions define specific subgroups of

patients with CP/CPPS. We will measure RNA and correlate with specific polymorphisms to confirm the mechanism of action.

- Title: Characterization of the Effects of Hypertension on Adult Brain Neurogenesis
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Our underling hypothesis is that hypertension impairs neurogenesis by decreasing the number of neural stem cells (NCS) in the subventricular zone (SVZ) and the dentate gyrus leading to changes in intrinsic properties and functional characteristics. Changes in intrinsic properties that affect subsequent neural progeny turn-over and diminished growth factor support to the neuronal environment. No studies to date have directly evaluated the effect of hypertension on the neurogenic response. Besides the well known susceptibility of hypertensive individuals to stroke there is also strong correlation between hypertension and mild cognitive impairment. The NSC dysfunction in hypertension being studied here would shed light into explaining the occurrence of both mild cognitive dysfunction and poor stroke recovery when hypertension is present.
- Title: PDMD: A Complex II-Regulated Form of Mitochondrial Dysfunction in Exhausted Cells
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Functional impairment of mitochondria contributes to many human diseases including myocardial infarction, stroke, cancer and aging. However, the underlying mechanisms of mitochondrial dysfunction are not well understood. Our preliminary studies elucidate a mode of mitochondrial depolarization that is independent of cyclophilin D, Bcl-2 family proteins, extra mitochondrial energy, or high amplitude swelling. We termed this mode of mitochondrial dysfunction proton-dependent mitochondrial depolarization (PDMD), which prominently manifests in ischemic cells. The evolutionarily conserved PDMD is dependent on dissipation of the mitochondrial potential and can be reversed by the mitochondrial substrate. This route of reversible mitochondrial impairment provides a potential target for rejuvenation of exhausted cells in acute injury.
- Title: Role of the B55α Protein Phosphatase 2A Holoenzyme in Modulating the Phosphorylation of p107 and Related Proteins
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Members of the retinoblastoma family of growth suppressor proteins are inactivated via phosphorylation by cyclin dependent kinases (CDKs) in mid-G1 through mitosis. Hyperphosphorylation of these proteins inactivates them as repressors of E2F-dependent transcription and prevents interaction with other proteins. Pocket protein phosphorylation is challenged through the cell cycle by protein phosphatase 2A (PP2A), and we have recently identified a trimeric PP2A holoenzyme containing the regulatory B55α subunit that dephosphorylates p107 and p130. The purpose of this work is to characterize this complex in reactivation of pocket proteins in response to anti-mitogenic signals, as tumor cells are often refractory to anti-mitogenic signaling.
- Title: Are There Sex Differences in Kappa Opioid Receptor-Mediated Pharmacology?
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: Activation of the kappa opioid receptor (KOPR), one of the three types of opioid receptors (mu, delta and kappa), produces effects such as analgesia, sedation, dysphoria, water diuresis, antipruritic effects and attenuation of cocaine craving in addicts. Clinical studies have suggested sex differences in KOPR-induced analgesia. We have demonstrated that the selective KOPR agonist U50,488H produces higher levels of antinociception and sedation-like behavior in male than female guinea pigs. The underlying mechanisms are unclear. In the proposed studies, we will examine whether sex differences exist in KOPR distribution and signaling and alteration of neuronal circuitry activities by KOPR activation. We will investigate in vivo sex differences by measuring 1) receptor autoradiography, 2) G-protein coupling using [^{35}S]GTPγS autoradiography and 3) immunohistochemical labeling of *p44/42* MAP kinase activation induced by systemic KOPR agonist, U50,488H using intact male and female guinea pigs across the estrous cycle. The guinea pig will be used as a model since its KOPR levels and distribution in brain resemble those of the human, unlike those of the rat and mouse.

- Title: Enhancing Stem Cell Engraftment and New Myocyte Formation in the Damaged Heart
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The purpose of this study is to develop and test novel approaches to enhance the survival and engraftment of cardiac stem cells in the injured heart. We have characterized a population of resident cardiac stem cells in the normal heart and have shown that these cells have the capacity to differentiate into new cardiac myocytes. In the proposed research we will modify the properties of these stem cells so that they have enhanced survival in the hostile environment of the injured heart. We will also modify the stem cells so that they have an enhanced ability to electrically couple to cardiac myocytes. The purpose of the research is to test the idea that enhancing coupling increases survival and induces differentiation.
- Title: Neural Effects of Acute Traumatic Brain Injury
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this research is to investigate how brain neural activity is altered in response to traumatic brain injury. Whereas other researchers have investigated both short and long term neural behavior in brain injury patients, there has been no systematic study of what changes occur in the moments immediately following the insult or how these changes vary as a function of the severity of the injury. That knowledge is a crucial missing link in understanding the mechanisms of brain injury; a deeper understanding will lead to enhanced strategies for prevention, detection, and treatment.
- Title: NIBP/NFκB Signaling in Neurogenesis
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Neurodevelopmental disorders and cognitive/mood dysfunction are major public health issues. Impairments in embryonic and adult neurogenesis are implicated in such diseases. The molecular mechanisms that control various stages of neurogenesis remain poorly understood. We have identified a novel protein NIBP that is required for NFκB activation and neuronal differentiation as well as trans-Golgi networking. NIBP has been also implicated in human mental retardation and autism. The goal of this project is to understand the underlying cause-effects and mechanisms of NIBP/NFκB signaling in neurodevelopmental disorders. We will test the central hypothesis is that NIBP acts as a novel proneuronal protein to guide neuronal lineage differentiation through NFκB signaling during neurogenesis.

- Title: Relationships of Histochemistry to Muscle Activity in the Child with Cerebral Palsy
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Cerebral palsy (CP) is characterized by altered muscle activity and decreasing function with age. Altered muscle physiology has also been reported in CP; however, the relationship between muscle activity and muscle physiology is not known. If relationships can be identified, it may possible to predict which clinical interventions will be appropriate for the child with CP. The significance of this study is that an understanding of the histochemical mechanisms behind observable changes in muscle activity will be determined and aid in the development of an assessment method that will allow clinicians to determine which child with CP will respond best to a given clinical intervention. This will reduce the number of ineffective treatments that a child with CP may undergo, and reduce the costs of care and risks to the child.
- Title: Stem Cell Mediated Repair of the Ischemic Heart
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The purpose of the research is to determine if cKit+ bone marrow derived stem cells, when injected into the border of the infarct border zone, can enhance endogenous repair.
- Title: Enhancing Effective Healthcare Decision Making with the Use of Brain Imaging Tools
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to enhance decision making in healthcare by identifying and suppressing self-positivity bias. Self-positivity bias is a major problem in healthcare by preventing people from pursuing healthy lifestyles, obtaining proper health care, and adhering to health recommendations. Self-positivity bias is especially serious among older patients, minorities, and the poor. Using functional Magnetic Resonance Imaging (fMRI) tools, we seek to identify the neural correlates of self-positivity bias to understand its neural origins and accordingly design customized decision aids that overcome it for specific diseases. In doing so, we aspire to help people engage in effective healthcare decision-making, pursue a healthier lifestyle, seek preventive medical care, and adhere to medical advice by healthcare providers to prevent diseases.
- Title: Temple PET/SPECT Imaging Tracer Initiative
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Positron emission tomography (PET) and single photon emission computed tomography (SPECT) have become invaluable clinical and preclinical tools for imaging, diagnosis, treatment, basic research, drug discovery and drug development. Several PET and SPECT ligands are known, but novel research requires the development of novel radioligands. Temple University does not have an internal resource for generating novel PET and SPECT imaging radioligands. The proposed initiative will put in place a multidisciplinary center with the expertise and resources needed to design, develop and produce novel PET and SPECT radioligands, and will provide a much needed platform to support collaborators' clinical, biological and drug discovery projects as well as a valuable training resource for scientists.
- Title: Egr-1 Tumor Suppressor of Chronic Myeloid Leukemia
  Type of Research: Biomedical

Focus: Oncological Sciences
Purpose: Chronic myeloid leukemia (CML) is one of the most successfully treated human malignancies, using the tyrosine kinase inhibitor imatinib. In spite of remarkable results continued treatment is necessary to prevent relapse; drug resistance is also a problem. There is a need to identify molecular markers that can predict if an individual will be receptive to therapy, and if during therapy the individual starts to become resistant. There is also a need for therapies using alternative strategies that can be used in combination with imatinib to prevent resistance or even to promote a permanent cure. We have data that early growth response gene (Egr)-1 is a tumor suppressor of CML. Our studies should provide new information about the initiation and progression of CML; this knowledge can be used for prognosis and to design novel therapeutics.

- Title: Identification of IFN Inducible STAT2 Regulated Apoptotic Genes
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Interferons-α/β (IFNs) are small proteins that are secreted by many types of cells. IFNs can cause tumor cell death or prevent tumor cell growth. This observation led to the approval of IFN for the treatment of certain types of cancer. Yet little is known about the mechanism of how tumor cells are eliminated by IFNs. STAT2 is one critical molecule IFNs activate to induce the expression of many genes whose protein products in turn elicit a biological response. Our recent work shows that deletion of STAT2 prevents the killing effects of IFN thus suggesting that STAT2 is important for promoting tumor cell death. The purpose of this project is to identify apoptotic (death inducing) genes induced by IFNs that are dependent on STAT2.
- Title: Integrin-Mediated Adhesion of Osteoblasts to CTGF Induces Intracellular Signaling and Differentiation
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Proposed studies will establish that connective tissue growth factor (CTGF) can function as an ECM-associated (matricellular) protein and demonstrate that some of its bone anabolic activities reside in its interactions with a specific integrin ($\alpha_v\beta_1$) expressed on the cell surface of osteoblasts. These CTGF-integrin interations can initiate intracellular signaling cascades that regulate cell growth and differentiation, thereby providing a mechanistic interpretation for some of the bone anabolic effects of CTGF. Proposed experiments are expected to generate novel information regarding CTGF-specific mechanisms of action in osteoblasts, and these data can ultimately be used to develop new therapeutic strategies to treat bone loss (osteoporosis).
- Title: Novel Targeted Drug Delivery System for Overcoming Chemoresistance
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Chemotherapy is considered standard of care for breast cancer, which often decreases tumor size allowing for subsequent breast surgery followed by radiation and further adjuvant chemotherapy. However, given that most current anticancer agents do not greatly differentiate between cancerous and normal cells, systemic toxicity and adverse effects associated with these chemotherapeutics limit their treatment efficacy. In addition, acquired drug resistance further decreases the treatment efficacy of the chemotherapy. Therefore, there is a critical need to develop more efficacious therapies or delivery methods that decrease systemic toxicity, side effects, and overcome the drug resistance in the patient.

Thomas Jefferson University ($3,746,521)

- Title: Genetic Targets of Breast Tumor-Initiating Cells
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Breast cancer is the second most prevalent cancer-related death in women in the United States. A subpopulation of breast tumor cells have been identified and are referred to as "breast tumor-initiating cells" or cancer stem cells (CSCs). These self-renewing CSCs were first described in the hematopoietic system, and have now been putatively identified in breast, colon and brain tumors. It has been proposed that all tumor metastasis are caused by CSCs, and it is suspected that these cells contribute to therapy resistance and tumor recurrence. The focus of this project is to determine new genetic mechanisms governing breast CSC expansion and invasion, and to identify specific secreted factors regulated by gene deletion, to provide CSC-based therapies.
- Title: Phosphorylated Proteins in Breast Cancer Prognosis
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Our overall objective is to develop techniques and protocols to measure quantitative changes in protein levels in the stromal and epithelial compartments of clinical samples to 1) identify new prognostic markers of response to therapy and outcome and 2) to understand the role of autocrine and paracrine signaling associated with the tumor microenvironment.
- Title: The Role of Lipogenesis Pathway in Endometrial Cancer Progression
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The number of women with newly diagnosed endometrial cancer (EC) increased 20% from 1987; however the number of deaths posted a 168% increase during the same time period. Estimated new cases and deaths from EC in the United States in 2009 are 42,160 and 7,780, respectively. As population size affected by this disease is expected to grow, particularly in developing countries, EC will continue to be a serious public health problem. Despite the fact that over-expression of lipogenic enzymes were observed in endometrial tumors, the role of the master regulator of lipogenesis, sterol regulatory element-binding protein 1 (SREBP1), is largely unknown. This project will determine the role of SREBP1 and DACH1, a newly identified transcriptional repressor, in endometrial tumorigenesis and the mechanisms by which lipogenic pathways regulate tumor progression.
- Title: Tailored Preference Intervention and Colon Cancer Screening in Primary Care
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to determine the impact of a mailed, preference-based intervention on colorectal cancer screening among African Americans.
- Title: MicroRNA Genetic Variations as Predictors of Hepatocellular Carcinoma Risk
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The project goal is to use a pathway-based polygenic approach to identify genetic variations in miRNA genes that can be used to predict the risk of hepatocellular carcinoma (HCC) in patients with chronic Hepatitis B virus (HBV) infection. The efforts will be essential for our ultimate aim to build up an HCC risk assessment model that can be applied in clinical settings.
- Title: Development of a Decision Aid for Hepatitis C Testing in High Risk Populations

Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: More than 3 million Americans are infected with Hepatitis C virus (HCV); many have no symptoms and are unaware of their HCV status. HCV infection is a leading cause of chronic liver disease and the most common reason for liver transplantation. Specific populations that are at increased risk for HCV infection have been defined, and a reliable diagnostic test to determine HCV status exists. However, there is disagreement among experts about the utility of routine testing for high-risk individuals. In situations like this, patients may benefit from additional information to assist them in deciding to be tested. This project lays the groundwork for a larger study that applies a technique called "mediated-decision counseling" to assist patients in making an informed decision about HCV testing.

- Title: CAV3, Myo-Epithelial Barrier Function and Breast Cancer
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Advanced medical technologies and therapeutic strategies are necessary for the successful detection, diagnosis, and treatment of human breast cancer. This project will identify new paracrine signaling mechanism(s) that contribute to breast cancer pathogenesis, using a new mouse model, the Cav-3 knock-out (KO) mice. These mice develop pre-malignant mammary lesions including mammary ductal thickening, increased primary ductal branching, and lobulo-alveolar hyperplasia. In addition, the mice will be crossed into the polyomavirus middle T-antigen transgenic mice (MMTV-PyMT) genetic background to determine the role of Cav-3 in mammary tumor formation and metastasis. This will allow the elucidation of the role of Cav-3 and myo-epithelial barrier function in ductal carcinoma *in situ* (DCIS) and invasive ductal carcinoma (IDC). The Cav-3 knock-out mice will also be valuable for testing new therapies for breast cancers.
- Title: Targeted Multidrug Delivery System to Overcome Chemoresistance in Breast Cancer
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: In this project, the Principal Investigators propose to develop a novel multidrug delivery system for the treatment of breast cancer. This novel treatment strategy would provide a significantly more efficacious platform for breast cancer treatment than current treatments.
- Title: Nanoconjugates for Targeted Treatment of Acute Lung Injury
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The development of the acute respiratory distress syndrome (ARDS) following infection or injury is a major public health problem and one of the leading causes of death in Intensive Care Units (ICU). ARDS is characterized by excessive neutrophil infiltration of the lungs and neutrophil-mediated lung tissue damage. To date, there are no specific pharmacologic therapies available that protect the lung from neutrophil-mediated damage. We identified the enzyme delta-Protein Kinase C (δ-PKC) as a critical regulator of the inflammatory response. The goal of this project is to develop a specific δ-PKC peptide inhibitor into a viable therapeutic by the use of nanocarriers to transport the inhibitor directly to the lung. If successful, this approach could significantly decrease the morbidity and mortality associated with sepsis, burns, hemorrhagic shock and trauma.
- Title: Role of Dorsostriatal Glutamatergic Signaling in the Regulation of Cocaine-induced Synaptic and Behavioral Plasticity

Type of Research: Biomedical
Focus: Neurosciences
Purpose: Chronic drug use leading to drug addiction is associated with impairments in reinforcement seeking behaviors. The pathological mechanisms associated with these maladaptive behaviors are not known. The primary goal of this project is to understand the role of dorsostriatal glutamatergic signaling in the regulation of drug (cocaine)-induced synaptic plasticity and behavioral sensitization. To accomplish this goal, we will utilize multidisciplinary approaches in neurosciences to gain an integrative perspective on the neurobiological basis of compulsive cocaine-seeking behaviors. Results from this project will provide important preclinical data on potential targets for treatment of cocaine addiction.

- Title: Genetic Variations in Inflammation-Related Genes in Patients with Chronic Pelvic Pain Syndrome
  Type of Research: Biomedical
  Focus: Renal and Urological Sciences
  Purpose: The etiology and pathogenesis of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) are unknown. The purpose of this study is to test the hypothesis that genetic polymorphisms of candidate genes *COMT, CGH1, IL10, TNF*, or *HMGB1* contribute to the development of CP/CPPS. We will also capture data on past medical history to assess whether specific medical conditions such as cardiovascular disease, hematologic disease and psychiatric conditions are associated with specific polymorphisms, and if these conditions define specific subgroups of patients with CP/CPPS. We will measure RNA and correlate with specific polymorphisms to confirm the mechanism of action.
- Title: Characterization of the Effects of Hypertension on Adult Brain Neurogenesis
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Our underling hypothesis is that hypertension impairs neurogenesis by decreasing the number of neural stem cells (NCS) in the subventricular zone (SVZ) and the dentate gyrus leading to changes in intrinsic properties and functional characteristics. Changes in intrinsic properties that affect subsequent neural progeny turn-over and diminished growth factor support to the neuronal environment. No studies to date have directly evaluated the effect of hypertension on the neurogenic response. Besides the well known susceptibility of hypertensive individuals to stroke there is also strong correlation between hypertension and mild cognitive impairment. The NSC dysfunction in hypertension being studied here would shed light into explaining the occurrence of both mild cognitive dysfunction and poor stroke recovery when hypertension is present.
- Title: PDMD: A Complex II-Regulated Form of Mitochondrial Dysfunction in Exhausted Cells
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Functional impairment of mitochondria contributes to many human diseases including myocardial infarction, stroke, cancer and aging. However, the underlying mechanisms of mitochondrial dysfunction are not well understood. Our preliminary studies elucidate a mode of mitochondrial depolarization that is independent of cyclophilin D, Bcl-2 family proteins, extra mitochondrial energy, or high amplitude swelling. We termed this mode of mitochondrial dysfunction proton-dependent mitochondrial depolarization (PDMD), which prominently manifests in ischemic cells. The evolutionarily conserved PDMD is dependent on dissipation of the mitochondrial potential and can be reversed by the mitochondrial substrate. This

route of reversible mitochondrial impairment provides a potential target for rejuvenation of exhausted cells in acute injury.

- Title: Role of the B55α Protein Phosphatase 2A Holoenzyme in Modulating the Phosphorylation of p107 and Related Proteins
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Members of the retinoblastoma family of growth suppressor proteins are inactivated via phosphorylation by cyclin dependent kinases (CDKs) in mid-G1 through mitosis. Hyperphosphorylation of these proteins inactivates them as repressors of E2F-dependent transcription and prevents interaction with other proteins. Pocket protein phosphorylation is challenged through the cell cycle by protein phosphatase 2A (PP2A), and we have recently identified a trimeric PP2A holoenzyme containing the regulatory B55α subunit that dephosphorylates p107 and p130. The purpose of this work is to characterize this complex in reactivation of pocket proteins in response to anti-mitogenic signals, as tumor cells are often refractory to anti-mitogenic signaling.
- Title: Are There Sex Differences in Kappa Opioid Receptor-Mediated Pharmacology?
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Activation of the kappa opioid receptor (KOPR), one of the three types of opioid receptors (mu, delta and kappa), produces effects such as analgesia, sedation, dysphoria, water diuresis, antipruritic effects and attenuation of cocaine craving in addicts. Clinical studies have suggested sex differences in KOPR-induced analgesia. We have demonstrated that the selective KOPR agonist U50,488H produces higher levels of antinociception and sedation-like behavior in male than female guinea pigs. The underlying mechanisms are unclear. In the proposed studies, we will examine whether sex differences exist in KOPR distribution and signaling and alteration of neuronal circuitry activities by KOPR activation. We will investigate in vivo sex differences by measuring 1) receptor autoradiography, 2) G-protein coupling using [^{35}S]GTPγS autoradiography and 3) immunohistochemical labeling of *p44/42* MAP kinase activation induced by systemic KOPR agonist, U50,488H using intact male and female guinea pigs across the estrous cycle. The guinea pig will be used as a model since its KOPR levels and distribution in brain resemble those of the human, unlike those of the rat and mouse.
- Title: Enhancing Stem Cell Engraftment and New Myocyte Formation in the Damaged Heart
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The purpose of this study is to develop and test novel approaches to enhance the survival and engraftment of cardiac stem cells in the injured heart. We have characterized a population of resident cardiac stem cells in the normal heart and have shown that these cells have the capacity to differentiate into new cardiac myocytes. In the proposed research we will modify the properties of these stem cells so that they have enhanced survival in the hostile environment of the injured heart. We will also modify the stem cells so that they have an enhanced ability to electrically couple to cardiac myocytes. The purpose of the research is to test the idea that enhancing coupling increases survival and induces differentiation.
- Title: Neural Effects of Acute Traumatic Brain Injury
  Type of Research: Biomedical
  Focus: Neurosciences

Purpose: The purpose of this research is to investigate how brain neural activity is altered in response to traumatic brain injury. Whereas other researchers have investigated both short and long term neural behavior in brain injury patients, there has been no systematic study of what changes occur in the moments immediately following the insult or how these changes vary as a function of the severity of the injury. That knowledge is a crucial missing link in understanding the mechanisms of brain injury; a deeper understanding will lead to enhanced strategies for prevention, detection, and treatment.

Treatment Research Institute ($171,222)

- Title: Assessing DUI Offenders' Needs and Risks to Improve Treatment and Supervision in Pennsylvania
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Current statutes do not take into account the full range of DUI offenders' needs and risks when determining their disposition and placement. Basing initial treatment considerations on blood alcohol concentration alone may result in missed critical opportunities for providing necessary treatment to those with severe drug or alcohol problems. Following in the footsteps of the Drug Court Risk and Needs Triage (RANT), the purpose of the current project is to develop a brief assessment that incorporates a comprehensive set of evidence based markers of alcohol dependence and predictors of DUI recidivism. The assessment will address both public health and public safety considerations by helping to determine the optimal combination of treatment and/or criminal justice supervision for DUI offenders and promote evidence-based dispositions for DUI offenders.

University of Pennsylvania ($9,897,440)

- Title: Renovation for Lab Space for the Fundamental Physics Techniques to Biomedicine
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to upgrade and renovate 4750 square feet of laboratory space to standards appropriate for a 21st century laboratory performing research at the interface between the physical and biological sciences. The renovations include outfitting the laboratory space with sophisticated instrumentation, including a two-photon microscope and a high-powered laser light source. The renovated space will be occupied by investigators from the Department of Physics & Astronomy, whose research has implications for biomedicine, including work at the frontiers of diagnostic imaging using infrared light as well as the use of innovative techniques to make measurements of unprecedented precision aimed at understanding how genes guide basic process of development of an organism.
- Title: Development of Laboratory Space at Penn Medicine
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this research infrastructure project is to renovate space in Stemmler Hall in support of Penn Medicine's Musculoskeletal and Neurosciences research programs. These closely related research programs are critical components of Penn Medicine's research strategic plan and address key needs common to Penn, the NIH road map, and the Commonwealth of Pennsylvania. The project will provide 4,900 SF of renovated laboratory space, creating an interactive environment that enables the recruitment of new faculty, promoting the study of musculoskeletal and

neurosciences issues, and ultimately leading to the translation of health advances for the benefit the citizens of the Commonwealth.

- Title: Generating Tissues from Stem Cells in the Pathways to Therapy
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: New technologies in stem cell biology, genetic manipulations and tissue engineering are enabling us to move closer to the dream of humankind of repairing tissues and organs that have been lost as a result of injury, disease or aging. In this application, we propose studies that will increase our knowledge of stem cells that are involved in heart, lung, cartilage and tendon development and/or maintenance that will be utilized to direct, promote or enhance the repair of these organs and tissues. The challenges in regenerative medicine are enormous and we need to gain more knowledge of the cells involved in these processes so that effective and safe therapies can be developed.
- Title: The Role of CCR5 Blockade on the Prevention of Graft-Vs-Host Disease
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Allogeneic stem cell transplantation (SCT) is the only cure for many patients with hematologic malignancies, but success is limited in large part by graft-vs-host disease (GVHD). There is an immediate need for more effective methods of GVHD prevention. Experimental data suggest a role for the chemokine receptor CCR5 in the pathogenesis of GVHD. Inhibition of lymphocyte trafficking to prevent GVHD explores a new paradigm in the pathophysiology of GVHD. The purpose of this project is to test the hypothesis that blocking lymphocyte trafficking using Maraviroc, an inhibitor of the chemokine receptor CCR5, after allogeneic SCT is feasible, safe and effective in preventing GVHD. Our long term goals are to understand the role of lymphocyte trafficking in the pathogenesis of GVHD.
- Title: Does Neural Activation During Nicotine Abstinence Predict Smoking Relapse?
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this research is to determine whether patterns of brain activity, assessed using functional MRI at rest and during performance of neurobehavioral tasks, predict smoking relapse over an 8-week observation period among smokers who wish to quit smoking. If the results of this study are positive, this work would lay the foundation for the refinement and validation of functional neuroimaging as a bio-marker of smoking relapse. Such novel approaches can be used to identify smokers at greatest risk for relapse and for screening novel medications under development to treat nicotine addiction.
- Title: High-Throughput High-Resolution Tools for RNA-Based Functional Genomics
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to develop new high-throughput tools that will allow high-resolution assays of RNA pools of cells and to quantitatively manipulate RNA levels in cells. In addition, these tools will be applied to a survey of cellular response to perturbations as well as normal development. The results of this study will generate new research capacities and form the basis for new instruments and procedures relevant to RNA-based therapeutics. The use of quantitative RNA manipulations of a cell and assays at the single-cell resolution will help researchers understand the heterogeneity of functional responses of cells and their consequences for therapeutics.

- Title: Phase II Trial of Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients with Cancer
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: A targeted approach to cancer treatment is proposed. Most tumors have abnormalities in the control of the cell cycle, permitting unregulated proliferation of cancer cells. We have established the safety of an oral agent targeted to the cell cycle proteins cdk4 and cdk6, and have characterized its pharmacology. In this proposal we are selecting patients whose tumors have molecular features that suggest they may respond to a cell cycle inhibitor, and in four different diseases perform clinical, biological, and imaging studies to identify the characteristics of responders, to better perform future trials in populations who may benefit.
- Title: Genomic Profiling for Molecular Diagnostics of Prostate Cancer
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: This project is designed to identify nucleic acid patterns in prostate tumors that predict the likelihood and time frame of cancer recurrence following radical prostatectomy. The patterns discovered in DNA or microRNA will be evaluated in the context of candidate markers from other genomic profiling techniques, different from those to be used in this project, that have been recently identified by researchers at the University of Pennsylvania and other institutions. The combined data sets will inform the design of focused panels of molecular tests that can be clinically evaluated for their potential to help guide decisions about cancer therapy. The molecular diagnostics developed during this project will be transferred to the Hospital of the University of Pennsylvania for clinical practice, and will serve as a model for translational genomics in the Abramson Cancer Center.
- Title: Infrastructure for a GMP Facility for Radiopharmaceutical Production
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The research infrastructure planned here will develop a facility for the production of experimental radiopharmaceutical under Good Manufacturing Conditions (GMP). This project leverages the ongoing instillation of a new cyclotron facility to develop an infrastructure to support the development and translation of new radiopharmaceuticals for imaging and targeted therapy. The addition of this facility will enhance our ability to produce new radiopharmaceuticals for human use. The development of targeted imaging agents will accelerate research efforts in neurodegenerative disease, psychiatry, addiction, cardiology and cancer. In addition, the facility will be unique in the region and be available to support research originating in other universities, biotech companies or pharmaceutical companies in the commonwealth.
- Title: Direct Reprogramming of Fibroblasts and Astrocytes to Dopaminergic Neurons
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We aim to directly reprogram fibroblasts and astrocytes to dopaminergic neurons using defined factors. This will provide a novel source of these neurons for use in pharmacological studies, cell-based therapies, and ultimately studies involving *in vivo* generation of dopaminergic neurons in patients with Parkinson's Disease.
- Title: Construction of Insect Growth Chambers - Research Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure Project

Purpose: The purpose of this research infrastructure project is to provide a state-of-the-art facility for a newly recruited faculty member of the Department of Biology, as well as six other Biology faculty, that will enable them to conduct research that focuses on reciprocal interactions between social behavior, reproduction, and aging using insect models, as well as neurodegenerative and infectious diseases. Moreover, its construction will enable the Department of Biology to expand its research scope using insect models to study human diseases. The facility will be comprised of two independent walk-in temperature- and humidity-controlled insect growth chambers that will be housed within a laboratory located in Leidy Laboratory.

- Title: Development of High Throughput Methods for Generation of Induced Pluripotent Stem Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Current methods for generating human induced pluripotent stem cells (iPSC) are labor intensive and inefficient. Recent publications have demonstrated improved efficiency of generating iPSCs using human adipose stem cells (ASCs). We also demonstrate an important advance in iPSC reprogramming using miRNA-mediated approaches, which may in the near future allow reprogramming to be accomplished without the need fortransfection or even recombinant DNA techniques. The purpose of this project is to optimize methods using current and the novel miRNA approaches to generate iPSCs that improve throughput and efficiency. These methods will allow large-scale studies requiring the generation of iPSCs from a large number of patients.
- Title: Ocular Surface Limbal Stem-Cell Therapy for Corneal Regeneration
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: A clear cornea is essential for good vision and depends on epithelial integrity and stromal avascularity. Corneal renewal and repair are mediated continuously throughout our life by adult stem cells of the limbus, the narrow zone between the cornea and the conjunctiva. Ocular burns and many other conditions may destroy the limbus, causing limbal stem cell deficiency with painful recurrent epithelial erosions, light sensitivity, scarring and permanent visual loss. Transplantation of limbal stem cells is the only definite treatment. The purpose of this project is to develop a reliable and reproducible technique for culturing human limbal stem cells in order to use them for transplantation and cornea regenaration in patients with limbal stem cell deficiency.

University of Pittsburgh ($9,897,440)

- Title: Application of Adult Stem Cells for Tissue Regeneration
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Degenerative skeletal diseases, like osteoarthritis, are the primary cause of disability, particularly in the elderly. The purpose of this research project is to develop novel tissue regenerative approaches for the treatment of such diseases. The included studies will investigate the regenerative activities of human adult stem cells, specifically the nature of the optimal physical and biological microenvironment that supports their activities. This knowledge will guide the design of biomaterial scaffolds and the selection of bioactive factors for effective stem cell-based therapy for the engineering, regeneration, and functional restoration of diseased or injured skeletal tissues.

- Title: Targeting Nrf2 for Cancer Prevention
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Cancer prevention involving reduction or elimination of human exposure to environmental carcinogens may not always be possible. The overriding goal of this project is to provide the mechanistic framework to facilitate the efficient translation of the most effective small molecule activators of the Nrf2 signaling pathway into use as protective agents in human populations exposed to environmental toxicants like aflatoxins. To facilitate this goal, we need better understanding of the molecular mechanisms of action of the chemo preventive agents, further validation of intermediate biomarkers, and assessment of efficacy in animal models with close relevance to human carcinogenesis.
- Title: Establishing New Biobehavioral Paradigms for Translational Research in Cancer Prevention and Control
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The possibility that "mind-body" effects may contribute to the risk of developing cancer and of experiencing debilitating cancer- and treatment-related symptoms has been examined in numerous studies over the past three decades, with mixed results and considerable controversy. These desultory results stand in stark contrast to the steady progress that has been made in biomedical cancer research, which is grounded in a translational approach where basic laboratory findings from tissue culture and animal models are brought to bear on critical clinical issues. The purpose of this project is to bring this translational approach to mind-body research. Both arms of the project use animal models; one will investigate vomiting and other aversive effects of chemotherapy, while the other explores animal and tissue culture models of human breast cancer progression.
- Title: Clinical Trials in Multiple Myeloma
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The University of Pittsburgh Cancer Institute's (UPCI) Clinical Research Service (CRS) provides valuable resources for researchers and clinicians seeking to improve clinical research as a means to elevate patient care standards and treatment efficacy. This project will examine two therapeutic trials in patients with multiple myeloma: (1) a safety and efficacy trial to determine a maximum dose of bendamustine combined with lenalidomide to establish a treatment modality for relapsed, refractory multiple myeloma; and (2) a randomized clinical trial to determine whether there is ultimately a need for autologous peripheral blood stem cell transplant in patients with newly diagnosed myeloma who are receiving lenalidomide and low-dose dexamethasone.
- Title: Improving the Therapy of Women with Metastatic Breast Cancer
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: While great advances in breast cancer therapy have been made in recent years, therapy for metastatic breast cancer (MBC) is not adequate. We propose three trials that can have a direct impact on the treatment of MBC. The first trial seeks to determine whether changes in positron emission tomographic (PET) scanning very early in the treatment of MBC can be used to predict response and outcome to therapy. The second and third trials investigate the activity of a novel agent (ABT-888), which inhibits a protein active in DNA repair in response to stress, in the treatment of BRCA 1/2 (breast cancer genes 1 and 2) positive metastatic breast cancer and other cancers.

- Title: Research Infrastructure: Neurological Surgery Laboratory Renovations
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: Neurological surgery research is a growing area of translational research and is rapidly expanding at the University of Pittsburgh. This infrastructure project will facilitate the renovation of neurological surgery laboratories in Scaife Hall on the main campus of the University of Pittsburgh. These new laboratories will enable more efficient use of space for the expanding department and will promote collaboration and shared resources both within and outside the Department of Neurological Surgery.
- Title: Racial Disparities in Associations between Chronic Airflow Obstruction and Cardiovascular Risk
  Type of Research: Health Services
  Focus: Cardiovascular Sciences
  Purpose: Cardiovascular disease (CVD) is the leading cause of morbidity in individuals with chronic obstructive pulmonary disease (COPD). COPD, which is characterized by airflow obstruction, is associated with a greater than two-fold increase in CVD mortality, independent of smoking. This association is amplified by CVD risk factors and may be related to a link between COPD and inflammation. We have shown that, in Western Pennsylvania, CVD risk factors and inflammation are more prevalent in blacks than in whites. This disparity may explain why, in Pennsylvania, the median age of death from chronic lung disease is 6.5 years younger in blacks. This project will identify racial disparities in associations among airflow obstruction, CVD risk factors, and inflammation. Anticipated findings will direct strategies toward reducing racial differences in the link between chronic airflow obstruction and CVD.

UPMC McKeesport ($48,585)

- Title: Transitional Care Coaching Intervention in Medicare Patients in a Medically Underserved Community
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project will assess the effectiveness of a transitional care coach focused on Medicare patients. The goal of the transitional care coach is to reduce hospital re-admissions in this population. While previous studies elsewhere have demonstrated effectiveness in reducing re-admissions in general populations, it is unknown if there are differences in re-admission rates relative to underserved individuals. UPMC McKeesport serves areas in the county region that have higher than state and county averages for elderly populations as well as for minorities and those of low socio-economic status. Should the data reveal a positive outcome relative to re-admission rates, it will assist in determining decisions to implement a transitional care coach program for the broader population to improve health outcomes and reduce the financial burden of patients as well as for hospital administration.

West Chester University of Pennsylvania ($4,080)

- Title: DNA Polymerase Expression of Human Colon Cell Lines following Chemotherapeutic Treatment
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Many of today's cancer treatments include chemicals which damage a cell's DNA resulting in the inability of the cell to replicate and survive. For the

chemotherapeutic treatments to be more effective, the relationship between DNA polymerase levels and the various drugs needs to be determined. This project would help define that relationship by studying the effect of chemotherapeutic drug on DNA polymerase levels in normal and carcinoma human colon cell lines.

Wistar Institute ($ 1,778,081)

- Title: Modeling the Epigenetic Changes in Alternative Promoters of Cancer Genes
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We propose a combination of computational, statistical and high-throughput experimental approaches to better characterize the use of alternative promoters of human genes in cancer cells, which will lead to improved biomarkers and drug discovery, one of the major challenges of cancer research. We will (1) develop an information resource of alternative promoters of cancer genes; (2) experimentally assess the active or repressed state of alternative promoters in different cancer cells relative to normal cells, using massive parallel sequencing approaches; and (3) develop statistical models to define unique and common epigenetic signatures across the promoters in different cancer cells.
- Title: Characterizing Mechanisms of Transcriptional Activation Using Live Cell Imaging
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Numerous diseases, including cancer, are caused by aberrations in transcriptional regulation. Gene activation requires the tight coordination of regulatory factors at the site of transcription. We propose to study the recruitment dynamics of these factors at a transcription site in single living cells in order to produce a high-resolution map of their recruitment order. A comprehensive understanding of transcriptional regulation is important for the development of new strategies to cure human diseases.
- Title: Elucidation of the Integrator Composition and Function
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This project is focused at elucidating the role of the Integrator, a complex that was discovered by research investigators at The Wistar Institute, in the control of transcription and cellular proliferation. We showed that Integrator is critical for transcription and processing of small nuclear ribonucleic acid (RNA) genes. Elucidation of the mechanism through which small nuclear RNAs are transcribed and processed to mature RNAs is of seminal importance in understanding regulation of gene expression and growth control. Aberrant regulation of small nuclear RNA processing could result in defective messenger RNA processing through deregulation of gene splicing and may lead to cellular transformation and oncogenesis.