

Health Research Formula Grants - State Fiscal Year 2010-11

Thirty-four organizations received health research formula grants totaling \$44,440,665 for the state fiscal year 2010-11. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2011 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 (\$74,176)

Research Projects:

- Title: Goal Intention Reminding for Treatment of Post-Acute Traumatic Brain Injury
Type of Research: Clinical
Focus: Neurosciences
Purpose: The purpose of this project is to pilot test the efficacy of a brief, innovative treatment designed to address the deficits in goal self-management and emotional regulation that are common after traumatic brain injury (TBI). The innovative treatment involves helping people with TBI to develop "implementation intentions"—if-then statements specifying when, where, and how goal-related behaviors will be carried out. The project will examine whether these implementation intentions, sent as periodic reminders to participants via Short Message Service (SMS) or voice mail messages, will help participants to meet goals related to prevention or amelioration of depression, anxiety, anger/ irritability, and/ or social isolation after discharge from an intensive outpatient therapy program.
- Title: Changes in Cardiac Anatomy and Physiology during the Mueller Maneuver
Type of Research: Clinical
Focus: Cardiovascular Sciences
Purpose: The purpose of this study is to simulate naturally occurring obstructive apneas by using the Mueller Maneuver (MM) in young healthy individuals. Doppler echocardiography will be utilized to assess right sided flows [superior vena cava (SVC), inferior vena cava (IVC), and tricuspid valve (TV)] and to measure changes in diameter of the ascending aorta at pre-specified anatomic points. This study seeks to define the direction and magnitude of changes in these parameters in normal subjects performing the MM. The knowledge gained will form a baseline data set that can be used in future studies comparing responses in patients with obstructive sleep apnea (OSA) and other cardiopulmonary diseases with the normal response.

Allegheny-Singer Research Institute (\$120,384)

Research Projects:

- Title: Complement Activation Product C4d Binding to Platelets in Systemic Lupus Erythematosus
Type of Research: Biomedical
Focus: Immunology
Purpose: We have previously observed that in 18% of patients with systemic lupus erythematosus (SLE) the protein C4d, a product of complement activation, is deposited on the surface of platelets. This project will explore the impact of this phenomenon on platelet function, based upon the hypothesis that these platelet C4d+ patients are a distinct subset of lupus patients. Given the established role of platelets in some of the pathological sequelae of lupus, we will explore differences in the expression of platelet proteins between C4d+ and C4d- platelets, in order to further characterize the mechanisms of platelet dysfunction in lupus.

American College of Radiology (\$1,700,785)

Research Projects:

- Title: Socio-demographic Factors, Workup, and Treatment for Cancer Patients in an Enhanced National Survey
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to test hypotheses relating to quality of care and differences in socio-demographic factors for patients treated with radiation therapy for cancer of the breast, cervix, stomach, lung and prostate. Quality of care is defined by compliance with detailed clinical performance measures that include the patterns and sequence of particular types of surgery, radiation therapy, chemotherapy, hormonal therapy. Based on these findings we will make recommendations for improvement in the care of these groups of patients.
- Title: Pennsylvania CT Dose Registry and Reduction Project
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: This project aims to study the effects of various interventions on radiation dose received by patients undergoing Computed Tomography (CT) scans at American College of Radiology Imaging Network – Pennsylvania (ACRIN PA) healthcare delivery sites in Pennsylvania. Dose data for all CT scans performed at the sites will be collected during a 6 month baseline period and analyzed to provide insight into practice variations resulting in different rates of exposure. Sites will then be randomized to one of several strategies for education and implementation of CT dose reduction techniques during a 6 month intervention period, and dose data recorded for a one-year follow-up period. It is hypothesized that the average radiation dose delivered subsequent to the intervention will be lower than the dose delivered prior to the intervention.
- Title: The Evaluation of Translational Research Program (TRP) Projects
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The Radiation Therapy Oncology Group (RTOG), a National Cancer Institute funded multi-institutional clinical cooperative group has been collecting and banking biospecimens (biopsies, blood, urine, etc.) from patients enrolled on its clinical trials for decades. Often these specimens are collected without a pre-identified analysis – they are “banked” for future use. As technology and new biomarkers are developed, investigators request permission to use the specimens for research to identify new biomarkers or validate new procedures. These “secondary” analyses are not required by the original protocol, and may not be funded as part of that protocol. This project will allow for the investigation, including the statistical analysis, of five specified translational research program (TRP) projects.
- Title: The Evaluation of Quality of Life (QOL) Endpoints in RTOG Studies
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The Radiation Therapy Oncology Group (RTOG), a National Cancer Institute funded multi-institutional clinical cooperative group, conducts clinical trials with the goal of improving the survival and quality of life (QOL) of patients with cancer. RTOG has collected QOL data from both caregivers and patients for many of its trials. QOL outcomes are often not listed as a primary endpoint of the trial and therefore not funded by the original protocol. This project will allow for the evaluation of QOL of cancer patients receiving treatment in six specified RTOG protocols. The results of these assessments will provide valuable information

regarding the treatments under study as well as the basis for the design of future studies.

- Title: Improving the Collection of Patient-Reported Quality of Life Data - Expansion of Web-based QOL Collection Strategy
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to test a novel strategy to reduce missing quality of life (QOL) data in clinical studies. While QOL is recognized as a key endpoint that provides direct patient reported outcomes, missing QOL data is a critical problem that plagues many clinical trials. Unlike other endpoints, such as survival, QOL data cannot be collected retrospectively. Typically, QOL forms are filled out on "hard" (paper) copies. This project will collect QOL using a real-time, privacy-secure, user-friendly, web-based software system such that patients can conveniently fill out their QOL forms on-line. The study will involve head and neck cancer patients with the goal of improving compliance of QOL data collection in this challenging population.
- Title: Leveraging the Androgen Receptor Axis to Improve Treatment of Locally Advanced Prostate Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Treatment of locally advanced prostate cancer remains a major clinical challenge. New studies in our laboratory indicate that the androgen receptor (AR) axis can be manipulated to enhance the response to radiotherapy. The goal of this project is to develop a means for optimizing combinatorial therapy for locally advanced prostate cancer. Multiple in vitro and in vivo approaches will be utilized so as to provide the foundation for new clinical trials.

Carnegie Mellon University (\$860,191)

Research Projects:

- Title: Research Program in Sensory Computation
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Sensory systems allow humans and other species to collect information about the world. Our brains then integrate information from a variety of sensory modalities with stored information to generate our beliefs about what is happening around us. For many kinds of stimuli – e.g., written words, voices, faces, smells – humans are much better at interpreting stimuli than any machine ever created. Our goal is to understand the kinds of computations that underlie our remarkable abilities to interpret complex stimuli. Improving our understanding of such sensory computations will allow us to better understand brain disorders that involve abnormal perception (such as hallucinations observed in epilepsy or schizophrenia or the heightened sensitivity to certain stimuli seen in autism) and also possibly to engineer devices to improve perceptual abilities in individuals, who have impaired vision, audition or other sensory systems.

Children's Hospital of Philadelphia (\$3,548,977)

Research Projects:

- Title: Magnetic Resonance Imaging and Neurocognitive Assessment in Chronic Kidney Disease
Type of Research: Clinical Research
Focus: Renal and Urological Sciences

Purpose: Utilizing state of the art neuroimaging technology, including standard MRI, arterial spin labeling, resting state functional MRI, and a concurrent matched control group in a cross-sectional study of 180 individuals, aged 8-25 years, we will test the mechanistic hypothesis that subclinical vascular disease affects cognitive function in chronic kidney disease (CKD). Using novel pattern recognition methods, we will integrate these measurements to develop a multi-parametric imaging phenotype in CKD that can identify high risk groups. We hypothesize that level of kidney function, hypertension and anemia affect resting cerebral blood flow and functional performance. Achievement of our aims will enable targeted interventions to prevent and treat the cognitive deficits associated with CKD, and improve the quality of life for this vulnerable population.

Children's Hospital of Pittsburgh (\$527,174)

Research Project:

- Title: Regulation of Aging by the Proteasomal Pathway
Type of Research: Biomedical
Focus: Biology of Development and Aging
Purpose: Aging is a universally relevant phenomenon and a fascinating biological process. Increasing age is the largest cause for pre-disposition to a spectrum of age-related diseases, including cancer and neurodegenerative diseases such as Alzheimer's disease. An understanding of the genetic mechanisms that determine the rate of aging can lead to preventive and therapeutic measures that simultaneously target multiple age-associated ailments. This study is aimed at understanding how a molecular pathway that controls the degradation of proteins in the body helps determine the rate of aging in response to reproductive signals. The studies described here can eventually help design preventive and therapeutic measures for age-related ailments.
- Title: Defining the Role of microRNAs in Podocyte Function and the Renal Stroma
Type of Research: Biomedical
Focus: Renal and Urological Sciences
Purpose: Endstage renal disease costs over 25 billion dollars annually in the United States, and individual patients with renal failure have significantly impaired quality of life and are at increased risk of mortality. The long-term objective of this project is to gain a better understanding of the molecular pathways that cause glomerular disease and congenital anomalies of the kidney, leading causes of renal failure in children and adults. Completion of these studies will have significant implications for patients with kidney disease and may lead to novel therapeutic avenues for the treatment of chronic kidney disease in patients.

Drexel University (\$1,275,294)

Research Projects:

- Title: Conformational Signatures of Neurotransmitter-Induced Gating and Desensitization of Nicotinic Ion Channels: A Collaborative Simulation and Experimental Approach
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This project launches a new collaboration between the PI (Abrams) and Mike White (DUCOM Biochemistry) dedicated to the study of nicotinic ligand-gated ion channels (LGIC's), the key proteins that mediate synaptic transmission in higher organisms. LGIC's are targets for drugs involved in treating behavioral problems, substance addiction (certain LGIC's are the chief targets of nicotine), muscle control

disorders, and pain. Our efforts here to elucidate the links between the molecular structure of LGIC's and their function form the foundation of longer-term rational drug design which would have a major, sustained impact on human health.

- Title: Ischemic Injury and Neuroprotection in Newborn Piglet Brain
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The objective of this research plan is to develop an in-depth understanding of the events that protect neurons from perinatal hypoxia-ischemia. At present, there are no therapies available to protect the infant brain from perinatal insults. One of the strategies of neuroprotection is neuronal hypoxic preconditioning (PC). PC provides a potential route for prophylactic intervention in patients in whom ischemic events are anticipated, such as those undergoing brain and heart surgery and those with transient ischemic attacks. We will elucidate a novel signaling pathway leading to neuroprotection by PC induced vascular endothelial growth factor (VEGF) and its receptor activation. These studies will demonstrate a key role for VEGF in facilitating neuroprotective processes and will determine the downstream signaling intermediates that suppress cell death and promote survival during hypoxia-ischemia following PC.
- Title: Targeted Gene Delivery for Treatment of Cardiomyopathy in Muscular Dystrophy
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of the project is to develop methodologies to deliver genes into the heart muscle cells safely and effectively to treat cardiomyopathy. These studies will assess the feasibility, safety and efficacy of gene delivery to restore myocardial structure and function. We also anticipate investigating the mechanisms of action and optimization of strategies of these methodologies.
- Title: Improving the Epidemiology of Alcohol-Related Violence and Morbidity in the City of Philadelphia
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The goal of this project is to use geographic information systems (GIS), spatial analysis and advanced statistical techniques to improve epidemiological studies of alcohol-related violence and injuries in the city of Philadelphia.
- Title: Identification of Genetic Modifiers in a Transgenic Model of Amyotrophic Lateral Sclerosis (ALS)
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Amyotrophic Lateral Sclerosis is a neurodegenerative disease leading to death in 3-5 years. Ten percent of all cases are familial; of these, 20% are caused by a mutation in the SOD1 gene. Transgenic (Tg) mice possessing the human G93A SOD1 gene also develop ALS. However, mice of the C57Bl6 strain carrying the Tg live significantly longer than do SJL mice. We have identified a Quantitative Trait Locus on the mouse Chromosome (Chr) 17 that is strongly linked to this difference in survival. The overall goal of this project is to identify genes within chr 17 that influence longevity in this ALS model. Identification of the responsible gene(s) will highlight cellular pathways involved in motor neuron degeneration and provide new targets for the development of therapeutics to slow or stop the progression of ALS.
- Title: Collaborative Analysis of Nuclear Pores: Protein Trafficking and Recognition
Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: This project will increase our understanding of the mechanisms by which the nuclear pore complex (NPC) operates. The NPC is an elaborate cellular machine that controls traffic of macromolecules between the nucleus and cytoplasm of living cells, and as such is critical for normal cellular functions. The NPC plays key roles in the delivery of viral DNA and gene therapy reagents, and its functions are thought to be hijacked or reprogrammed in disease states such as cancer; hence, it is a prime drug target. In addition to producing fundamental biological information about NPC functioning, this project will also produce new tools that will allow for rapid screening of potential drugs that can modulate NPC activity.

- Title: Can Up-regulation of Glutamate Transporters Be Protective in Traumatic Brain Injury?
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The purpose of this project is to investigate if a glutamate transport activator, Parawixin1, has protective effects on the pathology of traumatic brain injury (TBI). This hypothesis is suitable since TBI increases extracellular levels of glutamate resulting in injured tissue, membrane depolarization and calcium influx that activates phospholipases, endonucleases and proteases that can lead to apoptosis. Rats will be subjected to moderate TBI and glutamate transport with radioactive assays will be performed in synaptosome preparations of the brains of rats injected with Parawixin1 prior and after the injury. In addition, analyses of edema, tissue loss, activation of calpain and loss of neuronal MAP-2 (markers of neurodegeneration and apoptosis) will be done. This knowledge could provide new therapeutical strategies for amelioration of the secondary outcomes of TBI.
- Title: Mechanisms of Carbon Monoxide Mediated Hypercoagulability
Type of Research: Biomedical
Focus: Hematology
Purpose: Exposure to tobacco smoke has been associated with a variety of chronic and acute diseases, one of which is thrombotic disease (e.g., acute coronary syndrome, stroke). Among the many constituents of smoke, carbon monoxide (CO) has long been recognized as an important poisonous component. Critically, it has been recently recognized that exposure of human plasma to CO concentrations well within the range encountered during smoking results in enhanced coagulation and diminished fibrinolysis *in vitro*. The purpose of this project to further define the molecular mechanisms by which this occurs, specifically focusing on the heme-mediated modulation of fibrinogen and α 2-antiplasmin function by CO. It is anticipated that these insights will significantly impact on future diagnostic and prognostic management of patients exposed to CO.
- Title: Role of Cytoskeletal Dynamics in Radiation-Induced Breast Cancer Invasion
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The goal of the proposed research is to investigate the role of cytoskeletal-associated pathways in regulating radiation-induced invasion in ErbB2-positive breast cancers. We hypothesize that changes in cytoskeletal pathways that regulate neuronal branching may play a significant role in breast cancer cell invasion and invadopodia formation, and may offer novel therapeutic targets for treating invasive breast cancer including radiation-induced progression of pre-malignant state to invasive breast cancer. I propose to unveil new aspects of cancer invasion and to test relevant potential therapeutic targets for blocking the invasion of breast cancer cells using 3D cell culture systems developing in my laboratory.

- Title: Using Biowalls to Sustainably Reduce Human Exposure to Indoor Volatile Organic Compounds
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: Exposure to Volatile Organic Compounds (VOCs) has been associated with health effects that include cancer, as well as respiratory, immunological, neurological, and renal effects. This study centers on the future Drexel Biowall, an indoor, vertical wall of plants designed to remove VOCs from the indoor air by using the bio-degrading capacity of microbes that live around the plant roots. The purpose of this work is to measure the VOC removal kinetics of microbial communities on plant roots for a common suite of eight VOCs at typical indoor concentrations while simultaneously characterizing the diversity, species, and numbers of bacteria in those root communities with both culture-independent and culture-dependent techniques. This work will allow us to identify efficient VOC degraders and clear a path for research bent on engineering effective degraders.

Duquesne University (\$116,091)

Research Projects:

- Title: From Insoluble Perfluorocarbon Oils to Multifunctional Nanoparticles for Breast Cancer Imaging and Treatment
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of this project is the development of novel multifunctional perfluorocarbon (PFC) based magnetic resonance (MR) detectable drug delivery vehicles. Specifically, nanoemulsions, microemulsions and gels for localized delivery of anti-inflammatory agents to breast tumors will be prepared. The PFC based drug delivery vehicle localization, accumulation and distribution can ultimately be quantitatively and qualitatively assessed in vivo by ¹⁹F MRI. Fluorine-19 has very low biological abundance in tissues and ¹⁹F MR directly detects the density of ¹⁹F spins contained in the PFC molecules without background. We hope to develop true theranostic agents, therapeutic and diagnostic for breast tumor imaging and treatment. Recent epidemiological studies demonstrated that treatment with nonsteroidal anti-inflammatory agents (NSAIDs), such as COX2 inhibitors, can reduce the risk of developing breast cancer, with aspirin and celecoxib showing the most significant effects. Clinical and experimental evidence strongly suggest COX2 inhibitors as new adjuvant breast cancer treatments. The purpose of this project is to incorporate a COX2 inhibitor into a ¹⁹F MRI visible nanoreagent for anti-inflammatory adjuvant treatment in breast cancer.
- Title: Promoting Health and Health Care Access in the African Refugee and Immigrant Community: A Participatory Action Research Study
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this Participatory Action Research project is to understand specific culturally shared knowledge about health and to develop strategies to promote health and health care access in the African immigrant and refugee community. The overall goal is to engage the African immigrant and refugee community in identifying, planning, prioritizing and evaluating strategies to promote health from the unique cultural view and to empower people to create their own destiny regarding the reduction of health disparities in this community.

Fox Chase Cancer Center (\$2,851,328)

Research Projects:

- Title: The Role of Histone-Complexes in Residue Specificity of Post-Translational Modifications
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this project is to develop the technology to determine the impact of histone presentation on the location(s) of post-translational modification of histones. In vivo, histones are predominately either bound to DNA (nucleosome) or bound to a histone chaperone. While there are clear correlations between changes in histone modifications and histone chaperones, their relationship is still unclear. Histone chaperones could alter post-translational modifications by interacting with the modification enzyme, protecting specific residues, or by increasing their apparent concentration by disrupting specific complexes. We aim to determine the effects of histone complexes on the location and identity of histone modifications by developing mass spectroscopy based assays to monitor multiple modifications at once.
- Title: DUSP6 Regulates the Response to EGFR Inhibitors in Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Much effort has been devoted to the development of drugs targeted at signaling proteins thought to be essential for tumor cell viability. A central disappointment has been the fact that many of these inhibitors have limited efficacy in cancer patients in spite of potently inhibiting their drug targets. DUSP6 is a cytosolic member of the family of dual specificity phosphatases, a group of proteins that regulate ERK1/2 and p38. We have found that depletion of DUSP6 significantly increases the apoptosis caused by Epidermal Growth Factor Receptor (EGFR) blockade. Although DUSP6 expression is associated with poor prognosis in cancers, the mechanism for DUSP6 action is not well understood. The purpose of this project is to discover the mechanism by which DUSP6 regulates tumors responsiveness to clinically important EGFR antagonists.
- Title: A Gene Methylation Progression Model of Bladder Cancer
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this exploratory project is to identify the difference in aberrant gene methylation between non-invasive, low grade and high grade stromal invasive and muscle-invasive bladder tumors. The central question in the management of superficial bladder tumors, which comprise the majority of bladder cancer, is how to identify the superficial tumors that will progress from those that will not, and thereby avoid overtreatment or undertreatment. Knowledge of the molecular steps in progression of bladder cancer will likely provide insight into the biology of the disease as well as identify novel targets for therapy. It is likely that genes identified will also be involved in other types of cancer with similar management issues such as prostate cancer.
- Title: Targeting STAT3 in Ovarian Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to determine whether therapeutic targeting of signal transducer and activator of transcription 3 (STAT3) is effective for the treatment of ovarian cancer. Using an immunocompetent genetically engineered mouse model of epithelial ovarian cancer, we will determine the effect of STAT3

inhibition on tumor incidence latency and progression. Since activation of STAT3 in both tumor cells and immune/inflammatory cells in the tumor microenvironment is thought to contribute to cancer, this project is designed specifically to determine the effects of STAT3 inhibition on both cell populations.

- Title: Classification and Prediction of Protein-Protein Interactions in Biology and Medicine
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Protein interactions are central to all biological processes, including those leading to disease. Many proteins exist in complexes with other copies of the same protein and/or with other kinds of proteins critical to their function. Structural information on these interactions is essential for understanding basic biological processes and the development of therapeutics and diagnostics. However, the structures of these interactions are often unknown or ambiguous. We hypothesize that we can obtain far more information than currently available by exploiting evolutionary relationships among proteins and analysis of data from multiple biophysical experiments. To do this, we will classify domains in multi-domain proteins, cluster similar forms of interaction, and predict the structures of protein interactions that occur in signaling pathways associated with cancer.
- Title: Use of Somatic Cell Nuclear Transfer to Generate TCR Monoclonal Mice
Type of Research: Biomedical
Focus: Immunology
Purpose: A key approach in experimental immunology is to generate mice that express single T or B cell receptors (TCR, or BCR) in order to examine their specificity, function, and effect on development. Somatic cell nuclear transfer (SCNT) is a promising technique for the rapid generation of such TCR monoclonal mice, which involves replacing the oocyte's nucleus with a donor nucleus from a somatic cell. Here we propose experiments to improve the efficiency of SCNT for T lymphocytes and apply the approach to dissecting the mechanism of CD4/CD8 lineage commitment.

Geisinger Clinic - Weis Center for Research (\$80,673)

Research Project:

- Title: Rare Genetic Variants in Patients with Abdominal Aortic Aneurysm
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The goal of this study is to carry out whole exome DNA sequencing of individuals with abdominal aortic aneurysm (AAA). While AAA is known to have a strong genetic basis, functional genetic variants that cause AAA have yet to be identified. An emerging concept in human genetics research is that a substantial portion of the genetic basis of complex diseases results from rare sequence or structural variants in the genome. Recent advances in genomic technology, including next generation DNA sequencing, make it feasible to identify such variants in individuals with diseases of interest. Identifying functional genomic variants that cause AAA would pave the way for novel approaches to diagnose and treat this often fatal disease. Currently, AAA is often undiagnosed; when diagnosed surgical or endovascular repair are the only available treatment options.
- Title: The Natural History and Comparative Effectiveness of Electronic Alerts in Geisinger Health System's Electronic Health Record
Type of Research: Health Services

Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: The purpose of this project is to build a dataset of all electronic alerts that have been triggered in Geisinger's Electronic Health Record from 1/1/2002 through 11/30/2010. Data will include the type of alert (e.g., drug-drug interaction, best practice alert, etc.) as well as details regarding when/why the alert was triggered and the action taken by the provider in response to the alert. This information will be used to describe the "natural history" of the use of alerts within Geisinger's primary care practices, and will also lead to analyses focused on identifying the types of alerts that are most successful in improving the quality and safety of care. This project will create a valuable source of evidence on the "real-world" comparative effectiveness of various forms of alerts that are used in clinical practice.

Haverford College (\$30,855)

Research Projects:

- Title: Studies on the Bacterial RNA Polymerase Inhibitor Ripostatin A: Efforts to Synthesize an Orally Bioactive Antibiotic for Treatment of Tuberculosis
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of the work described in this project is to prepare and to study molecules that could lead to new drug treatments for tuberculosis (TB), particularly in cases of rifamycin-resistant strains. Compounds such as myxopyronin A and ripostatin A have been isolated, and recent research shows that these molecules inhibit bacterial growth through a novel binding action with the bacterial RNA polymerase enzyme. Thus, they serve as excellent lead candidates for new drug discovery in the treatment of TB, and the goal of this work is to synthesize ripostatin A, and its close relative, ripostatin B. Another goal is to prepare synthetic analogs of the ripostatins in order to more fully understand their structure activity relationship with bacterial RNA polymerase, and improve their pharmacokinetic profile, potency and bioavailability.
- Title: A Network of Chromosomal Proteins in the Germline of *C. elegans*
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this research is to understand the logic by which genes interact in complicated biological processes. Most of the life-threatening diseases in American adults are biologically complex, with both genetic and environmental risk factors. The interactions of these risk factors that result in disease are hard to predict. From the analysis of the interactions of a relatively small group of genes in *C. elegans*, a well-studied model organism, in a controlled laboratory environment, I will develop predictions about which genes are the most likely to have functional interactions and which are not. These predictions can be readily tested and refined to give us better insights into the logical network by which gene interactions produce complex phenotypes.

Hepatitis B Foundation (\$859)

Research Projects:

- Title: Determining Correlates of Hepatitis B Status Among High-Risk Asian and Pacific Islanders in Pennsylvania
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: The purpose of this project is to determine the sociocultural and demographic determinants associated with hepatitis B virus (HBV) infection or protection status among high-risk Asian and Pacific Islander (API) communities in Southeastern Pennsylvania. API communities have disproportionately high rates of chronic HBV infection and low rates of HBV vaccination. Using de-identified data collected from 650 individuals, we will use biostatistical methods to assess the factors associated with either chronic HBV infection or vaccination status. There is a current gap of knowledge surrounding chronic HBV infection patterns in this geographic area. The results of this study are a necessary step in developing population-based interventions to reduce the significant health disparities associated with HBV among APIs in this region.

Indiana University of Pennsylvania (\$9,268)

Research Projects:

- Title: Executive Function as a Predictor of Tobacco Dependence and Response to Treatment
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: This project will examine the relationship between executive function and tobacco use, dependence, and response to treatment. Executive functions represent a set of higher order regulatory abilities associated with the frontal lobes of the brain. While executive dysfunction has been well linked to addiction across many drugs, the relationship between executive dysfunction and tobacco dependence has received much less attention. This project will compare executive abilities across nonsmokers, previous smokers, and current smokers using a battery of neuropsychological tests. Executive abilities will also be compared across time and as a function of success in participants enrolled in two forms of tobacco cessation treatment.

Institute for Hepatitis & Virus Research (\$16,013)

Research Projects:

- Title: Selective and Therapeutic Elimination of Cells that Produce Hepatitis B Virus
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: This is a project to develop an entirely new way to treat chronic hepatitis B virus (HBV) infection. It has been shown that long term antiviral suppression often beneficially results in a decline in the number of HBV infected cells. However, a major problem in current HBV medical management is that virus production often rebounds following cessation of therapy, or because of drug resistance. Our concept is to use a small molecule pharmaceutical that has already been shown to be safe in people to selectively eliminate the cells that produce HBV. With the source of HBV production eliminated, viremia and antigenemia will be stopped. This is an innovative approach to chronic HBV treatment that can play an important role in reducing morbidity and mortality associated with chronic HBV infection in Pennsylvania, the U.S., and worldwide.

Lankenau Institute for Medical Research (\$175,518)

Research Projects:

- Title: Disulfides to Modulate Thiol Homeostasis in Human Colon Cancer Cells
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: The efficacy of most chemotherapeutic agents and radiation in cancer cells may be limited due to its detoxification by intracellular glutathione (GSH). Our preliminary results have demonstrated that hydroxyethyl disulfide (HEDS) depletes GSH and increases the response of glucose deprived cancer cells to radiation. However, HEDS treatment has only a limited success in increasing the response of rat tumor xenograft to chemotherapy since it is metabolized faster by cells with glucose. The next step in our drug discovery effort is to screen disulfides with different chemical structures that will identify disulfides with better stability than HEDS. These studies will also determine the impact of a low glucose microenvironment, which induces resistance to therapy, on the disulfides mediated depletion of GSH in human colon cancer cells.

- Title: Role of TIMP-4 in Breast Cancer Assessment and Treatment

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The planned work will assess the use of a new therapeutic agent to target the triple-negative breast cancers (TNBC) identified as highly aggressive even when diagnosed at a small size. We know from previous work that elevated levels of tissue inhibitor of metalloproteinases-4 (TIMP-4) in TNBC are associated with poor prognosis for disease-free survival. These tumors are highly aggressive and difficult to treat due to lack of targeted therapy and/or resistance to standard therapy. A new agent, which blocks the down-stream effects of TIMP-4, can be the first agent to improve response rates and thereby survival among TNBC patients, a group that contributes disproportionately to the breast cancer associated death rate.

Lehigh University (\$88,081)

Research Project:

- Title: Effects of Cx43 Over-expression on Cell Proliferation and Skeletal Patterning During Fin Regeneration

Type of Research: Biomedical

Focus: Musculoskeletal, Oral and Skin Sciences

Purpose: Mutations in connexin genes lead to a variety of human diseases. In particular, mutations in human CX43 cause skeletal malformations associated with oculodentodigital dysplasia. Remarkably, mutations in zebrafish cx43 cause skeletal defects similar to those observed in human, revealing that the function of cx43 is conserved. However, it remains unknown how connexin mutations cause defects in cellular functions leading to human disease. The purpose of this research is to identify changes in cell division and gene expression associated with overexpression of zebrafish cx43. Thus, results from this research project will provide insights into the underlying molecular mechanisms associated with changes in Cx43 activity. Revealing how connexin function regulates cellular function is the first step towards understanding how connexins mediate disease phenotypes.

- Title: Modular Design of Hybrid Nanoparticle-Peptide Systems as Novel, Stimuli-Responsive Cancer Therapeutics

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The purpose of this project is to design, synthesize and characterize a series of multifunctional, hybrid materials with unique, responsive physical and biological properties as drug delivery systems targeting cancer. Targeting cancer cells *in vivo* is a significant challenge due to the multifaceted nature of the process of metastasis, and therefore requires a sophisticated approach in which specificity and rate of drug release are tightly controlled. Nanoscale carriers offer an attractive method to deliver targeted therapies due to their ability to overcome *in vivo*

transport limitations, traverse cell membranes and control rate of intracellular drug release. By integrating peptide-based tethers to control biological targeting *in vivo* with inorganic hybrid nanoparticles, we will have multiple, independent methods to control the targeting, uptake and release of drugs *in vivo*.

- Title: Competition, Health Outcomes, and Resource Use in Hospitals
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Public disclosure of data rating the performance of hospitals and physicians -- often referred to as report cards -- has proliferated in the 1990s, with the rationale that providing more information may increase hospitals' incentive to provide a higher quality of care, particularly when hospitals engage in quality competition. In this project we will examine the effect of Coronary Artery Bypass Graft (CABG) report cards on quality competition among hospitals in Pennsylvania. Our goal is to examine whether the availability of quality information intensified hospitals' quality competition, as revealed by individual patient outcomes, and to determine whether the strength of this effect varied with market concentration.

Lincoln University (\$33,493)

Research Project:

- Title: Plasma Protein Biomarkers of Chronic Obstructive Pulmonary Disease in African Americans
Type of Research: Biomedical
Focus: Respiratory Sciences
Purpose: The goal of this project is to identify potential proteomic markers that may explain the differential susceptibility and increased prevalence of COPD among African American smokers. We will use protein-profiling to identify molecular pathways and targets related to COPD in an attempt to better understand the pathogenesis of this respiratory disease in African Americans.

Madlyn and Leonard Abramson Center for Jewish Life (\$17,571)

Research Project:

- Title: Examining Impact of Individualized Positive Psychosocial Interventions in Nursing Homes
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to examine the impact of an innovative intervention designed to enhance behavior and affective quality of life outcomes for frail, cognitively impaired elders residing in a nursing home.

Magee Womens Research Institute (\$1,209,415)

Research Projects:

- Title: Analysis of Small RNAs in the Fetal Placental Maternal Interface
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Small RNAs are present in the fetal and maternal circulations, and within the placenta. We recently found that maternal plasma microRNAs (miRNAs) inversely correlate with placental miRNAs. We surmised that small RNAs may serve as intercellular and systemic signals between the maternal and fetoplacental compartments. To test the hypothesis that discrete miRNA species are transported across the maternal-placental-fetal interface, we will use next generation sequencing technologies to comprehensively define the expression of miRNAs and other small

RNAs in the maternal plasma, placenta, and fetal blood, and deploy novel statistical-computational tools to interrogate the dynamic communication patterns of miRNA during human gestation.

- Title: miR-210 Regulation of Mitochondria Function
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: We plan to characterize the function of a hypoxia inducible microRNA, miR-210, in ovarian cancer oncogenesis, especially the mechanism of miR-210 regulating mitochondria metabolism and its contribution to ovarian cancer initiation and progression. By completing this study, we hope to establish miR-210's role in ovarian cancer and identify novel miR-210 target genes as potential targets for ovarian cancer therapy.
- Title: Functional Analysis of the C19MC MicroRNAs in Trophoblasts
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: Our goal is to better understand placental physiology and the causes of placental insufficiency leading to gestational diseases. MicroRNAs have emerged as critical regulators of virtually every biological process and their altered expression is increasingly found associated with pathological states. Recently, it was found that the placenta is the exclusive source of a large family of miRNAs originating from a unique cluster located on chromosome 19 (C19MC). While the expression of these miRNAs is normally restricted to placental trophoblasts, their aberrant expression in other cell types is often associated with malignant conditions. However, the relevant biological function of these miRNAs in the placenta remains poorly understood. In this project, we propose to investigate the function of the C19MC miRNAs in trophoblast cells.
- Title: Microtubule Post-Translational Modifications and Centrosome Dynamics During Mitosis in Normal and Cancerous Cells
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Microtubule defects and centrosome aberrations cause cancers and birth defects, since they induce chromosome aneuploidies after mitosis in both somatic and embryonic cells. They are responsible for inherited disorders and their functioning is essential for brain activities. Consequently, their activities span life from conception through death. While cell biologists a century ago were as familiar with the centrosome ('the cell's central body') as they were with chromosomes ('the cell's colored bodies' because they bind cytological stains), progress in characterizing the molecular constituents and mechanisms responsible for functional activities has paled when comparing centrosome molecular biology with chromosome molecular biology. Nevertheless, the essential roles of the centrosome for normal cell function are now incontrovertible and a panoply of diseases and disorders result from microtubule and centrosome dysfunctions or 'centrosomopathies.' In this project we will characterize the vital permanent molecules in the mitotic centrosome and discover which reside temporarily at the centrosome, along with the post-translational modifications of microtubules which occurs during normal and cancerous cell cycles.

Monell Chemical Senses Center (\$216,916)

Research Projects:

- Title: Effects of Environmental Tobacco Smoke Exposure on Cough in Adolescents and Adults

Type of Research: Biomedical

Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: Cough is a reflex that protects the lungs against noxious airborne molecules and smokers have impaired cough sensitivity, which contributes to their higher rates of respiratory illness. Parents who smoke expose their children to environmental tobacco smoke (ETS), but it is not known how ETS affects the cough sensitivity of these children. This question is especially important in Pennsylvania because the smoking rate here is in the top quintile. In our research study, we will determine whether adolescents who are exposed to ETS (because one or both parents smoke) have impaired cough sensitivity relative to children of non-smokers. The information gleaned will set the stage for investigating whether reduced sensitivity contributes to illness and early initiation of smoking during adolescence.

- Title: Effects of Chemotherapeutic Agents on the Peripheral Taste Structure and Function

Type of Research: Biomedical

Focus: Neurosciences

Purpose: Cancer patients undergoing chemotherapy frequently experience taste abnormalities. The severity of taste dysfunction is associated with high rates of weight loss and poor prognosis. To date, the underlying mechanisms of chemotherapy-associated taste disorders remain unclear. The purpose of this project is to investigate how chemotherapeutic agents affect the peripheral taste structure and function. The ultimate goal of this research is to identify approaches that can prevent or minimize the side effects of chemotherapy on the taste system.

National Disease Research Interchange (\$62,393)

Research Project:

- Title: The Development of Diabetic Retinopathy: Going from Genetic Susceptibility to Functional Analysis

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 (T1D) and its complications. Previously, our work has confirmed that genetic factors influence susceptibility to microvascular complications of diabetes. We will now test for functional gene expression differences in retinopathy-affected vs. non-retinopathy-affected diabetic retina and correlate the expression data with a) the results of case-control association studies in HBDI samples previously typed and b) the results of family-based association and linkage analysis on a candidate locus for susceptibility to retinopathy integrating newly typed HBDI family members. We will also continue our program of administering follow-up questionnaires to T1D families, allowing us to track clinical changes in T1D and complications.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation (\$967,922)

Research Project:

- Title: Next-generation Sequencing-based RNA Expression Profiling for Archived Tumor Tissue

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The purpose of this project is to develop a protocol for next-generation (NexGen) sequencing of RNAs isolated from formalin-fixed, paraffin-embedded tissues.

Pennsylvania State University (\$7,001,127)

Research Projects:

- Title: Research Infrastructure Renovation to Create the Penn State Center for Translational Informatics
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The purpose of this project is to create a Center for Translational Informatics that will provide the necessary software tools for researchers to collect and manage patient data, analyze genomic information, and mine the electronic medical record for data to support research into comparative effectiveness and personalized medicine. To create the Center, approximately 600 sq ft of existing space will be renovated to establish a collaborative workspace to house informaticists, IT analysts, and data analysts who will consult with basic and clinical researchers, develop software, and manage databases. Software and hardware will be purchased to allow the collection, management, analysis and transfer of large datasets.
- Title: A Trial to Evaluate the Safety and Tolerability of a Novel Oral Iron Supplement for the Treatment of Iron Deficiency Anemia
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: The purpose of this study is to conduct a Phase 1 clinical trial designed to evaluate the safety of a novel oral iron supplement utilizing a nutritional strain of yeast. Iron deficiency anemia (IDA) is a problem of world-wide importance that affects approximately 1.3 billion people. IDA has been identified by the World Health Organization as the number one nutritional disorder in the world. The elderly, infants, children, and women of reproductive age are particularly affected by iron deficiency and iron deficiency anemia. In the US, IDA is prevalent in lower socioeconomic groups. The impact on health, mother-child interactions, and days lost from the workplace is widely published. In many countries and among the poor in the US, the primary driver for iron deficiency is the lack of available iron rich foods. Current treatment strategies for IDA are inadequate because of poor absorption rates for iron in oral tablets and significant side-effects leading to non-compliance. The primary objective of this project is to demonstrate the safety and tolerability of a novel oral iron supplement. The secondary objective is to begin to evaluate efficacy and identify a potential therapeutic dose of this novel oral iron supplement.
- Title: Research Infrastructure Renovation to Create a Biomedical Research Imaging Core Facility
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The overall goal of the project is to establish an imaging core to meet existing and rapidly growing needs for an equipped biomedical research imaging facility dedicated to experimental approaches in the life sciences. We will do this by renovating 2300 sq ft of space to optimally place existing and/or acquired instruments that include (i) confocal, (ii) deconvolution (iii) electron microscopes with support equipment and (iv) a facility director (to be named) to provide expert guidance in optimal sample preparation, supervision of instrument use, data collection and training for researchers and students in imaging and image processing.
- Title: Sphingolipid-based Therapeutics for AML
Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The long term goal is to develop new therapies for the treatment of AML. These funds will support three specific aims that provide additional/ new/ critical data that are essential for submission of an integrated interdisciplinary NIH P01 application in 2011 that will investigate the role of dysfunctional sphingolipid metabolism in acute myeloid leukemia. The funds will support three team projects that will benefit each of the eventual P01 projects.

- Title: Genome-wide Mapping of Transcriptional Factors Involved in Pathogenesis of LGL Leukemia
Type of Research: Biomedical
Focus: Hematology
Purpose: LGL leukemia is characterized by a clonal proliferation of antigen-primed terminally differentiated effector memory cytotoxic T cells (CTL). The overall objective of this project is to understand the pathogenesis of LGL leukemia by identifying the key genes which promote leukemic LGL survival. This project capitalizes on strengths of Penn State University by investigating the pathogenesis of a leukemia discovered by the PI (Hershey) utilizing a genomic approach in collaboration with University Park. T-bet is considered the master switch for the generation of antigen primed effector CTL. We previously showed that leukemic LGL are characterized by T-bet upregulation. Thus, LGL leukemia provides us with a unique model to study the functional role of T-bet in generalizing and maintaining CTL response.
- Title: Gut Microbial Metabolism and Receptor-Mediated Regulation of the Host Environment
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: As a whole, the gut microbiota contains nearly 100 times more genes than that in the human genome of which some are used to tightly control and regulate the host environment. In spite of this, little is known about specific gut microbial metabolism, their positive or negative effects on the host, or how microbes use specific diet-derived substrates to modulate the host environment (e.g., receptor-mediated regulation of intestinal inflammation). This project seeks to understand and characterize—using advanced metabolomic approaches, mouse models, and high throughput sequencing—the gut microbiota metabolome and how specific diet-derived substrates (e.g., tryptophan) are used to influence and modulate the host environment.
- Title: Neurogenic Actions of Dietary Salt on Sympathetic-Cardiovascular Function
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: The purpose of this project is to identify how dietary salt acts within the central nervous system to adversely affect cardiovascular function and morbidity. Compelling evidence from clinical studies indicates excess dietary salt intake contributes to the pathogenesis of several cardiovascular diseases and increases morbidity. Recent observations from our research team indicate the central nervous system contributes to the adverse cardiovascular effects of dietary salt. Therefore, this project will (1) identify how the central nervous system detects changes in dietary salt intake, (2) determine how dietary salt affects sympathetic-cardiovascular circuits within the central nervous system, and (3) determine whether dietary salt intake affects sympathetic-cardiovascular regulation differently in males versus females.
- Title: Resolving the Structure and Function of Proteomes

Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology

Purpose: The project proposes to: (i) develop/refine computational methods capable of accurate assessment of domain boundaries, conservation profiles for predicting mutants, and fold-recognition and atomic-resolution structural models for proteins from large screens, (ii) integrate/synergize these computational endeavors with the updated mass-spectrometry (MS) core-center for high-throughput identification and computational characterization of proteins obtained from wet-lab experiments and (iii) build the infrastructure for interdisciplinary training for investigators/students involved in these endeavors. This is the next step towards an interactive, high-throughput, collaborative, and interdisciplinary Center for Computational Proteomics.

- Title: Genomics of Amyotrophic Lateral Sclerosis

Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: Amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, is a neurodegenerative disease in which the nerves that control voluntary muscle movement die, causing weakness, paralysis, and death, usually from respiratory failure, within 3-5 years of symptom onset. The disease can be inherited in a small number of cases. About a half dozen genes have been identified that can cause ALS in these families, but about half of the patients with familial ALS and the vast majority of patients with sporadic ALS do not have known genetic mutations. Our goals are to recruit patients with sporadic and familial ALS from the Penn State ALS clinic and to analyze their DNA for known and new genetic mutations associated with ALS that may aid in diagnosis and may serve as new targets for drug discovery.

- Title: Investigation of Molecular Contributors to Early Onset Parkinson's Disease in Identical Twins

Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: Identification of subtle genetic differences in groups of identical twins (one with Parkinson's disease and one healthy) will allow the identification of previously unknown mechanisms that may underlie disease pathology. This knowledge will then allow the investigators to have insight into the cause of the disease. As Parkinson's disease is considered to be caused by a combination of genetic and environmental factors, identical twins provide a very well controlled platform for the investigation of the molecular differences, hence the possible cause of the disease. Identifying subtle genetic alterations in the affected twin(s) will allow to us to obtain information about the changes that resulted in the formation of Parkinson's disease in the affected individual.

Philadelphia College of Osteopathic Medicine (\$19,326)

Research Project:

- Title: Effect of Liposuction Technique on the Viability and Differentiation of Adipose Derived Stem Cells

Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology

Purpose: Tissue engineering and regenerative medicine is a rapidly developing field of research in which new materials and strategies are proposed for the repair of lost or degenerative tissues. A key factor in these strategies is a ready supply of cells to populate these replacement materials. Adipose derived stem cells have been suggested as a source of autologous cells for potential use in numerous therapies.

However, while the use of liposuction techniques for the recovery of these cells from adipose tissue has been proposed, to date, no work has shown the desirability of one potential technique over another. We propose to determine the role of liposuction method on the ability to isolate stem cells from fat for tissue engineering purposes. The results of this work should guide reconstructive strategies in the future, significantly impacting the standard of care.

Philadelphia Health Management Corporation (\$17,081)

Research Project:

- Title: Assessment of Health Needs of LGBT Older Adults in Philadelphia
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Sexual minority older adults face barriers to health care in addition to those faced by older adults who are not sexual minorities. These barriers may include homophobia, lack of appropriate places to receive care and difficulties because partner relationships are not legally recognized. However, there are no local research studies identifying and documenting these barriers. In addition, LGBT populations are at increased risk for chronic conditions due to high rates of tobacco and alcohol use, among other factors. The proposed project will explore the health needs and barriers faced by sexual minority older adults in the Philadelphia region and will present research findings to inform policy decisions and the delivery of services.

Pittsburgh Tissue Engineering Initiative (\$9,815)

Research Project:

- Title: Acrylic-Bisphosphonate Polymer Mediated Cell Binding to Collagen-Hydroxyapatite Scaffolds
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: Retention of osteoblasts or progenitor cells is an important characteristic for scaffolds designed to enhance bone healing. We have developed a poly-functional polymer that can be attached to cells and direct their binding to bone or bone substitute materials that contain hydroxyapatite. The polymer has a succinimide functionality that allows covalent attachment to cell surface amine groups and pendant bisphosphonate groups that provide specific attachment to the hydroxyapatite component of bone tissue. In this project we propose to synthesize biomimetic scaffolding made up of electrospun collagen fibers containing hydroxyapatite nanoparticles. The scaffold will be tested for its ability to bind and retain cells and for its degradability under simulated in vivo conditions.

Salus University (\$45,203)

Research Project:

- Title: Role of RD3 protein in Leber Congenital Amaurosis LCA12
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The purpose of this project is to characterize new protein interactions in photoreceptor cells to extend our knowledge about the processes leading to photoreceptor death triggered by abnormal regulation of one of the key photoreceptor enzymes, guanylyl cyclase. In particular, we will characterize the functional effects of mutations found in human homolog of the *RD3 (Clorf36)* gene in patients with different retinal disorders and model in vitro its interactions with retinal

guanylyl cyclase pertinent to congenital blindness, Leber congenital amaurosis LCA12.

Temple University (\$2,050,596)

Research Projects:

- Title: The Effects of Music Therapy Entrainment on Pain, Vital Signs, and Bowel Function of Cancer Patients
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to gather preliminary data on the effectiveness of a specialized music therapy approach to pain management with cancer outpatients who have chronic pain. A cross-over design will be used to examine the effects of music therapy entrainment, a live music intervention based on principles of physics, on reported pain levels, vital signs, pain medication usage, and bowel function in 40 participants. Participants will receive one music therapy entrainment session and one sham treatment consisting of listening to pre-recorded music. In addition to measuring the above mentioned outcomes, three participants will be chosen at random to undergo MRI scans. The purpose of this is to assess brain activity while they listen to the recording of the music of their entrainment session as well as music of the sham treatment.
- Title: Place-Based Interventions for Public Health: A Cross-Disciplinary Approach to the Study of Policing
Type of Research: Biomedical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this study is: 1) to determine if the benefits of focused, foot patrol policing to reduce violent crime translates to a decrease in the incidence of drug-related illnesses (such as overdose) and physical assaults; and 2) to identify community variables that are associated with rates of crime-related illness or injury. Community variables include micro-places (e.g. alcohol outlets, parks) that serve as perpetual 'crime generators' as well as facilities (e.g. churches, health clinics) that contribute to the promotion of healthy behaviors. These data will provide evidence to support ways in which the police, along with city agencies and services can leverage their different tools and resources in a more targeted and collaborative manner to prevent crime and achieve shared health and safety outcomes.
- Title: Inflammation and Organ Tissue Damage
Type of Research: Biomedical
Focus: Immunology
Purpose: This project seeks to clarify the mechanisms by which alteration in the inflammatory response cause tissue damage and organ failure. Specifically, we will study critical steps of the inflammatory response to understand how: 1) adhesion receptors expressed on endothelial cells and circulating leukocytes affect the immune response and subsequent organ damage, 2) signal transduction processes initiated by such receptors regulate the inflammatory response, and 3) cytokines produced by immune cells affect the overall outcome of the inflammatory response toward resolution or chronic inflammation. The overall goal is to uncover novel pharmacological strategies to prevent or treat the organ complications associated with chronic inflammation (e.g., neurodegenerative disorders, cardiovascular disease, obesity with insulin resistance, and physiological aging). These results will advance our understanding of the mechanism by which systemic inflammation increases organ morbidity and all-cause mortality in the population of the USA.
- Title: Inhibition of Leptin Receptor Signaling in Cellular Models of Rheumatoid Arthritis and Osteoarthritis

Type of Research: Biomedical

Focus: Musculoskeletal, Oral and Skin Sciences

Purpose: Osteoarthritis (OA) and rheumatoid arthritis (RA) are debilitating diseases whose progression can be promoted and/or aggravated by obesity. Leptin is a satiety factor regulating appetite and energy expenditure by acting on leptin receptors (ObR) in the hypothalamus. Leptin represents a critical link among nutritional status, metabolism and immunity. Recent evidence suggests a major role of the leptin / ObR system in the pathogenesis of OA and, perhaps, RA. Consequently, pharmacological downregulation of leptin activity could become a novel treatment for OA and RA. Our laboratories developed highly efficacious, specific and safe leptin-based peptide antagonists of ObR. This collaborative project will explore the applicability of our lead ObR antagonists in reversing characteristic OA and RA processes in vitro.

- Title: Research Infrastructure Project: Multiphoton Imaging Facility

Type of Research: Biomedical

Focus: Research Infrastructure Project

Purpose: This project will fund a laboratory renovation to create a new Multiphoton Imaging Facility. Renovations will be made to existing space in the Department of Biochemistry located on the 6th floor of Kresge Hall. The updated facility will greatly improve capabilities for confocal microscopic imaging.

- Title: Immunomodulatory Cannabinoids as Potential Therapeutics for Transplant Graft Rejection

Type of Research: Biomedical

Focus: Immunology

Purpose: Compounds that bind to Cannabinoid Receptor 2 will be investigated for their potential to increase survival of skin and organ grafts. Compounds of this type should suppress immune reactions but not have psychotropic activity. The efficacy of these compounds in combination with standard anti-rejection therapy will also be investigated.

- Title: Differentiation Therapy for Leukemia

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The purpose of the project is to evaluate the therapeutic efficacy of the peptide, angiocidin, for the treatment of leukemia. We propose to determine if angiocidin can block the engraftment of human leukemia cells in a mouse model of leukemia. We will evaluate the effect of angiocidin on the engraftment of at least three patient leukemia cells. These will be patients with acute myeloid leukemia.

- Title: Social Influences on Alcohol Consumption in Adolescent Versus Adult Mice

Type of Research: Biomedical

Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: The presence of peers is associated with increased risk taking during adolescence, including alcohol and drug use, but the underlying neural mechanisms for this "peer effect" are not understood. Importantly, a similar effect is not seen among adults. Previous research by one of the present investigators indicates that the effect may operate via the impact of peer presence on the adolescent brain's reward processing system, such that the presence of peers increases the salience of other rewards and thereby biases individuals toward the potential benefits of a risky choice. This project will examine the feasibility of modeling this process in rodents, and will examine the differential impact of "peer" presence on alcohol consumption among juvenile and adult mice.

- Title: The Role of G Protein-Coupled Receptor Associated Sorting Protein 1 (GASP-1) in Breast Cancer Progression

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The purpose of the project will be to evaluate the prognostic significance of GASP-1 in breast cancer detection and diagnosis.

- Title: p38SJ, a Novel DING Protein from St. John's Wort Inhibits Tumor Cell Growth via Induction of Cell Cycle Arrest

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: p38SJ is a novel DING phosphatase isolated from St. John's Wort. Our preliminary data demonstrate that p38SJ inhibits proliferation of human T98G glioblastoma cells, as increased toxicity was observed upon treatment of cells with p38SJ. Furthermore, pre-treatment of rapidly proliferating U87MG cells with p38SJ leads to cell growth delay and induces cell cycle arrest in G0/G1 phase. Our observations provide evidence that p38SJ alters signaling pathways that impact cell growth and proliferation. The purpose of this project is to demonstrate that treatment of primary glioblastoma tumors from patients with p38SJ will result in the suppression of tumor growth. Thus p38SJ can be developed and used as an anti-cancer agent.

- Title: Body Sensor Networks and Their Applications in Maternal Fetal Monitoring

Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology

Purpose: Assessment of fetal health during pregnancy constitutes a very important task of modern obstetrics. It is applied in high risk patients in the third trimester and in almost all patients during labor and delivery. Currently, the monitoring devices needed for fetal heart rate (FHR) and uterine contractions are hardwired to a large monitor (about 15 lbs), and require the patient to remain relatively immobile in order for the monitor to function optimally and continuously. Many women feel more comfortable if they are able to move during labor, and therefore feel constrained by the monitor. The project seeks to design a body sensor network (BSN), a network consisting of one or more on-body sensing units coupled with a smart local processing unit, to allow normal mobility during the monitored period. The BSN system has to be both energy-efficient and secure.

- Title: Clinical Management of Anxiety and Access to Health Care

Type of Research: Clinical

Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: The purpose of this project is to develop and evaluate a computer-administered dental anxiety management program that can easily be implemented in dental and non-dental healthcare settings. Anxiety is a major reason for avoidance of dental health care, especially among low-income individuals. The proposed dental anxiety management program will have the following features: 1) A dental anxiety screening questionnaire for patients; 2) a computer-administered algorithm to classify patients according to their level of dental anxiety, 3) a menu of interventions for managing dental anxiety endorsed by each patient and delivered using a tablet PC and 4) an evaluation component (pre-post intervention) The program will also be designed so that it can be administered online and accessed from a prospective patient's home.

- Title: Relationship between Neuropsychological Function and Monocyte Dysregulation in HIV Infection

Type of Research: Biomedical

Focus: AIDS and Related Research

Purpose: The purpose of this project is to investigate the expansion of a circulating monocyte subset that may be important to development of neurocognitive

impairment in HIV infection and how it relates to neurocognitive function in a small cohort of HIV infected subjects.

Thomas Jefferson University (\$3,085,950)

Research Projects:

- Title: Network-Directed Therapy of Prostate Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Although considerable progress has been made in the understanding of cancer genes, only a handful of molecular therapies have become standard of care for cancer patients in the last thirty years. The management of prostate cancer remains challenging, and confusion still exists regarding the molecular networks that drive the disease, the reliability of biomarkers, and the appropriateness of treatment options. The present application will address these problems taking an innovative approach. This project will focus on a single gene network, the survivin pathway, which plays a critical role in prostate cancer. This will involve analysis of tumor initiation and metastasis, *in vitro* and *in vivo*, supported by mechanistic studies on receptor ligation, gene expression, and intracellular signaling pathways.
- Title: Cell Cycle Regulation in Prostate Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: In the United States, prostate cancer (PCa) is the most frequently diagnosed malignancy, and the second leading cause of cancer death, in men. The morbidity associated with this tumor type is attributed to ineffective means in combating advanced disease. Local PCa can be definitively treated by radical prostatectomy or radiation therapies. However, disseminated PCa is largely resistant to standard cytotoxic chemotherapeutics. The androgen receptor (AR) is the therapeutic target of disseminated disease. As such, first line therapies for disseminated disease are centered on the addition of this tumor type to androgen. This project will utilize the combined knowledge of AR and cell-cycle based cytotoxic action, to design strategies for maximal PCa cell death.
- Title: Increasing Colorectal Cancer (CRC) Screening in Primary Care among African Americans
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Determine the impact of behavioral interventions on CRC screening, and the use of CRC screening tests among African American patients, in primary care practices 12 months after enrollment in the study.
- Title: Targeting Endoplasmic Reticulum Stress (ERS) Signaling for Overcoming Lung Cancer Resistance
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Lung cancer patients die as a consequence of therapeutic resistance and treatment failure. One of the important features of cancer resistance is the inability to undergo apoptosis. Ongoing research from this laboratory supports the idea of inducing ER stress-mediated autophagy as a way of combating resistant lung cancer cells. Therefore we will investigate the underlying mechanisms and preclinical concepts of using ER stress activators for enhancing radiotherapy in treating lung cancer.
- Title: New Stem/Progenitor Cell-Related Biomarker(s) for Predicting DCIS Prognosis and Progression
Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: Ductal Carcinoma *In Situ* (DCIS) is characterized by a clonal proliferation of malignant epithelial cells confined within the lumens of mammary ducts, without invasion into adjacent stroma. Since DCIS represents a group of biologically and morphologically heterogeneous diseases, its classification and management remains very challenging. Breast conserving therapy with or without radiotherapy is the accepted treatment for most cases of DCIS. However, the local recurrence rate with such therapy ranges from 10 to 40% with half of these patients developing invasive carcinoma. Previous studies have attempted to identify prognostic molecular markers. Many of the molecules thought to play critical roles in progression of invasive breast cancer have not been shown to be independent prognostic markers for local recurrence or progression of DCIS. Therefore, there is a critical need to identify novel predictors of DCIS progression and potential targets for therapy.

- Title: Phenotypic and Molecular Characterization of Occult AML

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The high incidence of relapse in acute myelogenous leukemia (AML) observed after induction of complete remission (CR) is thought to be due to the persistence in a protective niche in the bone marrow (BM). The residual AML cryptic cells are a rare population with self-renewal potential, representing Minimum Residual Leukemic Myeloblasts (MRLM). Homing of these AML cells in the BM is largely mediated through the interaction of the chemokine receptor CXCR4 expressed by AML cells with its ligand CXCL12 expressed by BM stromal cells. The objective of this project is to establish a rationale for mobilization of AML occult cells from the BM by treating patients in CR with a CXCR4 antagonist and demonstrating that AML precursor cells will be detected in bone marrow and peripheral blood as early predictor or relapse using cytogenetics, multiparameter flow cytometry and next generation DNA sequencing.

Treatment Research Institute (\$139,351)

Research Project:

- Title: Medication Assisted Treatment for Opioid, Alcohol Dependence: Improving Knowledge, Attitudes & Referrals
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: There is strong evidence supporting the effectiveness of medication assisted treatment (MAT) at reducing substance use, criminal behaviors, and fatal overdose among people with substance dependence. However, the widespread utilization of MAT has been impeded by misperceptions, negative attitudes, and a general lack of awareness of MAT. The purpose of this project is to reduce these barriers among critical stakeholders by developing a brief training, delivering it to treatment referrers and policymakers situated in the criminal justice system, and assessing its effect on knowledge, attitudes, and willingness to refer to MAT. The training aims to improve the health and safety of all Pennsylvanians by promoting the utilization of treatment that reduces the negative consequences associated with substance use among a subpopulation where this problem is rampant.

University of Pennsylvania (\$8,236,620)

Research Projects:

- Title: Research Infrastructure: Renovation for Laboratory Space for Biological Chemistry

Type of Research: Biomedical

Focus: Research Infrastructure Project

Purpose: The purpose of this project is to upgrade and renovate 4186 square feet of laboratory space to standards appropriate for a 21st century laboratory performing research at the interface between chemistry and biology. The renovations include outfitting the laboratory space with modern fume hoods, electric, air-handling as well as the creation of a room for radioactive work and a dark room for work with light sensitive nucleic acids. The renovated space will be occupied by researchers from the Chemistry Department whose research includes work at the frontiers of gene regulation, magnetic resonance imaging, and mechanistic studies of anesthesia. Renovations will also include the creation of a shared Biochemistry Instrumentation Core Facility in the Department of Chemistry.

- Title: Enhancing Cognitive Neuroscience and Neuroimaging Research at Penn – Research Infrastructure
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: In order to support interdisciplinary lines of inquiry related to the areas of cognition, cognitive neurology, brain imaging, and cognitive neuroscience, the Centers for Cognitive Neuroscience (CCN) and Functional Neuroimaging (CFN) will be coalesced within 40,000 square feet of newly renovated space at Penn. This multi-phase project – approximately 20,000 sf for Phase II, which is described in this strategic plan – will unite members of the CCN who study cognitive effects and defects with members of the CFN who develop the machine and mathematical interfaces for imaging. The resultant facility will provide access to emerging technologies and shared resources and dramatically promote collaborative science within the neurosciences. This facility will also foster the recruitment and development of new faculty and programs.
- Title: Control of Somatic Stem Cell Potency and Tumorigenesis by Musashi RNA Binding Proteins
Type of Research: Health Services
Focus: Oncological Sciences
Purpose: Mammalian genetic studies have suggested an interconnection between mechanisms governing the symmetry of cell division, somatic stem cell potency, and cancer progression. The Msi RNA binding proteins govern asymmetric cell division and have been implicated in stem cell potency and tumorigenesis in the hematopoietic system, providing a potential link between these processes. In the intestine, Msi proteins are expressed in putative stem cell compartments where asymmetric cell division is observed and in colorectal cancers. We propose to determine the functional contribution of Msi proteins to the progression of colorectal cancer. Gain and loss of function approaches for Msi proteins in a murine model of colorectal cancer will provide a foundation for determining the clinical value of Msi proteins as diagnostic markers and therapeutic targets.
- Title: Translational and Personalized Genomics of Inherited Retinal Degenerations
Type of Research: Health Services
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Inherited retinal degenerations (IRDs) are important causes of blindness. Over 190 different types of IRDs have been identified by clinical and genetic studies. However, we hypothesize that the identified mutations account for only ~50% of patients with these disorders. The purpose of this project is to use next-generation sequencing (NGS) approaches to test the hypothesis that novel IRD disease genes contribute to genetic causes of blindness, and to test the hypothesis that the

pathogenesis of retinitis pigmentosa is caused by mutations in RNA splicing factors, with the long term goal of developing genetic therapies for these blinding disorders.

- Title: Pharmacogenetics of Nicotine Addiction
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: In this prospective pharmacogenomic trial of different smoking cessation treatments, we will: (a) examine whether a genetically informed biomarker of nicotine metabolism rate predicts medication response; and (b) test whether pretreatment $\alpha 4\beta 2^*$ neuronal nicotinic acetylcholine receptor availability predicts smoking cessation and medication response.
- Title: Therapeutic Response in Genetically Engineered Mouse Models
Type of Research: Health Services
Focus: Oncological Sciences
Purpose: We will measure changes in the apparent diffusion constant using diffusion MRI. Diffusion weighted MRI imaging has been shown to be sensitive in monitoring early response to therapy and is sensitive to changes in extracellular water. In this aim, the apparent diffusion constant (ADC) will be quantified in a panel of mammary tumors arising in a conditional bitransgenic system for mammary tumor development before, and at increasing intervals after, oncogene down-regulation and tumor regression.
- Title: The Unfolded Protein Response in Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to identify novel points within the neoplastic process that can be attacked through the development of novel therapeutics. The experiments described will provide proof-of-principle data supporting these novel concepts.
- Title: Identifying Genetic Determinants of Mammographic Density
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Mammographic density is one of the strongest known predictors of breast cancer risk, but its basis is largely unknown. The realization that mammographic density is primarily determined by genetic factors, rather than reproductive endocrine events, suggests that the genetic pathways that control mammographic density may reflect entirely novel pathways and mechanisms of breast cancer susceptibility. Identifying the genes that control mammographic density would be enabled by a validated animal model for the effect of genetics on mammographic density. The objective of this pilot project is to validate a rat model for the genetic effects of mammographic density on breast cancer risk using in vivo and ex vivo imaging in combination with inbred strains of rats with differing intrinsic susceptibilities to breast cancer.
- Title: Personalized Cancer Vaccines and Somatic Tumor Mutations
Type of Research: Clinical
Focus: Immunology
Purpose: The purpose of this project is to understand whether personalized cancer vaccines can be based on the identification of somatic mutations on individual tumors.
- Title: CD40 and Notch as Novel Therapeutic Targets of Pancreatic Carcinoma
Type of Research: Health Services
Focus: Oncological Sciences
Purpose: The purpose of this project is to identify new therapeutic approaches for the treatment of pancreatic ductal adenocarcinoma (PDA). The approach is focused

on the CD40 and the Notch pathways and is designed to test relevant compounds for efficacy using a spontaneous, genetically engineered mouse model of the disease. Compounds or combinations that result in tumor regression can be taken forward as priority approaches for eventual clinical evaluations.

- Title: Customization of Advanced Non-small Cell Lung Cancer Treatment Based on Emerging Histologic and Molecular Markers
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The main purpose of this project is to show that non-empiric therapy that is scientifically chosen on the basis of existing clinical and molecular markers, including EGFR and KRAS mutation and EML4/ALK translocation, can result in improved progression-free and overall survival (PFS and OS) in good performance status patients with advanced *non-squamous* Non-small Cell Lung Cancer (NSCLC), compared to historic controls and contemporaneous subjects who are treated empirically.
- Title: Infrastructure: Small Animal Imaging Facility Expansion in the John Morgan Building
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The existing Small Animal Imaging Facility (SAIF) lab in the Richards Medical Building on the University of Pennsylvania's Campus in Philadelphia is being relocated to the basement of the John Morgan Building. Imaging equipment and animal holding capacity will be moved from the 5th floor of the Richards Building to be co-located with existing holding and imaging areas. This co-location and expansion will enable more collaborative research efforts on small animal models of human disease which are employed in a broad range of disciplines in biomedical research, including the study of cancer biology, genetics, developmental biology, cardiovascular biology, neurobiology, stem cell research, infectious disease, and experimental therapeutics.

University of Pittsburgh (\$8,236,620)

Research Projects:

- Title: Cellular Systems Biology in Cancer Drug Discovery
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The project focuses on the development of a research program to discover and develop small molecule anticancer therapeutics. At the University of Pittsburgh, novel chemistries are combined with cellular systems biology and computational pharmacology approaches to drug discovery. The overriding goal of this project is to further enhance the broad scientific capabilities at the University of Pittsburgh in these research areas and to deploy them for the development of novel anticancer drug candidates and ultimately commercial drugs.
- Title: Complex Genetics of Congenital Heart Disease
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: This study will examine the complex genetics of congenital heart disease (CHD), specifically, the role of genetic variants of genes encoding ciliary proteins (the ciliome) in the pathogenesis of CHD. Previous studies have suggested an association between ciliary dysfunction and CHD with heterotaxy, a birth defect characterized by discordant cardiac, lung, and visceral organ situs resulting from aberrant embryonic left-right patterning. This study will use next-generation sequencing technologies to analyze whole exomes of CHD patients to identify

disease-causing polymorphisms, specifically in the genes comprising the ciliome. These findings will likely shed light on the complex genetics of CHD and may lead to new diagnostic genetic tests that can help identify patients, specifically infants and children, at high risk for ciliary disorders.

- Title: Breaking Metabolic Symbiosis in Tumors: A New Cancer Treatment Paradigm
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: As cancer cells grow and evolve into tumors, they need specific nutrients and oxygen to fuel cellular metabolism, namely, through mitochondrial oxidative phosphorylation and glycolysis. This project will test the hypothesis that those cancer cells with the highest metabolic flexibility are most successful at developing tumors. In a tumor, the populations of cells farthest from an oxygen supply produce energy through glycolysis and create lactate, a waste product. That lactate is used by the more oxygenated cell population to produce energy by oxidative phosphorylation. This project will examine how this metabolic symbiosis drives rapid tumor growth. Understanding how this interdependent, metabolic sharing of carbon sources occurs in a growing tumor and learning how to break the cycle will enable improved therapeutic approaches to cancer.
- Title: Prostate Cancer Vaccine Clinical Trials
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: This project encompasses investigator-initiated clinical trials that explore the safety and efficacy of novel therapeutic cancer vaccines, with the overarching goal of improving outcomes of patients with cancer. Aim 1 includes therapeutic trials of novel cancer vaccines based on polarized alpha dendritic cells (α DC1s) for the treatment of prostate cancer, and Aim 2 examines the efficacy of novel tumor peptide-based cancer vaccines for the treatment of prostate cancer.
- Title: Melanoma Vaccine Clinical Trial
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: This project is an investigator-initiated clinical trial that explores the safety and efficacy of novel therapeutic cancer vaccines based on polarized alpha dendritic cells (α DC1s) for the treatment of melanoma.
- Title: Glioma Vaccine Clinical Trials
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The University of Pittsburgh Cancer Institute's Clinical Research Service (CRS) provides valuable resources for researchers seeking to improve patient care standards and treatment efficacy. This project encompasses investigator-initiated clinical trials that explore the safety and efficacy of novel tumor peptide-based cancer vaccines for the treatment of low-grade glioma (LGG).

UPMC McKeesport (\$32,934)

Research Projects:

- Title: Outcomes of Disparate vs. Non-Disparate Cancer Patients Undergoing Patient Navigation
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: We will study the clinical and functional outcomes of cancer patients who have undergone patient navigation to better understand health disparities in a community healthcare setting. We will evaluate self-reported insurance coverage to determine socio-economic status, minority status and age to define disparate elderly

populations. Navigator follow-up data will be used to assess outcomes and health status.

Wistar Institute (\$ 1,582,665)

Research Projects:

- Title: Isoform Specific p73 Regulatory Networks in Neurogenesis
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This systems biology project will unravel the isoform specific regulatory networks of *TP73* (tumor protein p73) gene involving complex cross-talk with other p53 family members and other transcription factors which control the expression of p73 target genes in normal neuronal development and in perturbed cellular conditions. This problem will be addressed by integrative computational modeling and NextGen sequencing-based experimental approaches using *in vitro* neuronal differentiation of P19 cells (embryonal carcinoma) treated with retinoic acid. This work will not only pave a new way to think about how to approach the problem of gene regulatory networks, but will also lead the research effort to understand the molecular mechanisms of cancer and other developmental disorders.
- Title: SECTM1 is a Novel Mediator of Melanoma Tumorigenesis and Progression
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Interaction of melanoma cells and melanoma-associated macrophages (MAMs) plays a critical role in melanoma development. However, the molecular mechanism by which this interaction contributes to melanoma progression is poorly defined. We have identified a novel factor, SECTM1, in the tumor microenvironment that can recruit and interact with MAMs. We have evidence that melanoma cells frequently express SECTM1, causing them to be more invasive and to migrate to distant sites more readily in experimental systems. In this project, we will try to determine the manner in which overexpression of SECTM1 causes melanoma invasive phenotype and the significance of SECTM1 on recruitment of macrophage associated with melanoma. This study will provide insight into the possibility that SECTM1 may be a potential new therapeutic target for melanoma therapy.
- Title: Regulation of EBV Infection and Latency by Editing of Viral MicroRNAs
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: Primary transcripts of certain microRNA (miRNA) genes (pri-miRNAs) are subject to one type of RNA editing that converts adenosine residues into inosine. Editing of pri-miRNAs controls synthesis and function of miRNAs. Epstein-Barr virus (EBV) infects more than 90% of the world's population. EBV causes a variety of human cancers such as Burkitt's lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma. EBV genome encodes multiple miRNA genes of its own. Primary transcripts of ebv-miR-BART6 (pri-miR-BART6) are edited in latently EBV-infected cells. The significance of pri-miR-BART6 RNA editing in viral latency and lytic replication will be investigated. Information obtained through this research project is essential for the future development of a new intervention for prevention and treatment of human diseases caused by EBV.
- Title: Laboratory Renovation Research Infrastructure
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The Wistar Institute is planning essential laboratory renovations to enable development of a new programmatic initiative in "Integrated Cancer Therapeutics."

This initiative is consistent with the Institute's long-term strategic plan and will provide a better understanding of the tumor microenvironment, resulting in the development of novel, more effective anticancer therapies. In support of this initiative, we plan to renovate an 1,800 square foot laboratory unit located on the first floor of the 1894 main research building of The Wistar Institute. The planned renovations, with their resultant creation of a new, state-of-the-art laboratory unit, is essential to the successful recruitment of a new leader to strengthen our integrated cancer therapeutics initiative.

May 29, 2013