

Health Research Formula Grants - State Fiscal Year 2011-12

Thirty organizations received health research formula grants totaling \$42,126,900 for the state fiscal year 2011-12. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2012 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 (\$52,011)

Research Project:

- Title: Task-switching: A Window to Cognitive Control Deficits in Aphasia
Type of Research: Clinical
Focus: Neurosciences
Purpose: Although aphasia has been characterized as a language disorder, the affected individuals show various non-linguistic problems, especially with cognitive control functions such as holding and manipulating information in working memory, and switching between tasks. A clearer understanding of these problems will bring us closer to understanding aphasia syndromes, and is likely to open new doors for rehabilitation methods that go beyond traditional linguistic therapies. This study launches a new investigation of task switching in aphasia, using a simple, well-controlled experimental design that has the potential to pinpoint the reasons why task-switching deficits arise in aphasia.

Allegheny-Singer Research Institute (\$98,254)

Research Project:

- Title: Utility of Cognitive Testing in the Detection of Residual Impairment Following Concussion
Type of Research: Clinical
Focus: Neurosciences
Purpose: This project will evaluate data obtained in the clinical evaluation of individuals who have sustained a concussion. The purpose of this research is to: 1) ensure that clinical evaluations and the tools that we use to evaluate patients following concussions are sufficiently comprehensive to be sensitive to the sequelae of concussion; 2) make the best-informed decisions regarding returning to normal activities and minimizing the risk of re-injury and problems at school and work; and 3) reduce the likelihood that financial resources are used to obtain data that are redundant, not clinically useful, and unnecessarily increase health care costs.

American College of Radiology (\$1,777,126)

Research Projects:

- Title: Evaluation of Biomarker Focused 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 biomarker focused projects.

- Title: Development and Evaluation of Novel Methods for Cancer Clinical Trial Interim Monitoring
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: Clinical trials provide first line scientific evidence necessary to advance treatment for cancer. With the increasing number of new treatment options being tested, there is a need for improvements in trial design and monitoring in order to a) terminate a trial in a timely manner when the therapy is ineffective, b) plan activities that take place during the trial efficiently (for example, interim safety and efficacy analyses), and c) derive and apply trial stopping rules and statistical power estimates that realistically reflect the interim data structure. To address these needs, we propose a series of methodological projects aimed at addressing current questions in clinical trial monitoring. These projects encompass a range of challenges in clinical trial conduct that apply broadly to cancer research as well as clinical research in general.
- Title: Biological Modeling of Tumor Control and Normal Tissue Complication for NSCLC Treated with SABR
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: Hypo-fractionated stereotactic ablative radiation therapy (SABR) is currently being used to treat early stage non-small cell lung cancer patients. The responses of tumor and nearby critical structures to SABR may be quite different from that of the conventional radiation therapy (RT) for which dose and radiobiological parameters for tumor control and toxicities of critical organs have been accumulated over the past two decades. Such parameters are still sparse and far from consensus for SABR treatment for lung cancer. The purpose of this study is to establish clinically useful nomogram for dose tolerance parameters and model the biological parameters for tumor control and normal tissue complication based on institutional data for hypo-fractionated lung SABR.
- Title: Quantitative Uncertainty Investigations for Clinical Trial Protocols
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: There are many factors that can confound the interpretation of results from cancer clinical trials that use radiation for therapy. Focus on such factors increases when a study gives an unexpected result that is counterintuitive. This was the case for a recent Radiation Therapy Oncology Group (RTOG) protocol, #0617 for Non-Small Cell Lung Cancer (NSCLC) where a lower dose arm gave significantly improved survival. The research proposed here examines radiation dose uncertainties that are either intentionally included in the protocol design process to improve accrual, or are unanticipated. Uncertainties for the RTOG 0617 protocol will be carefully analyzed to identify and quantify potential uncertainties.
- Title: Arterial Stiffness and Wave Reflections as Determinants of Regression of Left Ventricular Hypertrophy and Fibrosis Assessed with Cardiac MRI After Aortic Valve Replacement for Severe Aortic Stenosis
Type of Research: Clinical
Focus: Cardiovascular Sciences
Purpose: This project will evaluate the importance of arterial stiffness and wave reflections as determinants of persistent left ventricular (LV) hypertrophy and fibrosis (assessed using cardiac magnetic resonance imaging [MRI]) after correction of

severe stenosis (tightness) of the aortic valve. We aim to test the hypothesis that stiff arteries and increased wave reflections impede pumping of blood by the LV after aortic valve replacement and prevent adequate regression (improvement) of hypertrophy and fibrosis of the myocardium despite correction of aortic valve stenosis. Proof of hypothesis would identify potentially treatable abnormalities identifiable on imaging for future targeted therapy. This project also will assess the value of a novel cardiac MRI sequence to characterize myocardial fibrosis without the use of gadolinium.

Carnegie Mellon University (\$943,032)

Research Projects:

- Title: Correlated Structure in Motor Cortical Populations
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Motor control is one of the most important tasks the brain performs, and disorders of motor control affect millions of people. Although a wealth of psychophysical studies have led to good descriptions of the phenomenological processes underlying motor control and adaptation, the neural implementations of these processes are not well understood. One problem is that motor control is inherently a neural population phenomenon: movements are generated by groups of neurons that must work in a coordinated fashion to produce precisely timed muscle activation patterns. Using brain-computer interfaces, we will study how various features of the motor task act to shape the correlation structure of cortical population activity.
- Title: Non-invasive Optical Imaging of Perceptual Learning and Development
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The reliability and consistency of ordinary sight and hearing makes it natural to presume that perceptual systems are hard-wired and stable. Instead, however, they are highly dynamic and adapt flexibly to allow perceivers to discover regularities in the environment. In fact, over time perceptual expertise develops such that the brain's response to some classes of highly significant stimuli (faces, written words, speech) is markedly distinct. Our ultimate objective is to understand the learning mechanisms that serve the development of perceptual expertise to better understand developmental disorders (autism, dyslexia) and brain injuries that affect perception and to engineer devices to improve perception among those with impairments.

Children's Hospital of Philadelphia (\$3,521,179)

Research Project:

- Title: Highly Active Cell Therapy of Cancer
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: Our purpose is to develop engineered T cell therapies for B cell malignancies, leukemias, and certain specific solid tumors such as neuroblastoma and synovial sarcoma. Using chimeric antigen receptors (CARs) which target tumors and activate T cells, and an efficacious clinical-grade (GMP) ex vivo cell manufacturing system, we will continue our highly promising use of CAR-engineered T cells. This grant will support preclinical studies to optimize CARs in mouse xenograft models, as well as early phase clinical trials testing a variety of CAR-mediated T cell therapy approaches.

Children's Hospital of Pittsburgh (\$228,401)

Research Project:

- Title: Regulatory T Cells and Tolerance after Blood and Marrow Transplantation
Type of Research: Clinical
Focus: Immunology
Purpose: Tolerance after blood and marrow transplantation (BMT) is achieved eventually in most patients after 1-2 years post-BMT as they become independent of drugs to avoid rejection or graft-versus-host-disease (GVHD). Regulatory T Cells (Tregs) are known to be important in sustaining tolerance, however, there is a great gap of knowledge after BMT in humans regarding their activity in disease state (GVHD) compared to health (tolerance). In this project we will isolate and analyze Tregs from patients experiencing GVHD and contrast these to Tregs isolated from patients free of GVHD. Once functional prerequisites for tolerance are discovered, novel targeted therapies can be devised for those patients who suffer from GVHD.

Drexel University (\$1,320,271)

Research Projects:

- Title: An Interdisciplinary Approach to Directly Identify Changes in the miRNA-targeted mRNA Population Induced by HBV Infection
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This project will identify specific changes in the population of RISC-associated micro(mi)RNAs and their targeted mRNAs in HBV-infected hepatocytes. Further, bioinformatic analyses and data-mining will be used to define signaling networks that are affected by these alterations in miRNA targeting. We will use these results to propose mechanistic studies to determine how HBV controls miRNA signaling networks in ways that promote HBV replication and sensitize hepatocytes to the continued inflammatory insults associated with chronic HBV infection, ultimately leading to liver cancer. An understanding of these regulatory networks will help to identify new points of intervention in the treatment of HBV-induced progressive liver disease.
- Title: Novel Anti-Pancreatic Cancer Peptides from the ras-p21 Protein
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: We will establish that a kinase super-complex with oncogenic k-ras forms in pancreatic cancer, but not in normally proliferating cells, that is disrupted by peptides synthesized from oncogenic ras-p21 containing oncogenic amino acid substitutions that induce stereotypical changes in the three-dimensional structures of six domains of the oncogenic proteins. Two such peptides corresponding to these domains, PNC-2 and PNC-7, will then be tested to selectively arrest pancreatic cancer cell growth. We will test PNC-2 and PNC-7 for their ability to eradicate human pancreatic cancers transplanted into nude mice. We will also test the ability of these peptides to eradicate a syngeneic pancreatic cancer utilizing an established murine model.
- Title: Impaired T Cell Immunity and Survival in Neonatal Influenza Virus Infection
Type of Research: Biomedical
Focus: Immunology
Purpose: In order to simulate more closely neonatal infection and determine the neonatal responses to viral infection, we have developed a neonatal mouse model to examine acute influenza infection at day 2-3 of life. Preliminary data shows that the neonatal C57Bl/6 mice exhibit significant mortality compared to adult mice. The

specific aims of this project are to: 1) determine the mechanism of increased mortality in viral pulmonary infection of neonatal mice and 2) investigate influenza virus-specific CD8⁺ T cell responses in neonates.

- Title: Epigenetic Modulation in an Animal Model of Depression
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The purpose of this project is to understand the neuroadaptive mechanisms that occur in the central nervous system (CNS) in response to chronic inflammation and immune dysregulation and contribute to a depressive behavioral phenotype. We will study a model of chronic inflammation in the mouse where immunization with Bacille Calmette Guerin leads to activation of the innate immune response and the development of a depressive phenotype. We expect that the findings from these studies will suggest novel targets for treating patients with inflammation related Major Depressive Disorder (MDD).
- Title: Characterization of the Effects of Non-thermal Plasma on Liquids and Cells
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: In order to exploit the potential for clinical applications, from enhancing wound healing, to sterilizing tissues, to inducing localized apoptotic cell death in tumor tissue, a mechanistic understanding of the interaction of non-thermal plasma with living tissues is required. Our initial studies using mammalian cells in culture revealed that non-equilibrium plasma (NEP) has dose-dependent effects that range from increasing cell proliferation to inducing apoptosis; these effects are primarily due to formation of intracellular reactive oxygen species (ROS). We propose to study the effect of NEP on molecules in solution and on DNA damage pathways to better understand the biological effects.
- Title: Novel Antagonists of CX₃CR1 to Prevent Skeletal Metastasis
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The overall goals of this proposal are to synthesize the first small-molecule, non-peptide antagonists of CX₃CR1 and produce pre-clinical evidence that these compounds, by interfering with CX₃CR1-FKN interactions, impair the dissemination of breast cancer cells to the skeleton. We propose a radical switch in the current standard of care for breast cancer patients, with the implementation of systemic therapeutic measures to be started immediately after breast surgery and maintained during the time preceding second surgery or local adjuvant treatments.
- Title: Astrocyte Senescence as a Component of HIV-related Neurodegeneration
Type of Research: Biomedical
Focus: AIDS and Related Research
Purpose: Aging of the HIV-infected population places the disease in a distinctive set of biological and psychosocial influences. Our main purpose is to identify common factors and mechanisms in the interplay of aging and HIV. We find that astrocytes enter into senescence in response to oxidative stress and HIV-1 proteins and that the brains of aged individuals and individuals with Alzheimer's disease are highly populated by senescent astrocytes. Because HIV infection is associated with the release of neurotoxic factors which induce cell stress, we plan to evaluate the impact of viral factors on astrocyte senescence. Our studies will provide information for successful therapeutic efforts to alleviate HIV-associated neurocognitive disorders during aging.
- Title: A β Peptide and Vascular Dysfunction in Alzheimer's Disease
Type of Research: Biomedical

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

Purpose: Vascular dysfunction occurs in Alzheimer's disease, however, the role of vascular dysfunction in Alzheimer's disease initiation and progression is not known. Furthermore, the effect of the mechanical environment on brain microvascular endothelial cells has not been extensively studied. This project will determine the effect of A β peptide on vascular endothelial cell response to fluid shear stress and angiogenesis. While current medications can slow the progression of dementia symptoms, there are currently no treatments to prevent, halt, or cure Alzheimer's disease. These fundamental studies will elucidate new roles for A β peptide and the microvasculature in the disease, and lead to new targets for pharmaceutical therapies.

- Title: Interactive Roles of Interstitial Flow and Hepatitis B Virus in Liver Cancer Progression

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The purpose of the project is to determine how interstitial flow affects the invasive behavior of primary liver cancer cells, and whether this process is potentiated by hepatitis B infection. Liver cancer is one of the most common cancers worldwide, resulting primarily from chronic hepatitis B infection, and incidence in the United States is rising. The processes underlying the link between liver cancer and hepatitis B remain poorly understood. At the same time, the role of biomechanical forces in cancer progression is increasingly being appreciated. Our project will elucidate interactions between biomechanical forces and hepatitis B infection to understand their contributions to liver cancer invasion, and develop targeted therapies to halt these processes.

- Title: Encapsulation Systems with Tunable Permeability for Improved Stability and Release Profile of Encapsulated Materials of Biomedical Importance

Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology

Purpose: Oxidation of encapsulated bioactive molecules such as drugs and vitamins results in loss of their activity. The oxidation process within these encapsulation systems is initiated by transport of oxidants such as free radicals generated in the aqueous phase and transported across the interfacial layer of the encapsulation system and into the encapsulation system. In the present research, we propose to design encapsulation systems with tunable permeability to minimize the transport of these free radicals across encapsulation system, thus reducing the oxidation of encapsulated materials of biomedical importance. Tunable permeability will also enable enhanced control over the release profile of these encapsulated bioactive molecules.

Duquesne University (\$107,464)

Research Projects:

- Title: A Biomaterial Approach to Inhibit Melanoma Growth and Metastasis in Mice
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of this project is to test a novel strategy that aims to neutralize transforming growth factor-beta (TGF β), a cytokine implicated in cancer immune escape and metastasis. Antibodies have been developed to inhibit TGF β functions in cancer patients. It was thought that anti-TGF β antibodies could be more effective when administered directly into tumors, but studies have shown that even locally injected antibodies do not accumulate in cancer lesions. We have designed

and characterized a peptide-based injectable system that can circumvent this problem. In essence, we are proposing a novel way to use antibodies to inhibit dissemination of cancer cells by decreasing local TGF β concentration.

- Title: Determination of the Role of Pilin Glycosylation in *Pseudomonas Aeruginosa* Infections

Type of Research: Biomedical

Focus: Infectious Diseases and Microbiology

Purpose: The purpose of this project is to discover new knowledge concerning the distribution, among clinical isolates, of *Pseudomonas aeruginosa* strains producing glycosylated pili. This organism is a major cause of hospital-acquired pneumonia. We have found that *P. aeruginosa* strains producing glycosylated pili are associated with acute pneumonia. Respiratory tract damage caused by smoking includes a greatly increased susceptibility to pneumonia. The information gained from this project can be applied to the prevention or treatment of acute pneumonias caused by this organism. Prevention would be through vaccine design based on pilus structure. Treatment would be through the development of chemotherapeutic agents that interfere with pilin glycosylation.

Fox Chase Cancer Center (\$2,472,183)

Research Projects:

- Title: Impacts of Inhibitory Receptors on Signaling Competence of NK Cells
Type of Research: Biomedical
Focus: Immunology
Purpose: Mature natural killer (NK) cells express inhibitory receptors that prevent autoimmune attack by recognizing MHC class I molecules on all normal cells of the body. During NK cell development, however, inhibitory receptor signaling paradoxically promotes maturation to functional competence. We have previously shown that NK cells from genetically-modified mice with reduced activation signaling are more mature and more functional. In this project, we will define how inhibitory receptors and their MHC class I ligands promote and suppress the signaling competence of NK cells. Our findings could lead to immunotherapies that enhance the signaling competence of NK cells to improve their attack of tumor cells in patients.
- Title: Pre-BCR Function Selecting Novel B Cell Receptors in Chronic Lymphocytic Leukemia
Type of Research: Biomedical
Focus: Immunology
Purpose: B cell chronic lymphocytic leukemia (CLL) is the most common leukemia of adults in Western countries, characterized by usage of distinctive B cell receptor (BCR) heavy and light chain genes. We will test CLL heavy chains for capacity to associate with surrogate light chain into a pre-BCR. Our hypothesis is that the striking biases seen in CLL heavy chains arise because their precursors come from a distinctive B cell development process that selects for weak association with surrogate light chain. We will utilize procedures for measuring pre-BCR assembly and compare this with the induction of proliferation. Our work will establish the significance of BCR in development of CLL precursors, potentially revealing new avenues for treatment.
- Title: Dissecting Role of ThPOK in T Cell Development through TALEN-mediated Exon Swapping
Type of Research: Biomedical
Focus: Immunology

Purpose: ThPOK belongs to the POK family of transcription factors, which are known to play critical roles in development and cancer. We have shown that ThPOK has a non-redundant essential function in T cell development, and is a potent oncogene when overexpressed in T cells. Here we propose to elucidate how ThPOK carries out these functions using genetic approaches in mice. In particular, we will use site-specific TALE nucleases to generate knockin mice in which either the entire ThPOK coding region or individual functional domains are replaced by the corresponding region of related POK factors. This will establish whether the requirement for ThPOK in T lymphoid development and cancer reflects a unique function or expression pattern.

- Title: Characterization of Novel Epigenetic Factors
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Epigenetics describes the process through which specific cell types are programmed from a single DNA blueprint. This is accomplished through chromatin modifications that direct activation or silencing of specific gene sets. Epigenetic factors that guide and place these modifications can thereby control cellular identities, e.g., differentiated, pluripotent, aged, and cancer. We used an unbiased functional screen to identify novel human factors that control epigenetic processes. The purpose of this research is to characterize these novel epigenetic factors and their networks. This work will contribute to our understanding of development, epigenetic diseases, and normal aging.
- Title: Role of Lin28B in the Enhanced Cancer Susceptibility Caused by Inactivation of Rpl22
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to investigate the basis for induction of the stemness factor, Lin28B, by inactivation of Rpl22 and to determine how Lin28B induction increases the susceptibility of Rpl22 mutant cells to malignant transformation.
- Title: Chemosensitization of Cancer Cells by Inhibition of a Transcription Network
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Tumor recurrence is a major obstacle to effective cancer therapies. This is of the utmost urgency for cancers that escape early detection because their response rate is usually poor by the time of diagnosis. We conducted a genome-wide siRNA screen of pancreatic cancer cells and identified a transcription network that was critical for survival to gemcitabine. We hypothesize that this transcription network was usurped during tumorigenesis to allow cancer cells to survive intrinsic and extrinsic stresses. This project will test: 1) if these transcription factors are also important for survival to other chemotherapeutics besides gemcitabine, and 2) if this pathway is used in other cancers such as ovary, lung and colorectal.

Geisinger Clinic (\$75,516)

Research Project:

- Title: Reducing the Burden of Breast Biopsy in Women with Abnormal Screening Mammograms
Type of Research: Clinical
Focus: Immunology
Purpose: The impact of screening mammography in reducing the rate of breast

cancer mortality is indisputable but it has limitations, largely due to false negative and false positive results. Annually, of the 1,700,000 women who undergo breast biopsies, 80% are diagnosed with benign conditions of the breast of no clinical significance, at an economic cost of \$3.5 billion. High throughput and genomic technologies allow the use of auto-antigen-antibody complex as serologic biomarkers for breast cancer screening. The objective of this study is to employ these technologies to improve and validate the performance precision of a panel of serum autoantibody to autologous cellular antigens expressed in breast cancer among women with mammograms requiring breast biopsies.

Haverford College (\$28,802)

Research Project:

- Title: Mapping Influenza Hemagglutinin Proteins by Raman Spectroscopy
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Hemagglutinin (HA) is one of the two main surface proteins on the influenza virus, and changes in its shape and amino acid sequence have been associated with increased virulence in strains like the 1918 "Spanish flu" and the 2009 "swine flu" outbreaks. The aim of this project is to use epsilon-deuterated histidine (His) as a site-specific probe of each of the surface histidine residues in HA to report both their protonation states and their level of solution exposure. Using Raman spectroscopy of C-D vibrations located on surface His residues as a novel spectral approach, we will establish a spectral map of the HA surface and then observe how the environment of the His residues changes across different strains.

Hepatitis B Foundation (\$654)

Research Project:

- Title: Assessing Hepatitis B Knowledge Change Following Education Among High Risk Asian and Pacific Islander Communities in Pennsylvania
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: This project will determine the current level of hepatitis B knowledge and awareness, and test the ability of a culturally and linguistically competent educational intervention to improve hepatitis B knowledge among high-risk Asian and Pacific Islander (API) communities in Southeastern Pennsylvania. API communities have disproportionately high rates of chronic HBV infection and traditionally low rates of accurate hepatitis B knowledge. Using anonymous data collected from 300 individuals, we will use biostatistical methods to assess the baseline knowledge levels in the community and assess knowledge change after education. Results from this study will allow us to better define appropriate public health education programming for these high-risk communities. 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.

Lankenau Institute for Medical Research (\$136,919)

Research Project:

- Title: 2-Deoxyglucose and Hydroxyethyl Disulfide in Improving the Response of Human Colon Cancer Cells to Radiation
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: Hydroxyethyl disulfide (HEDS) inhibits the function of DNA repair protein and glutathione resulting in a better response of oxidative pentose phosphate cycle deficient or glucose deprived cancer cells to radiation. However, it is not efficient in improving the response of glucose containing cancer cells to radiation due to its detoxification by the oxidative pentose phosphate cycle, which requires glucose for its function. Increasing the susceptibility of the glucose containing tumor cells to HEDS is clinically relevant since all tumor cells are not glucose deprived. We will determine the effects of HEDS and 2-deoxyglucose, a competitive inhibitor of pentose cycle, in increasing the radiation response of glucose containing human cancer cells.

Lehigh University (\$80,151)

Research Projects:

- Title: Automated Analysis of Microtubule Dynamics to Study Cytoskeleton-Targeted Chemotherapies
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purposes of this project are to determine whether the tumor suppressor protein, p53, regulates the dynamic turnover of the microtubule cytoskeleton and whether p53 expression protects cells from the chemotherapeutic drug, Taxol. Automated computer-based image analysis methods will be applied throughout.
- Title: Cortisol, Estradiol, and Psychosocial Stress as Predictors of Postpartum Depressive Symptoms
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to examine how prenatal psychosocial stress and the hormones cortisol and estradiol interact to affect risk for postpartum depression (PPD). Research shows that prenatal stress can increase risk for PPD. The body's reaction to stress is regulated by cortisol, and elevated levels of estradiol can inhibit cortisol's ability to do so. Both cortisol and estradiol increase dramatically during pregnancy, which may increase sensitivity to stressful events. This project uses twice-daily saliva samples and brief questionnaires to examine bidirectional associations between these hormones and reports of stress during a one-week period during pregnancy, as well as how their connections predict postpartum depressive symptoms.

Lincoln University (\$47,451)

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.

Magee Womens Research Institute (\$971,921)

Research Projects:

- Title: In Vivo Analysis of Human C19MC MicroRNAs in a Transgenic Mouse Model
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: The C19MC locus on chromosome 19 harbors the largest cluster of microRNAs (miRNAs) in humans. Interestingly, these miRNAs are primate-specific and uniquely expressed in placental trophoblasts although they were recently found expressed in several forms of cancers. In trophoblasts the C19MC miRNAs constitute the most abundant family of miRNAs and hold a considerable regulatory potential. In this project, we seek to develop a transgenic mouse model that will allow us to investigate the function of this unique family of miRNAs.
- Title: Glycocalyx Syndecan-1 and Preeclampsia Pathogenesis
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: The purpose of the project is to learn more about what causes the human pregnancy-specific hypertensive disease preeclampsia. Our preliminary data suggest that women with preeclampsia have reduced expression of the heparan sulfate proteoglycan syndecan-1 (SDC-1; CD138) in the placenta, correlating with reduced concentrations of soluble SDC-1 in the maternal circulation. SDC-1 and the related protein glypican-1 (GPC-1) may play pivotal roles in regulation of cell interactions and function. The project will 1) test if changes in maternal plasma soluble SDC-1 or GPC-1 herald the development of preeclampsia, and 2) study the expression and biologic function of these factors in normal and abnormal placenta.
- Title: Targeting Women's Cancer Cells with Novel Cell Cycle Inhibitors Blocking Centrosome Clustering
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Centrosome aberrations cause cancers and birth defects by inducing chromosome errors leading to aneuploidies after mitosis. Genomic instabilities correlate with the degree of centrosomal abnormalities. At mitosis, extra centrosomes increase spindle multipolarity, a hallmark of many cancers. Recently, some cancers cluster supernumerary centrosomes at a bipolar spindle, avoiding multipolarity and activation of the internal cell death program while preserving reasonable genomic stability after cell division. Here, dynamic confocal imaging with living markers for centrioles and microtubules is used to investigate cell cycle inhibitors' impact on centrosome clustering and multipolarity at mitosis in normal somatic and cancerous cells.
- Title: Regulation of Spermatogenesis by Classical and Non-classical Testosterone Signaling
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: Testosterone (T) is essential for male fertility. However, there is a lack of information regarding the mechanisms by which T acts to support spermatogenesis and male fertility. Our studies will identify the molecular and cellular mechanisms by which T supports critical spermatogenesis processes including maintaining the blood testis barrier (BTB), preventing the premature release of developing germ cells and stimulating the release of mature spermatozoa. These studies will provide 1) information needed to treat specific male infertility conditions and 2) long-needed new targets for male contraceptive research.

Monell Chemical Senses Center (\$210,715)

Research Projects:

- Title: Characterization of the Lgr5-expressing Adult Taste Stem Cells
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Identification and characterization of adult taste stem cells may lead to therapies for those most affected by loss of taste cells: the elderly, patients with head and neck cancers and patients undergoing radiation or chemotherapy. Regenerative medicine approaches that coax adult taste stem cells into dividing, differentiating and repopulating taste buds may have therapeutic value leading to improvement of taste function and quality of life for those affected.
- Title: Salivary Calcium and Taste
Type of Research: Biomedical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to study the influence of salivary calcium content on taste perception in humans.

National Disease Research Interchange (\$59,685)

Research Project:

- Title: Genetic Variants that Affect Susceptibility to Microvascular Complications of Diabetes
Type of Research: Health Services
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: The 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. The overall aim of this project is to identify genetic variants that predispose type 1 diabetes patients to, or protect them from, the development of microvascular complications of diabetes (MCD). Identification of these variants will contribute to understanding the genetic mechanisms and pathways of T1D-associated retinopathy, nephropathy and neuropathy. We will also continue tracking clinical changes in T1D and complications.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation (\$851,360)

Research Project:

- Title: Markers and Mechanisms of Trastuzumab Resistance and Cardiotoxicity
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to identify molecular changes associated with treatment failure in Her2-positive breast cancer patients treated with trastuzumab and chemotherapy. Specifically, specific molecular changes that have been implicated in preclinical models to be responsible for trastuzumab treatment failure will be investigated. Identification of molecular changes that are associated with treatment failure helps to identify those patients who may need additional treatment and may help to identify those pathways that are most critical to trastuzumab response and to understanding treatment success as well as failure.

Pennsylvania State University (\$6,637,701)

Research Projects:

- Title: Development of Bioinformatics Methods for Medical Research
Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology

Purpose: The purpose of this project is to develop and implement a wide array of bioinformatics tools for the analysis of large biological datasets, including those related to genomic, epigenetic, protein, and metabolomics experiments.

- Title: How Cells Respond to Stress
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Recent studies have highlighted the fact that persistence of cancer cells depends on their successful adaptation to local stresses induced by local hypoxia and acidification. Moreover, our recent data indicating that eukaryotic cells exhibit stress induced mutations may suggest a mechanism for increased mutations rates in cancer cells. We plan to determine the mechanisms underlying stress resistance and stress induced mutation in a tractable model system. These components could provide novel targets for therapeutic intervention and our experimental system provides a test bed for evaluating the feasibility of such approaches.
- Title: Anal Human Papillomavirus Infection in HIV-infected Women
Type of Research: Biomedical
Focus: AIDS and Related Research
Purpose: Human papillomavirus (HPV)-related anal cancer is an emerging health problem in people infected with human immunodeficiency virus (HIV). Few longitudinal studies have been conducted to understand the natural history of anal HPV infection in HIV-infected women. We propose this project with the goal to prospectively investigate risk factors associated with incident and persistent anal HPV infection in a cohort of rural HIV-infected women. This project will provide new evidence on the epidemiology and immunopathogenesis of anal HPV infection, and will help clinicians to plan appropriate strategies for anal cancer prevention in HIV-infected women.
- Title: Structural Studies of Virus and Receptor Interactions
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: Cryo-electron microscopy and X-ray crystallography will be used to pursue a structural study of the neurotropic enterovirus 71. The virus will be reconstructed in 3-D alone and complexed to receptor to investigate receptor use and the pathogenic consequences. There are no known structures, little understanding of virulence determinants, and no vaccine for EV71. The aim of our study is to support other ongoing efforts by elucidating the capsid structure to understand viral function, especially the mechanism of receptor recognition.
- Title: T-Cell Immunity to Polyomavirus Infection
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: Polyomaviruses silently infect most humans, but can cause life-threatening disease in the setting of depressed immunity. No effective antiviral therapies are available. Because these viruses only infect their natural host reservoirs, we have limited understanding of the immunological mechanisms required to contain them. Studies proposed in this project use mouse polyomavirus to define determinants guiding differentiation of effective antiviral CD8 T cell responses that are needed to keep these smoldering infections in check.
- Title: Computational Tool Development for Supporting Biomedical Research
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: We will develop an integrated software system for biomedical applications

of human genetic-variation data, ranging from single-base differences in DNA sequence, to variation in the number of copies of a gene, to differences in abundance of certain gene transcripts, to perturbations in a network of protein interactions. The goal is to provide, in an easily accessible form, the tools needed to reliably infer biological function and consequences of variation from human genome data. The choice of tools to implement will be driven by the needs of collaborating physicians at Penn State's College of Medicine.

- Title: A Pilot Study of Personalized Medicine for Pediatric Asthma
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: We propose to conduct a pilot study to evaluate the effectiveness of personalized asthma care for children, a new treatment approach for this complex disease. The control arm of the trial will involve the current standard primary care asthma management guided by the National Institutes of Health's National Asthma Education and Prevention Program (NAEPP), and the intervention arm will involve personalized asthma management (NAEPP management enhanced by incorporating genetic and environmental information).
- Title: Development of Pharmacophore-based QSAR of Sphingosine Kinase 1 Inhibitors
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The long-term goal of this project is to develop potent sphingosine kinase 1 (SphK1) inhibitors (SKI) as effective therapeutic agents for pancreatic cancer (PC). In this regard, we have already identified several novel lead "drug-like" SphK1 inhibitors. However, before any target-specific lead compound is used as a therapeutic agent in human studies, a lead compound must be optimized to maximize the therapeutic index and minimize side effects. To optimize these SKI lead compounds, we will develop 3D pharmacophore models for the SKI lead compounds and perform quantitative structure activity relationship (QSAR) analyses. We will then test the *in vitro* efficacy of the QSAR analysis generated "hit" SKI compounds.
- Title: Pharmacoeconomic Analysis of Current and Alternative Reimbursement Models for Actinic Keratoses
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: This project describes a 3-phase project to investigate and implement an innovative method of reimbursement for a common and important skin condition, actinic keratoses (AK). AK are premalignant skin lesions; the management by various means, is the most common outpatient dermatologic procedure and in 2004 accounted for over \$1 billion in direct healthcare costs. The overall goals of this project are to describe the current patterns in AK management, to develop an alternative model for reimbursement of AK and to test this model in a real-world clinical setting to ensure quality patient care and financial feasibility.
- Title: Development and Testing of a Novel Simulation Technology for Fracture Treatment
Type of Research: Health Services
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of the project is to develop and test a novel simulation technology for complex bone fracture treatment. The simulation technology will estimate the biomechanics involved in the fixation and repair of complex fractures. Simulations will be validated by biomechanical experiments. Potential uses include determining the optimal surgical fixation strategy for repair of difficult fractures in

civilian and military patients. The project also aims to test the ability of the simulation to convey fundamental treatment concepts in a group of orthopaedists.

- Title: Does Enhanced Cannabinoid Receptor 1 (CB1) Signaling Increase the Risk of Drug Abuse?
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The primary focus of my laboratory is to determine how activation of the endocannabinoid system modulates alcohol and opiate addiction. We have produced mutant mice expressing a hypersensitive for cannabinoid receptor 1 (CB1). These S426A/S430A mutant mice also show an exaggerated and prolonged response to the treatment with $\Delta 9$ -THC, the principal psychoactive component of marijuana. The exaggerated and prolonged response to $\Delta 9$ -THC and endocannabinoids establishes these mice as a novel model for testing the effects of enhanced CB1-mediated endocannabinoid signaling on drug addiction in vivo. This project will determine whether "overactive" cannabinoid signaling potentiates reward and dependence for alcohol and morphine. Completion of this study will shed light on whether abuse of these drugs might be potentiated by consumption of marijuana or medical conditions such as obesity that lead to increased systemic levels of endocannabinoids.
- Title: Mechanisms Underlying Retrovirus Genomic RNA Packaging
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: The purpose of this research project is to elucidate the molecular mechanisms underlying retroviral RNA encapsidation using the oncoretrovirus Rous sarcoma virus (RSV) as a model system. RSV is unique among retroviruses because viral RNA packaging appears to be initiated in the nucleus of infected cells. Understanding the detailed mechanism of retroviral genome incorporation is important for the development of novel antiretroviral therapies that disrupt genomic RNA encapsidation and to design optimal gene therapy delivery using retroviral vectors.
- Title: Mechanism of Red Cell Invasion by Malaria: Role of Antibodies and Complement
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: *Plasmodium falciparum* is the most virulent of all the human malaria parasites and there is no effective vaccine against this parasite. The invasion of red blood cells (RBCs) is an appealing target for vaccine development. However, this goal has been elusive. Although volunteers immunized with parasite antigens produce antibodies that can inhibit the parasite *in vitro*, there is no protection *in vivo*. We believe the explanation for this discrepancy lies in the parasite's ability to use complement activation for its own advantage, but this has never been demonstrated. Therefore, in this study we will test whether complement activation via antibody-dependent or independent mechanisms enhances the invasion of RBCs by the malaria.
- Title: Oncogenic Drivers/Mutations/Biomarkers in Screening Participants for Early Detection of Lung Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to identify and validate oncogenic drivers (mutations and biomarkers) for the early detection of lung cancer in individuals at high-risk for lung cancer and characterize the nodules and preneoplastic lesions in screening participants with presence/absence of oncogenic drivers (mutations and biomarkers). Testing for mutations/gene rearrangements as biomarkers for early

detection with integration of molecular diagnostics in tissue samples/bronchial lavage will be key to develop and validate personalized management approaches. The current project is designed to pave the way for individualizing therapy for these subjects at high risk for development of lung cancer.

- Title: Genetic Analysis of a Multigenerational Cohort with Familial Interstitial Pneumonia
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this study is to phenotype; establish a bio-repository and genotype a multigenerational Pennsylvania family with familial interstitial pneumonia (FIP) with the goal of discovering the genetic cause of this devastating disorder in this family and to seek evidence of genetic anticipation across the generations. The discovery of this new knowledge will lead towards better understanding of the pathogenesis of this disorder in this afflicted family with potential application to familial interstitial pneumonia as well as to sporadic pulmonary fibrosis and to future prevention and treatment.
- Title: 3D Printing of Personalized Artificial Bone Constructs Having Stem Cell Mobilizing Nanotopographic Surfaces
Type of Research: Biomedical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: Cortical bone allografts can be limb sparing when used to treat critical sized bone defects that result from traumatic injuries or resection of an osteosarcoma. However, there are many complications associated with these procedures. We propose a radically new approach in which we will use 3D printing and bioimaging to create an artificial bone construct (ABC), with a specific scale nanotopographic surface, personalized to a particular defect in a particular patient. The nanotopographic surface we will use has previously been shown by us to stimulate osteogenesis by mobilizing stem cells, enhancing their adhesion to the graft and stimulating their differentiation to bone forming osteoblasts.
- Title: Nanodiscs as a Vehicle for Rapid Throughput Membrane Protein Characterization
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Membrane proteins are the hallmark of cancer and consequently one of the major targets of various drug therapies. Therapy development relies on structure-guided inhibitor design, which requires protein structures. However, membrane proteins account for ~2% of all available structures as they are labor-, time- and capital- intensive and are often of distantly related bacterial homologs or heavily engineered, limiting their relevance to human health. We will develop a high throughput system (HTS) to extract membrane proteins in lipid nanodiscs; a near native environment. This HTS will allow, for the first time, rapid characterization of membrane protein structure by biochemical and biophysical methods including small-angle X-ray scattering (SAXS), NMR and EM.
- Title: Restoration of Wntless Function: A Novel Approach for Pharmacotherapy of Opioid Addiction
Type of Research: Biomedical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Opioid drugs are the first line of therapy for over 75 million Americans who suffer from chronic pain. However, the addiction risk associated with their use has become a major public health problem. We have developed a novel paradigm to

assess addiction-like behavior for heroin in rats. This model revealed that greater addiction-like behavior for heroin is linked to reduced expression of Wntless (WLS), a mu-opioid receptor (MOR) interacting protein whose function is inhibited by opioid drugs. In this project, we will test the hypothesis that restoration of WLS levels in the brain will prevent acquisition of addiction-like behaviors for heroin as well as relapse.

- Title: Astrocyte-Neuron Transformation: A Novel Approach to Stroke Recovery
Type of Research: Biomedical
Focus: Neurosciences
Purpose: An entirely novel approach to neuronal regeneration has been developed in which activated astrocytes can be induced to undergo transdifferentiation to glutamatergic neurons by infection with a retrovirus that expresses a specific neuronal promoter. This study will determine whether such an approach is able to promote the regeneration of neurons by infecting the astrocytes surrounding the core of the stroke, and whether these neurons are able to integrate with neurons in surviving tissue and ultimately promote the re-establishment of motor and sensory functions lost following stroke.
- Title: Fundamental Properties of Tissue-associated HSC-T_{regs} that Relate to Anti-Autoimmunity
Type of Research: Biomedical
Focus: Immunology
Purpose: Regulatory T cells (T_{reg})-based immunotherapy is a highly promising treatment for a variety of autoimmune diseases. Monoclonal tissue-associated effector T_{regs} are the optimal populations for T_{reg}-based immunotherapy. However, such immunotherapy is often not feasible due to difficulties in obtaining sufficient cells from patients. We have developed a novel system to generate antigen (Ag)-specific T_{regs} from hematopoietic stem cells (HSC). The *objective* in this application is to mechanistically define the fundamental properties of tissue-associated HSC-T_{regs} that relate to anti-autoimmunity activity. The proposed research will provide new insight for generating highly reactive tissue-associated HSC-T_{regs} and in so doing drive forward use of therapeutic T_{regs} for cell-based therapies.
- Title: Development of Artificial Red Cells as a Tool To Understand the Biology of Malaria Parasite
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this project is to develop simplified artificial red cells from the ground up that can be invaded by *Plasmodium falciparum* malaria parasites.

Philadelphia College of Osteopathic Medicine (\$16,761)

Research Project:

- Title: Evaluation of Tetrahydrobiopterin/Dihydrobiopterin Ratio in Vascular Injury Tissues
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: Vascular endothelial dysfunction is an early event in vascular injuries, such as ischemia/ reperfusion injury, diabetes, hypertension and extracorporeal shock wave lithotripsy. Endothelial nitric oxide (NO) synthase (eNOS) is the primary enzyme to release NO in the presence of tetrahydrobiopterin (BH₄) to facilitate normal vascular function. In vitro, eNOS can be a source of superoxide when the ratio of BH₄ to dihydrobiopterin (BH₂) is reduced, and is referred to as eNOS uncoupling. However, the role of eNOS uncoupling in vascular injury has not been

well established in vivo. Therefore, measuring the ratio of BH_4 to BH_2 in vascular injury tissues is critical to identify a potential treatment strategy (e.g. BH_4) to reduce endothelial dysfunction.

Pittsburgh Tissue Engineering Initiative (\$8,731)

Research Project:

- Title: Electrospun Scaffold Substrata for Culture of Osteoprogenitor Cells
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Osteoblasts and/or osteoprogenitor cells are crucial in bone healing. In this project we will synthesize biomimetic scaffolds made up of electrospun collagen fibers containing hydroxyapatite nanoparticles. These scaffolds will be tested for their ability to bind to allow the propagation and expansion and differentiation of osteoprogenitor cells in vitro.

Salus University (\$39,748)

Research Project:

- Title: Study of a Calcium-Sensor Protein Related to Retinal Dystrophy
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Calcium-binding proteins, GCAPs, regulate activity of guanylyl cyclase in photoreceptors. They have been linked to various types of hereditary retinal dystrophy. The purpose of this project is to investigate the structural and functional properties of GCAP1 as a calcium sensor of guanylyl cyclase. We want to establish how the naturally occurring co-translational modification in GCAP1 known as N-myristoylation interacts with the protein environment and how this interaction determines affinity for the cyclase and calcium in normal GCAP1 and in GCAP1 affected by mutations linked to congenital retinal dystrophy.

Temple University (\$2,186,053)

Research Projects:

- Title: Infrastructure: Construction of the Temple Clinical Research Institute
Type of Research: Clinical
Focus: Research Infrastructure Project
Purpose: Academic medical centers have an obligation to pursue cutting-edge research that links the research bench with the clinical arena and facilitates the ability to bring cutting edge technologies to the community that the academic center serves. There is a particular need to improve the access of ethnic and racial minorities to clinical research protocols as these groups have historically been excluded from many clinical research studies. The purpose of the Temple Clinical Research Institute is to facilitate and enhance our ability to undertake cutting-edge clinical research both in our community and across the Commonwealth.
- Title: The Development of Biofilm Inhibitors
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This project will develop a library of synthetic analogs of the natural product cyclic diguanylate, which is involved in many processes in pathogenic bacteria. The compounds will be tested for biofilm inhibition and antibacterial properties. Ultimately this work has the potential to yield an entire new class of antibiotics.

- Title: Effects of Obesity and Environment on Oocyte Quality and Inheritance
 Type of Research: Biomedical
 Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
 Purpose: Recent studies in mice indicate that maternal obesity can lead to intrauterine growth restriction and subsequent obesity in progeny. Obesity can lead to disruptions in oocyte-follicle communication, and reduced egg quality that is later manifested as altered embryo phenotype. Maternal exposure to environmental “obesogens” can promote obesity in progeny. The goals of this project will be to define the impact of maternal obesity and environmental obesogens on oocyte quality, define the mechanisms of these effects in the oocyte and early embryo, determine the ability to mitigate these effects via changes in maternal diet, and investigate the potential contributions of environmental obesogens to the obesity epidemic.
- Title: Breast Lesion Characterization Using Tactile Imaging System for Patient-Centric Healthcare
 Type of Research: Biomedical
 Focus: Bioengineering, Surgical Sciences and Technology
 Purpose: The long-term goal of this research is to develop an easy-to-use premalignant tumor identification system for breast tumors. This will be available in primary care physicians’ offices near the patients’ homes. The purpose of this project is to develop a tactile image platform for *in vivo* breast lesion characterization using a tactile imaging system, which is a critical step towards our long-term goal. The literature shows that malignant breast tumors are stiffer than benign tumors. If a system can detect the size, mobility, and elasticity of the tumor, this information can be used to decide whether further medical help should be sought. We propose to develop a tactile imaging system that characterizes the lesion through its mechanical properties.
- Title: Neurodevelopmental Markers of Intermittent Explosive Disorder: From Neurotransmitters to Neighborhoods
 Type of Research: Health Services
 Focus: Health of Populations, Behavioral and Biobehavioral Processes
 Purpose: The proposed study will evaluate neurodevelopmental and contextual processes linked to Intermittent Explosive Disorder (IED). This will be done by comparing 30 youth with IED and 30 youth without IED aged 12-14 at baseline, 6 month and 1 year follow-up on a comprehensive battery of self-report, behavioral, neurofunctional and biological measures. This will be the first comprehensive examination of neurodevelopmental and contextual factors associated with IED among at-risk adolescents. Study data would be used for a large scale (R01) multi-site extension of the proposed study and a (R34) treatment study to address biological, cognitive-affective, and contextual problems identified during this developmental period.

Thomas Jefferson University (\$2,899,793)

Research Projects:

- Title: FOXD3-ErbB3 Signaling as an Adaptive Response to RAF Inhibitors
 Type of Research: Biomedical
 Focus: Oncological Sciences
 Purpose: Melanoma is the deadliest form of skin cancer and represents a paradigm for drug resistance. The serine/threonine kinase, B-RAF, is somatically mutated in 40-60% of melanomas. In phase 1-3 trials with mutant B-RAF melanoma patients, the RAF inhibitor, PLX4032/vemurafenib, has yielded promising results. However, some patients are intrinsically resistant to PLX4032 and initial responders relapse

from acquired drug resistance. The mechanisms underlying resistance to RAF inhibitors are poorly characterized and must be elucidated in order to optimize future clinical trials. The purpose of this proposal is to understand mechanisms of resistance in melanoma in order to improve targeted therapeutic strategies.

- Title: A Pilot Study of IL-2 and Rituximab Maintenance in High Risk B Cell Non-Hodgkin's Lymphoma (NHL)
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The purpose of this project is to assess the safety and efficacy of combination immunotherapy with rituximab and interleukin-2 in patients with NHL, and investigate disease-free as well as overall survival rates.
- Title: Transcription Independent Regulation of Liver Repair
Type of Research: Biomedical
Focus: Digestive Sciences
Purpose: The purpose of this project is to delineate the regulation of liver progenitor cells that influence the development of chronic liver injury, facilitate repair and impact the extent of liver fibrosis. The two aims will investigate mechanisms by which inhibition of target gene expression by notch receptor-mediated inhibition of β -catenin activity (Aim 1) and by miRNA mediated inhibition of target gene expression (Aim 2) regulate progenitor cell expansion and maturation during chronic liver injury. Understanding the biology of hepatic progenitor cells will have a wide-ranging impact on the development of therapeutics for acute liver failure, chronic cirrhotic liver disease and hepatocellular carcinoma.
- Title: Role of Retinoblastoma Tumor Suppressor in Estrogen Receptor Negative Breast Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Breast cancer is a major health concern, with over 200,000 new diagnoses rendered each year in the United States. Approximately 1 in 8 women will develop breast cancer; thus, substantial effort has been directed at defining the basis of tumor development and progression. Breast cancer is represented by multiple disease-subtypes which are distinguished by differential markers, prognoses, and treatment regimens. In general, estrogen receptor (ER) negative disease is faster progressing and more difficult to treat. Genetic analyses established the paradigm that specific tumor suppressor pathways are differentially disrupted in ER-negative disease, but the specific relevance of these events for tumor behavior or therapeutic response remains unclear. Here, we will delineate the role of retinoblastoma tumor suppressor (RB) in the progression to ER-negative disease and the treatment of such tumors based on rational drug delivery.
- Title: Chromosomal Instability (CIN) in Tumorigenesis
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Chromosomal instability (CIN) is a characteristic of human solid tumors. Genomic instability is defined as a persistently high rate of loss and gain of whole chromosomes and may be observed as an elevated rate of gain or loss of whole chromosomes (aneuploidy) and/or as structural chromosomal aberrations (translocations, deletion, inclusions). The molecular mechanisms underlying CIN and the relative contribution of CIN to tumor progression, invasion and metastasis is poorly understood. Using engineered mice models and reconstitution assays we will determine the mechanism by which cyclin D1 regulates CIN in cells and *in vivo*.
- Title: Involvement of Hedgehog Signaling in Muscle Wasting of Cancer Cachexia
Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: Cachexia with its progressive wasting of fat and skeletal muscle is a devastating complication of cancer. There are no approved, effective treatments and the molecular pathways linking cancer to muscle wasting are ill-defined. The sonic hedgehog (Shh) and related ligands mediate embryogenesis, including specification of skeletal muscle. This project will define the links among the hedgehog pathway, inflammation and muscle wasting in cancer. Ultimately these studies will provide a rationale for screening patients for hedgehog pathway activation in cachexia as well as for new therapeutic approaches for muscle preservation, including hedgehog pathway inhibitors already in clinical trials for anti-tumor therapy.

- Title: Role of Dietary Cholesterol in Cancer

Type of Research: Biomedical

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

Purpose: The hypothesis of this project is that plasma cholesterol levels play a crucial role in the regulation of mammary tumor onset and progression. During mammary tumor development, tumor cholesterol requirements are very high compared to other tissues, since tumor cells divide more rapidly than other cell types. Therefore, the project will examine the i) regulation of plasma cholesterol (in the form of lipoproteins) and ii) the role of a key cellular protein involved in lipoprotein metabolism (Caveolin-1) during mammary tumor formation and lung metastasis.

- Title: New Methods of Detection of Residual AML Cells in Patients in Remission after Allogeneic HSCT

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) and allogeneic hematopoietic stem cell transplantation (HSCT), is thought to be due to the persistence in a protective niche in the bone marrow (BM) of a rare population of cryptic AML stem cells. New prospective therapies, such as those aiming at mobilizing these AML stem cells from the patient's bone marrow, are conditioned by the capacity to detect and quantify these rare cells in blood and bone marrow samples. The objective of this project is to develop new high-sensitivity methods based on next-generation sequencing, to detect both recipient-specific and AML-specific genetic markers that will allow detection of rare AML cells.

Treatment Research Institute (\$155,813)

Research Project:

- Title: Community-based Recovery: A Feasibility Study of Recovery Homes and Residents

Type of Research: Health Services

Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: The aims of the project are threefold. This project seeks to: (1) assess the feasibility of recruiting recovery home directors and recruiting and tracking residents in Philadelphia; (2) evaluate the appropriateness and acceptability of instruments used to assess recovery homes and recovery home residents; (3) gather basic descriptive data on a sample of recovery homes and residents that can be used to generate specific hypotheses about different types of recovery houses and how they may increase recovery capital among residents for a subsequent federally-funded grant application.

University of Pennsylvania (\$7,809,060)

Research Projects:

- Title: Cognitive Training for Nicotine Dependence
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to evaluate cognitive enhancing interventions for smoking cessation. The focus will be on an alpha4beta2 nicotinic receptor partial agonist medication.
- Title: Mesothelin Chimeric Antigen Receptor Lentiviral Vector Production and IND Development
Type of Research: Health Services
Focus: Immunology
Purpose: The overall hypothesis of this project is that immuno-gene therapy with chimeric antigen receptor (CAR) T cells with specificity for the tumor antigen mesothelin can be used successfully to treat cancers that overexpress mesothelin: most commonly, pancreatic cancer, ovarian cancer and mesothelioma. In order to advance to clinical trials to test the safety and feasibility of mesothelin CAR T cell therapy, a number of translational steps need to be met in the aspects of manufacturing and regulatory. This research project will enable the manufacturing of the mesothelin CAR lentiviral vector that will be used to transduce T cells, and facilitate development of an investigational new drug (IND) application for submission to the FDA.
- Title: Identification of Moderate Penetrance Alleles in Young Women with Breast Cancer: A Multiplex Approach
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The use of genetic testing to guide cancer risk management improves patient survival. However, most individuals and families in whom genetic susceptibility is suspected have uninformative results using current approaches for clinical genetic testing. As one such example, 10% women diagnosed with breast cancer are under age 40. Whereas a genetic contribution to the development of such early onset cancer is suspected, at most 10% of such women will have a detectable mutation in *BRCA1* or *BRCA2*. However, large scale genetic studies of early onset breast cancer have not been done examining many of the recently identified moderate risk breast cancer susceptibility genes.
- Title: Mechanisms of Cancer Progression
Type of Research: Health Services
Focus: Oncological Sciences
Purpose: The natural history of human cancer is characterized by the progressive selection and outgrowth of cells that possess increasingly aggressive properties. Among these properties, the propensity of cancers to recur following surgery and adjuvant therapy is the most important determinant of clinical outcome, since recurrent cancer is often incurable. This project will purchase the equipment and fund the operator to analysis the experiments elucidating the pathways that contribute to cancer recurrence. The studies proposed in this application will advance the therapeutic goals of preventing cancer recurrence. This knowledge has the potential to facilitate the development of more effective therapeutic approaches for treatments.
- Title: High Resolution RNA Functional Genomics
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: The purpose of this project is to utilize the state-of-art RNA sequencing technology, molecular imaging, and computational analysis to address problems in cellular fate decisions and responses to drugs. In the first part, we will use marker-assisted RNA sequencing measurements to test the hypothesis that a dynamical sequence of regulatory protein expression governs cell fate decisions. In the second part, we will use RNA sequencing and digital gene expression assay to address the hypothesis that dynamic variability of model genomes to pharmacokinetic treatments will identify components of the Non-Steroidal Anti-Inflammatory Drug response network.

- Title: Enhancement of Systems and Computational Neuroscience Space - Research Infrastructure Project
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The purpose of this research infrastructure project is to renovate the vivarium in Stemmler Hall to support systems and computational neuroscience. The project will provide a total of 15,059 square feet of renovated space and infrastructural improvements. This includes the consolidation and improvement of research functions such as animal holding, testing and procedure space from different locations of outmoded areas in the Richards Building. In addition, the renovated space will support investigators across multiple departments, including Otorhinolaryngology, Neuroscience and Psychology, whose closely related research programs address critical needs common to Penn, the NIH road map and the Commonwealth of Pennsylvania.
- Title: The Dynamic Microbiome of Chronic Diabetic Foot Ulcers
Type of Research: Biomedical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: Bacterial colonization and infection significantly impair healing of the diabetic foot ulcer (DFU). This study will utilize less-biased genomic methods of surveying microbial diversity and functionality to more precisely track and characterize temporal microbiome dynamics of the DFU. Analyzing how the dynamic microbiome correlates with clinical phenotypes and wound outcomes provides a vital foundation for the development of improved biomarkers and therapeutics that leverage microbial community dynamics.
- Title: Direct Reprogramming of Somatic Cells to Spermatogonial Stem Cells
Type of Research: Clinical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: We propose to directly convert fibroblasts using defined factors to spermatogonial stem cells, those stem cells in males which give rise to sperm. This research will provide a new mechanism by which men rendered infertile without the opportunity for sperm-banking will have the opportunity to repopulate their testes through the generation of patient-specific stem cells.
- Title: Causes and Consequences of Altered Dosage Compensation in Humans
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Female reproductive cancers exhibit epigenetic instability of X-Chromosome Inactivation (XCI): loss of XIST RNA expression, loss of heterochromatic markers of the inactive X (Xi), partial reactivation of Xi, and acquisition of additional copies of active Xs. Consequently, these cancers suffer from improper dosage of X-linked genes, yet it is unknown how this misregulated expression contributes to the initiation and pathogenesis of disease. Human female pluripotent stem cells (hPSCs) also exhibit XCI instability (similar to reproductive

cancers), and are a powerful model system to investigate the causes and consequences of altered dosage of X-linked genes.

- Title: Optimizing Production of Cardiac Myocytes from Stem Cells and by Direct Reprogramming
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: The purpose of this study is to enhance understanding of the production of cardiac muscle to replace cardiac muscle lost in the setting of myocardial infarction (heart attack). Recent work in mouse models indicates that defined combinations of transcription factors can convert connective tissue and fibroblasts into cardiac muscle cells. We propose to extend this work to human tissue and to explore the role of small molecules in enhancing this process. We will also extend to humans preliminary findings in mice that a gene called *Hopx* specifically identifies cardiac muscle precursor cells. This could allow for the isolation and purification of human cardiac precursors from stem cells to be used for cell-based therapy of myocardial damage.

University of Pittsburgh (\$7,809,060)

Research Projects:

- Title: Research Infrastructure: Structural Biology Renovations
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The purpose of this project is to renovate two areas of the University of Pittsburgh's Biomedical Science Tower 3 (BST3) to meet the evolving needs of the Department of Structural Biology and to alleviate overcrowding among all departments housed in the BST3.
- Title: Thermodynamic Studies of Ligand Binding
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Advances in the development of predictive levels of understanding of biological processes at a systems level as well as the development of methods for the design of molecules that can perturb biological systems, including drugs, depends on a thorough understanding of the physical parameters associated with the interactions between biological molecules including binding affinities. This project aims to complement ongoing activities in structural biology, molecular biophysics, computational chemistry, and systems biology at the University of Pittsburgh.
- Title: Neurobiology of Addiction
Type of Research: Clinical
Focus: Neurosciences
Purpose: Substance use disorders and addiction are major public health problems, yet few effective treatments or preventions exist. Recent advances in understanding the factors associated with increased risk for addiction (e.g., alterations in circadian rhythms) and in the neuroscience of reward-related circuitry make it possible to take new approaches to understanding the neurobiology of addiction and, thus, enhance our capacity to develop novel preemptive interventions. We propose three aims that will address key issues in the neurobiology of addiction.
- Title: Postoperative Radiation, Cisplatin, and Panitumumab in Head and Neck Cancer
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: Locally advanced squamous cell carcinoma of the head and neck (SCCHN)

is treated with various combinations of radiation and chemotherapy. Epidermal growth factor receptor (EGFR) is highly expressed in SCCHN; and its overexpression is associated with poor patient outcome, making EGFR a promising target of anticancer therapy. This Phase II clinical trial seeks to determine whether the addition of an EGFR-specific monoclonal antibody, panitumumab, improves survival of patients with locally advanced SCCHN when combined with the standard of care (radiation plus cisplatin) in the adjuvant setting following surgical resection.

- Title: Radiation, Cetuximab, and Pemetrexed With/Without Bevacizumab in Head and Neck Cancer

Type of Research: Clinical

Focus: Oncological Sciences

Purpose: Patients with squamous cell carcinoma of the head and neck (SCCHN) are increasingly treated with primary chemoradiotherapy (CRT). The incorporation of novel targeted therapies to CRT is of major interest since it may potentially improve efficacy without significantly increasing toxicity. This project will test the anti-tumor efficacy of radiation, cetuximab (a chimeric anti-epidermal growth factor receptor [EGFR] monoclonal antibody [mAb]) and pemetrexed (an anti-folate) with or without bevacizumab (an anti-vascular endothelial growth factor [VEGF] antibody) in patients with locally advanced SCCHN.

- Title: Comparison of Biomarker Modulation in Head and Neck and Lung Cancers

Type of Research: Clinical

Focus: Oncological Sciences

Purpose: This project will examine the pharmacodynamics of erlotinib versus dasatinib or a combination of erlotinib plus dasatinib versus placebo in a presurgical setting of head and neck and lung cancers. This four-arm randomized clinical trial will determine whether biomarkers are modulated by epidermal growth factor receptor (EGFR) and/or Src kinase targeting and whether biomarker modulation is associated with reduction of tumor volume and/or evidence of histologic response in the tumor; the project will also evaluate the safety and tolerability of the treatment regimens. The long-term goal is to determine which patients are most likely to respond to treatment with EGFR inhibitors, Src inhibitors, or a combination of the two.

- Title: Phase I Study of ABT-888 in Combination with Carboplatin/Paclitaxel in Solid Tumors

Type of Research: Clinical

Focus: Oncological Sciences

Purpose: Significant advances in cancer treatment have been made over the past 10-15 years. However, when metastatic disease is diagnosed, overall prognosis remains poor. It is clear that new, effective, and less toxic drugs and treatment regimens are needed for our cancer patients. We describe a novel phase I clinical trial that focuses on improving the clinical efficacy of cytotoxic chemotherapy by modulating the process of deoxyribonucleic acid (DNA) repair through inhibition of the key DNA repair enzyme poly(ADP-ribose) polymerase (PARP). We plan to combine the novel PARP inhibitor compound veliparib (ABT-888) with weekly carboplatin and paclitaxel in patients with advanced solid tumors.

- Title: Veliparib Therapy in Advanced Biliary, Pancreatic, Urothelial, and Non-Small-Cell Lung Cancer

Type of Research: Clinical

Focus: Oncological Sciences

Purpose: Significant advances in cancer treatment have been made over the past 10-15 years. However, when metastatic disease is diagnosed, overall prognosis remains poor. It is clear that new, effective, and less toxic drugs and treatment regimens are needed. We describe a novel phase I clinical trial that focuses on

improving the clinical efficacy of cytotoxic chemotherapy by modulating the process of deoxyribonucleic acid (DNA) repair through inhibition of the key DNA repair enzyme poly(ADP-ribose) polymerase (PARP). We plan to combine the novel PARP inhibitor compound veliparib (ABT-888) with cisplatin plus gemcitabine in patients with advanced biliary, pancreatic, urothelial, and non-small-cell lung cancer (NSCLC).

- Title: Early Phase I Study of ABT-888 in Patients with Hepatic/Renal Dysfunction and Solid Tumors

Type of Research: Clinical

Focus: Oncological Sciences

Purpose: Significant advances in cancer treatment have been made over the past 10-15 years. However, when metastatic disease is diagnosed, overall prognosis remains poor. It is clear that new, effective, and less toxic drugs and treatment regimens are needed for our cancer patients. In this project, we will conduct a novel phase I clinical trial that focuses on improving the clinical efficacy of cytotoxic chemotherapy by modulating the process of deoxyribonucleic acid (DNA) repair through inhibition of the key DNA repair enzyme poly(ADP-ribose) polymerase (PARP). We plan to combine the novel PARP inhibitor compound veliparib (ABT-888) with carboplatin and paclitaxel in patients with solid tumors who have underlying liver or kidney dysfunction.

- Title: Proteomics Analysis of Human Lung Disease

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: We will use state-of-the-art mass spectrometry (MS) and multiplexed immunoassay platforms and workflows to discover and validate candidate lung disease biomarkers in lung tissue and plasma/serum and to develop biomarker panels and predictive models of nonmalignant chronic lung disease (CLD) and malignant lung disease. These models will find potential clinical application in early detection and diagnosis of disease and prediction of disease progress and patient survival in patients with chronic obstructive pulmonary disease (COPD), emphysema, idiopathic pulmonary fibrosis (IPF), and non-small-cell lung cancer (NSCLC).

- Title: Mechanisms of Myeloma Cell Regulation of Gfi1 Function in BMSC

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: Osteolytic lesions in multiple myeloma (MM) rarely heal, even when patients are in long-term remission, due to the persistent MM-induced suppression of bone marrow stromal cell (BMSC) differentiation into bone-forming osteoblasts (OB). We have shown that MM cells induce the expression and function of the transcriptional repressor growth factor independence 1 (Gfi1) in BMSC, which binds to and represses the key transcription factor, Runx2, driving OB differentiation. In this study, we will investigate the mechanisms by which MM cells elevate Gfi1 and induce its nuclear translocation, and its repression of Runx2. This information may lead to the development of bone tissue targeted therapies that block Gfi1 and recover bone formation.

- Title: Analysis of Hsp90 and Oct3/4 Function in Radiation-induced Stemness in NSCLC

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: Radiotherapy for patients with non-small cell lung carcinoma (NSCLC) remains largely palliative due to resistance, which is thought to be associated with the existence of cancer stem cells (CSCs). This project is designed to answer fundamental radiobiological questions and generate new knowledge regarding lung CSC biology and the role of the molecular chaperone heat shock protein 90 (Hsp90)

and the pluripotency gene octamer binding transcription factor 3/4 (Oct3/4) in radiation-induced stemness. Results of this project may lead to the development of new treatment approaches in NSCLC.

- Title: Regulation of the Estrogen Receptor in Anchorage Dependent and Independent Conditions
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The estrogen receptor (ER) is a critical target in breast cancer, and a better understanding of ER action may lead to novel approaches for treatment or combating resistance to hormone therapy. Estrogen, and anti-estrogens such as fulvestrant, cause degradation of ER protein, which may subsequently limit ER activity. We have found that fulvestrant degrades ER via two specific lysine residues. In this project, we will investigate mechanisms of ER degradation using 2D and 3D cell line models to provide novel insight into therapies targeting ER in breast cancer.
- Title: Research Infrastructure: Biomedical Science Tower (BST) Animal Facility Caging Upgrade
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The specific aim of this project is to improve the capacity and quality of the vivarium on the 9th floor of the Biomedical Science Tower. Capacity and quality will be expanded by reconfiguring three undersized rodent holding rooms totaling 561 net square feet, currently at our exceeding capacity, to create two larger holding rooms, both designed to accept high-density rotary individually ventilated caging (IVC) systems with significantly expanded holding capacity.

University of the Sciences in Philadelphia (\$32,583)

Research Projects:

- Title: Integrated Behavioral Treatment for Co-Morbid Obesity and Chronic Pain
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Evidence suggests individuals with co-morbid chronic pain and obesity experience reduced treatment success in traditional programs designed to address either pain or obesity in isolation. Little is known about how to successfully treat individuals with co-morbid pain and obesity, and to date no programs are available to simultaneously treat pain and obesity. To address this deficiency, the proposed program will compare traditional self-management approaches to treat chronic pain and obesity with an integrated program designed to simultaneously treat pain and obesity. The primary hypothesis is that individuals enrolled in an integrated program will experience increased treatment success compared to those enrolled in a traditional program.
- Title: Experimental and Computational Analysis of GPCR Phosphoregulation
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This project will use a combination of experimental and computational biochemical studies to investigate the invasive function and structural dynamics of phosphorylated CXCR4, a chemokine G protein-coupled receptor (GPCR) known to play a critical role in cancer metastasis and HIV-1 infection. The molecular understanding of CXCR4 phosphorylation-dependent functions and conformational changes will aid in the rational design of novel therapeutics that target CXCR4 for anti-cancer and anti-HIV properties.

Wistar Institute (\$ 1,548,502)

Research Projects:

- Title: Determining How Antigenic Mutations Compromise Fitness of Influenza Viruses
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: Influenza vaccines need to be updated most years because influenza viruses constantly accumulate mutations in antibody-binding sites, a process termed 'antigenic drift'. Recent studies show that some of these mutations compromise viral fitness. The purpose of this project is to identify specific antigenic mutations that compromise viral fitness and to mechanistically determine how antigenic mutations compromise viral fitness. Armed with this knowledge, predicting future evolution of influenza viruses might be possible.
- Title: Characterizing Mechanisms of Transcriptional Activation Using Live Cell Imaging
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Numerous diseases, including cancer, are caused by aberrations in transcriptional regulation. Therefore, a comprehensive understanding of this process is important for developing new strategies to cure human diseases. We have developed a method to visualize the activation of a chromatinized transcription site in single living cells with high temporal and spatial resolution. We are using it to determine the exact timing and order of recruitment of transcriptional regulatory factors. It is our goal to use this methodology to develop a high-resolution regulatory pathway map of transcriptional activation, which will provide new insight into the kinetic control of human transcriptional activation.
- Title: Developing Potential Strategies to Overcome Drug Resistance in Melanoma
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The goal of this project is to characterize mechanisms of drug resistance to inhibitors of the MAPK pathway, which is activated in the majority of melanomas, and delineate potential therapeutic strategies to overcome it.
- Title: Microenvironmental Regulation of ROR Receptors during Mesenchymal Mimicry
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Melanoma is a deadly disease due to its enormous plasticity. What is particularly intriguing is that aggressive melanomas are largely devoid of fibroblasts, and fibroblast infiltration is indicative of less aggressive tumors. Yet, depletion of fibroblast growth factors results in decreases in melanoma cell survival, suggesting melanoma cells produce their own fibroblast-like growth factors. We have shown that the Wnt signaling pathway guides the transition of melanoma cells to a highly invasive, mimicking a fibroblast-like state. Understanding the mechanisms that underlie this mimicry will lead us not only to a better understanding of melanoma metastasis, but also to identifying new therapeutic options in this deadly disease.