Health Research Formula Grants - State Fiscal Year 2008-09

Thirty-two organizations received health research formula grants for the state fiscal year 2008-09. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2009 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 ($135,484)

- Project Title: E-Coaching to Support the Modification of Risk Factors of Metabolic Syndrome using Mediterranean Diet
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The Mediterranean Diet has been found to improve risk factors associated with Metabolic Syndrome. The purpose of this study is to determine if it is feasible and effective to deliver support for the Mediterranean Diet using interactive email support and coaching (e-coaching), and educational materials and links found on the internet. In addition, results of this study will be compared to a similar study that examines the effectiveness of face-to-face support for the Mediterranean Diet. This methodology will allow an examination of the feasibility of both modes of delivering MED diet education and support, as well as, an examination the effect of each method on outcome variables.
- Project Title: The Use of High Flow Oxygen during ED PSA with Propofol: A Randomized Trial
  Type of Research: Clinical
  Focus: Respiratory Sciences
  Purpose: The drugs used during emergency department procedural sedation and analgesia (PSA) can depress breathing and can cause patients to have dangerously low levels of oxygen (hypoxia) in their bloodstream. In previous research that we have conducted, extra low flow oxygen (3 liters a minute via nasal cannula) during PSA does not improve the rate of hypoxia during PSA with one common drug combination (midazoalm and fentayl). With another drug, propofol, it only has a small benefit. Because of the way propofol works in the body, we believe that high flow oxygen (15 liters a minute via mask) may reduce the rate of hypoxia.. The purpose of this project is to evaluate whether high flow oxygen significantly lowers the rate of hypoxia during emergency department procedural sedation with propofol.
- Project Title: Performance Evaluation of Spatial Normalization Protocols for Brains with Focal Lesions
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of the current project is two-fold. First, we will evaluate several different protocols that involve spatially transforming images of focally lesioned brains. The evaluation will be conducted in a quantitative manner. The second purpose of the project is to build a small database of images of brains with focal lesions where anatomical landmarks are planted. These brain images with landmarks can be used for future studies that aim to evaluate more spatial transformation protocols.
- Project Title: Development of a Haptic Virtual Environment for Upper Limb Rehabilitation
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology

Purpose: The overall goal of the project is to develop a low cost virtual reality (VR) system for upper limb rehabilitation that provides both visual and haptic feedback to participants. This goal will be accomplished with three specific development aims. The first aim will be to test several system components before final acquisition. The second aim will be to construct and test the system to ensure proper functioning. The third aim will be to prepare for future use of the system by planning experiments with stroke patients and developing proposals for additional funding.

Allegheny-Singer Research Institute ($202,774)

- Project Title: Analysis of Ulnar Collateral Ligament Reconstruction
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: The ultimate purpose is to improve elbow ligament repair and ensure that outcomes maintain necessary functional activities such as grooming and eating. Specifically, the project will determine whether repair techniques recreate the original physiologic condition and analyze the hypothesis that repair could lead to fracture. Although biotenodesis screw fixation and tunneled docking fixation of the graft substance in elbow repair can both provide the necessary joint stability, neither technique ensures long-term success. Failure to recreate the native ligament kinematics may be an important indicator of poor surgical outcome. The project will first measure the native case and then determine which surgical interventions may lead to subsequent failure. The project will provide surgeons with vital information upon which to base surgical reconstruction.
- Project Title: A High Fidelity Rat Model of Pulmonary Arterial Hypertension
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The immediate scientific purpose of this project is to deploy a rat model of Pulmonary Arterial Hypertension (PAH) in the McGinnis Cardiovascular Institute (CVI). The strategic purpose of this project is to make available to CVI researchers a relevant animal model of PAH in which to test genomic and gene therapy technologies currently being developed in the CVI for PAH and other diseases.
- Project Title: Myofibroblast Inhibition in Dupuytren's Contracture
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The current treatment for Dupuytren's contracture, a localized scar tissue formation in the palm has proven to be ineffective in preventing the disease from advancing or to limit its recurrence. In this context, a new course of therapy is required which takes into account both cellular and molecular biology events as contributors to palmar fascia fibrosis. This will have the highest likelihood of therapeutic success against this currently incurable condition. The multiple approaches that are proposed prove that cyclic AMP (cAMP) pathway is an important regulator of palmar fascia fibroblast proliferation/contraction and function. The therapies that raise cAMP levels may become a mainstay of treatment for Dupuytren's contracture.
- Project Title: Flooring Renovation of the ASRI Rodent Animal Facility Research Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: Current flooring has deteriorated from 20 years of normal traffic in an animal housing facility and repairs are beyond the scope of a "patch and paint repair." In order to remain compliant with the institution's PHS Assurance, USDA

guidelines, and the recommendations set forth in "The Guide for the Care and Use of Laboratory Animals," a more permanent repair is required. Funds will be used to install a "seamless" flooring product which is resistant to moisture, non-absorbent, impact resistant, easily cleaned and sanitized. The new floor covering should provide regulatory compliance for the continuance of Allegheny-Singer Research Institute's (ASRI) funded research for the next 5-10 years with minimal maintenance and expense.

American College of Radiology ($2,144,345)

- Project Title: Methods and Strategies to Incorporate Radiotherapy Delivery Uncertainties in Clinical Trials Outcome Analysis
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Randomized clinical trials provide evidence-based medicine that has become the foundation of radiation oncology. Numerous technologies are being used to deliver targeted radiotherapy. These technologies all have their own operational characteristics and uncertainties. Significant variations also exist in individual implementation of these technologies. These uncertainties may influence, to a critical extent, the outcome of clinical trials. However, they have not been addressed so far in a systematic manner in the outcome analysis. This study aims at bridging this gap with theoretical methodologies for critical assessment and propagation of uncertainties of radiation deliveries as a complement to current clinical trial analysis. Our hypothesis is that by properly accounting for the delivery uncertainties, we will allow better prediction of outcome.
- Project Title: Development and Analysis of an Infrastructure for Review of Modern Clinical Trials that Include Radiotherapy
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Cooperative group protocols have greatly increased in complexity over the past 15 years. At least for the radiotherapy component of these protocols, this dramatic change has created considerable difficulty when reviewing dose distributions to determine whether protocol requirements have been met. Much of the difficulty is due to the time it takes to review advanced technology protocols. This research study is designed to demonstrate that analysis tools are now available that can shorten the time for case review to the extent that accuracy is not lost in a tradeoff with efficiency. This study will also provide information for designing the review tools needed for future cooperative group protocols that might include one or more advanced technologies such as IMRT, IGRT, SBRT, 4D respiratory control, or deformable image registration using PET and/or MRI.
- Project Title: Screening For Depression and Referral for Treatment of Cancer Patients
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The first purpose of this project is to determine the usefulness of screening for depression among cancer patients receiving radiation therapy, in terms of the proportion of patients who are identified as depressed and who are not currently receiving mental health treatment. Patients who are found to be depressed will be offered a referral to a mental health professional or primary care physician, depending on their preference. Three months later, they will receive a follow up telephone interview. The goal is to evaluate the efficiency of screening and to identify and find ways of overcoming the significant barriers to cancer patients receiving care for depression.

- Project Title: Assessment of Methods to Increase Latino Enrollment into Cancer Clinical Trials
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Despite national initiatives to increase the enrollment of racial and ethnic minorities into cancer clinical trials, participation by Latinos remains low. The Radiation Therapy Oncology Group (RTOG), which conducts cancer clinical trials involving radiotherapy, will develop and evaluate evidence-based, cuturally and linguistically appropriate patient education materials and investigator training programs to increase the enrollment of Latinos into cancer clinical trials in Pennsylvania and nationally. We will also use cartographic modeling techniques to do a gap analysis through identification of current RTOG sites and their Latino population density compared to high density areas of Pennsylvania and the United States where we do not have RTOG sites. This will help us strategically identify sites to recruit into the RTOG that will facilitate Latino access to state-of-the-art cancer clinical trials.
- Project Title: Remote Review of Quality of Radiation Treatment for Lung Cancer: A Pilot Project
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Definitive radiotherapy is the standard therapeutic approach for inoperable lung cancer. However, this treatment can potentially result in fatal treatment complications. The purpose of this pilot project is to develop methods of collecting clinical data directly from distinct electronic medical record systems at a variety of radiotherapy facilities to assess quality of treatment delivery in lung cancer. The clinical data will be standardized and aggregated in a central database from which queries will be performed to retrieve critical data. The methods developed will assure secure transfer, review, and analysis in compliance with regulatory requirements. The overall goal will be to scale this approach for automated collection of quality of care data across multiple institutions to analyze and improve radiation treatment delivery for lung cancer patients.
- Project Title: Quantitative Imaging Biomarker Tools
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this study is to evaluate, develop, unify, and evaluate standards-based tools that are used to collect, record, and analyze quantitative imaging data in order to discover imaging biomarkers for more accurate analysis of image results collected in clinical trials. The critical barriers being addressed by our study are that at present, the assessment of cancer treatment response based on image assessment is cumbersome, with poor tools for measuring and capturing vital image metadata required for this assessment. Our outcome will bridge these barriers and advance the field by improving the efficiency of response assessment evaluation on images.

Bryn Mawr College ($12,570)

- Project Title: Analysis of Epigenetic Modifications at Imprinted Loci in Mouse
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The majority of genes in mammals are expressed from copies inherited from both the mother and the father, but a small number of genes are only expressed from one of the two copies. The two copies of these genes must be

distinguished to properly control expression; the distinguishing mark is referred to as the imprinting mark. For some genes, the imprinting mark has been shown to consist of modifications to the DNA and/or to the proteins DNA wraps around in the cell; such modifications are called epigenetic because they affect DNA structure but not DNA sequence. We plan to analyze epigenetic modifications at the mouse *Rasgrf1* gene, which is expressed solely from the paternal copy in some tissues, but is expressed from both copies in other tissues. This work will further our understanding of which epigenetic modifications are required to regulate *Rasgrf1* expression.

Carnegie Mellon University ($747,818)

- Project Title: Mellon Institute Vivarium – Research Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: Many faculty in the Mellon College of Science, which includes the departments of Biological Sciences, Chemistry, Mathematics and Physics, as well as several associated interdisciplinary centers, conduct research that uses vertebrate animals. This infrastructure project will contribute to the design and construction of a new vivarium, the facility in which those animals are kept. It is located in the historic Mellon Institute building.
- Project Title: Computational and Neural Basis of Visual Inference
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this project is to understand how neurons in the visual cortex work together to resolve ambiguity during object perception from both a computational and a neurophysiological perspective. The basic idea is that prior visual experiences, encoded in connections among neurons, constrain the visual computations underlying the interpretations of visual scenes. We will test this idea by monitoring the activities of neurons in the earliest visual area (V1), an intermediate visual area (V4), and the highest visual area (IT) of the primate visual system. The computational studies will assess how robust visual inference can be accomplished in the framework of hierarchical Bayesian inference. The electrophysiological studies will study the dynamics of neuronal activities during visual processing to test the computational hypotheses.
- Project Title: Memory-Based Neural Activity in the Hippocampus
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The hippocampus, located in the temporal lobe of the brain, is known to be involved in both memory formation and the representation of spatial information. Early studies in rats showed that the activity pattern of hippocampal cells correlates strongly with the animal's current location in its environment. But later experiments have revealed that hippocampal activity can be much more dynamic, replaying trajectories the animal experienced previously, or producing trajectories that correspond to a path it is anticipating taking. This project will analyze data on hippocampal trajectory encodings and explore computational mechanisms to account for the phenomenon.

Children's Hospital of Philadelphia ($3,640,981)

- Project Title: Role of Crk and CrkL in Normal and Neoplastic Growth
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: Normal growth requires a delicate balance among the processes that grow new cells and those that eliminate superfluous cells. Cancer arises because of a breakdown in this balance between cell division and cell death. Cancer cells continue to grow as they fail to respond to signals that tell them to stop. The investigator proposes to study the role of two growth control genes, Crk and Crk-like (CrkL), in normal growth and development as well as in cancer cells. The strategy involves the use of genetic techniques to remove Crk and CrkL from different kinds of cells, in culture and in mice, and then to examine the consequences for cell growth. In addition, the genes will be removed from tumor cells to determine if they function in similar or different ways in cancer.

- Project Title: Gene Transfer of Activated FVII for the Treatment of Inherited Coagulation and Platelet Disorders
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: The treatment of hemophilia (a bleeding disorder) is complicated by the development of antibodies (inhibitors) against the therapeutic factor (Factor VIII or Factor IX) infused in response to bleeds. Clinical data demonstrate the successful but costly treatment of such patients with infusion of high-dose FVIIa. To address this with gene transfer, an engineered FVIIa transgene has been developed and delivered, the expression of which resulted in a substantial improvement in the bleeding diathesis of hemophilic mice and dogs. The experiments here aim to further demonstrate the feasibility of this approach in animals with inhibitors as well as other inherited coagulation defects, and the further optimization of the gene delivery vehicle and transgene. These are critical steps towards a clinical application that can result in a single, simplified treatment for bleeding disorders.

Children's Hospital of Pittsburgh ($958,038)

- Project Title: A Genetic Model of Congenital Obstructive Nephropathy
  Type of Research: Biomedical
  Focus: Renal and Urological Sciences
  Purpose: End-stage kidney disease costs over 15 billion dollars annually in the United States and represents a major cause of death and impaired quality of life. The long-term objective of this project is to gain a better understanding of the most common cause of kidney disease in children - a blockage in urine flow. Completion of the studies outlined in this proposal will help us design new diagnostic tests and treatment strategies for children and adults with kidney disease.
- Project Title: Novel Mouse Model of Vesicoureteral Reflux and Dysfunctional Voiding
  Type of Research: Biomedical
  Focus: Renal and Urological Sciences
  Purpose: Vesicoureteral reflux (VUR) or backtracking of urine from the bladder back up into the kidneys, is the most common urinary tract birth defect. Reflux nephropathy or kidney injury associated with reflux is the 4th leading cause of kidney failure in children. Reflux is also associated with dysfunctional voiding (DV) (abnormal bladder contractions) and patients with both conditions have a high risk for reflux nephropathy. Despite the association between reflux and voiding dysfunction, no one has found a genetic link. Our lab has developed a genetic mouse model that has very high rates of reflux and also has evidence of voiding dysfunction (as well as evidence of long term injury resembling reflux nephropathy). Using this mouse, we can identify treatments for patients with VUR and DV to decrease the incidence of long term injury from reflux nephropathy.

Drexel University ($1,215,241)

- Project Title: Triggers of Inflammation in Scleroderma
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Scleroderma is a disease caused by uncontrolled accumulation of collagen in the soft tissues. Its cause is unknown and the progression of the disease is not well understood. Recent research has identified a new inflammatory pathway that does not reflect traditional T cell activation. This pathway senses danger signals from the tissues that are external to the cells. The goal of this project is to understand the role of this new inflammatory pathway and other inflammatory signaling pathways in early scleroderma skin lesions and to investigate the signaling in several mouse models that have had pertinent proteins in this new pathway deleted.
- Project Title: Developing Therapies for Treating Hereditary Spastic Paraplegia
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The goals of this project are to: (1) Identify the deficits in nerve cell shape as well as the transport of substances within nerves when DNA is expressed in the nerve that comprises mutant forms of a protein called spastin that goes awry in a disease called hereditary spastic paraplegia, and (2) Test various potential therapies for alleviating these deficits, once identified, in order to provide a basis for the development of new therapies for treating patients with the disease.
- Project Title: Role of CTF18 in Female Germ Cell Development and Fertility
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Infertility is a major medical concern that affects about 1 of every 10 individuals of childbearing age worldwide. Although a significant proportion of infertility is accounted for by identifiable causes, the molecular basis of these defects is often not known or well characterized. Ovulatory dysfunction and diminished ovarian function in infertile women, and low sperm count in infertile men are examples. It is becoming increasingly clear that many more disorders in medicine, including infertility, have a genetic basis than was previously realized. It is our goal to advance the field so that a better understanding of the underlying defects of infertility disorders will lead to improved treatments.
- Project Title: A Microfluidic Model of Drug-induced Liver Toxicity
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Drug-induced liver injury (DILI) is a common reason for terminating drug development, failing to acquire governmental drug approval, or withdrawing a drug from the market. There is no authentic human liver model for predicting DILI in humans. Attempts to make a human liver model have been impeded by the lack of readily available, large quantities of normal human liver cells. A human liver model that retains normal liver architecture and function, while only requiring small numbers of liver cells, is needed. In this project, we will use rat liver cells and fabricated microchannels to produce a mini-liver unit to test DILI. Our long-term goal is to use parameters derived from studies of the rat mini-liver system to generate a human mini-liver system that can be used for human liver biology and DILI studies.
- Project Title: Identification of Biomarkers and Therapeutic Targets in 3D Hypoxic Breast Cancer Model
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Breast cancer is the most common female cancer in the Western world, affecting 1 of 8 women over their lifetime. One critical prognostic indicator for many

tumor types including breast cancer is decreased oxygen levels or hypoxia. Hypoxic cancers are generally associated with aggressive growth, metastasis, and poor response to radiation treatment and chemotherapy. Understanding the molecular mechanisms and signaling pathways driving breast cancer development is critical for developing diagnostic and therapeutic agents. The purpose of this project is to use molecular techniques to analyze the role of hypoxia in regulating gene expression during breast cancer development and to utilize this information to identify novel diagnostic markers and therapeutic targets that can be used to detect and treat breast cancer.

- Project Title: Role of O-GlcNac Transferase as a Biomarker and Therapeutic Target for Prostate Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: In cancer a number of signaling pathways including phosphorylation/dephosphorylation cascades that add or remove phosphate residues are over-activated. Accumulating evidence suggests a less studied protein modification, known as O-GlcNAc (O-linked N-acetylglucosamine) may globally regulate cell growth and death. The role of O-GlcNAc modifications in prostate cancer phenotypes and signaling is not known. Moreover, we hypothesize that targeting enzymes which regulate O-GlcNAc modifications, such as O-GlcNAc transferase (OGT), may be a novel therapeutic treatment for prostate cancer. Using cell biological, chemical, and proteomic approaches, this project will test the novel hypothesis that O-GlcNAc modifications are increased in prostate cancer, they regulate cancer growth, and thus may serve as novel biomarker and therapeutic targets for prostate cancers.
- Project Title: Piezoelectric Microcantilever Sensors (PEMS) to Detect Methicillin-Resistant Staphylococcus aureus (MRSA)
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of the project is to develop a real-time, highly-sensitive, highly-specific, portable, cost-effective sensor that can be used to detect MRSA in patient samples in the field (doctors' offices, hospitals, university and college infirmaries, and others), leading to an improved treatment outcome measured by decreased mortality and morbidity.
- Project Title: RNA Interference-based Therapy for HIV-1 Associated Neurologic Disease
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: The purpose of this project is to lay the foundation for a new method to intervene in the progression of neurologic disease that often develops in HIV-1 infected individuals. We will investigate a method designed to reduce the ability of HIV-1 infected immune cells to migrate into the brain. This migration is enhanced by signals released from brain-resident infected cells in a positive feedback loop that we will disrupt using a strategy based on RNA interference. Certain receptors that are present on the surface of immune cells, and that allow these cells to respond to the migratory signals, will be down-regulated specifically in HIV-1 infected cells. If successful, this will lead to therapies designed to reduce the overall inflammatory immune response to infection in the brain and help to curb the progression of neurologic disorders.
- Project Title: Somatostatin Signaling in Alzheimer's Disease
  Type of Research: Biomedical
  Focus: Neurosciences

Purpose: A common feature of Alzheimer's disease (AD) is a decrease in the neuropeptide somatostatin in brain. The degree of somatostatin reduction has been correlated with the degree of cognitive decline. However, the role of somatostatin in AD has not been defined. This project is designed to test the function of somatostatin in cognition and cellular models of learning and memory in a mouse model of AD. This project will validate whether somatostatin and its receptors could be utilized as novel therapeutic targets for treating this devastating disease, for which there are currently no effective drugs.

- Project Title: Characterization and Application of a Novel *Drosophila* Model for CHARGE Syndrome
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The long term goal of this project is a deeper understanding of the pathogenesis of CHARGE Syndrome, a rare autosomal dominant disorder that affects roughly 1 in 10,000 live births. We plan to examine these mechanisms by modeling the disorder in the fruit fly *Drosophila melanogaster*. By creating and validating a working model of CHARGE Syndrome in *Drosophila*, we will be able to genetically test the contribution of candidate genes towards the phenotypes associated with these flies, in order to predict whether these genes may be involved in the symptoms of CHARGE patients. We will also be able to analyze the effect(s) of mutation in these genes on neuronal morphology and connectivity within nerve cells in the fly brain. This approach has been very successful in the past in understanding complex forms of mental retardation.
- Project Title: Multidimensional Shape/Color Distributions as a Computational Biomarker for Cancer Pathology
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of the project is to develop computational techniques for analyzing histology images of breast cancer tumors. The computational techniques will derive shape and color information from the images that will enable automated evaluation of the tumor. Specifically, the techniques will be used to determine if a patient's breast cancer has spread to nearby lymph nodes by examining a primary tumor that has been removed from the patient. This image analysis capability will eliminate the need for exploratory surgical removal of lymph nodes; thus eliminating the associated side effects, e.g. pain, swelling and morbidity, and costs.

Duquesne University ($94,131)

- Project Title: Investigation of the Hepatitis C Virus 3'-Untranslated Region, as a Potential Target for New Antiviral Nucleic-acid Based Strategies
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to develop novel nucleic-acid based therapeutic agents against the Hepatitis C virus (HCV). In the first phase of the project, we will employ fluorescence and NMR spectroscopy to obtain detailed information about the HCV RNA 3'-untranslated (UTR) region, a highly conserved region which has been proposed to be involved in specific interactions with a fragment of the HCV coding region. Genetic data showed that these interactions are absolutely required for the viral replication, making the HCV 3'-UTR region an attractive target for antiviral therapy. In the second phase of the project, we will screen for peptide-nucleic acid aptamers that have the ability to inhibit these essential interactions, and thus, to inhibit the HCV RNA replication.

- Project Title: Impact of Parental Smoking Cessation and Residential Hazard Reduction on Pediatric Respiratory Health: A Pilot Investigation
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This two-year pilot project involves research-based residential assessments and interventions designed to directly and positively influence the respiratory health of children of smokers by reducing the ambient levels of tobacco smoke and other environmental triggers. It is anticipated that a total of 50 families will participate over the course of the project. Triggers of primary concern are environmental tobacco smoke and combustion fumes, insect, rodent, pet, and dust mite allergens. Secondary triggers such as mold, dust, and household chemicals will also be monitored. Based on the triggers identified in the initial assessment, a plan for parental education intervention with follow-up monitoring of participant respiratory health and ambient hazard levels will be created for each family.

Fox Chase Cancer Center ($3,131,563)

- Project Title: A Growth-Regulating Protein Tyrosine Phosphatase
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We seek to understand how an enzyme called PTP1B is regulated and how it, in turn, regulates other proteins that control blood sugar, body weight, and, in women, the development of breast cancer. The knowledge we gain from these studies will help us better understand these processes and could also lead to the development of better drugs to treat these diabetes, obesity, and breast cancer.
- Project Title: Characterization of the Role of MTAP Gene in Tumorigenesis
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Methylthioadenosine phosphorylase is a highly evolutionarily conserved metabolic enzyme involved in methionine and adenine metabolism that is expressed in all tissues throughout the body. Deletion of the gene for methylthioadenosine phosphorylase (*MTAP*) is one of the most frequent genetic changes observed in many different types of human tumors. Because *MTAP* is located near the *CDKN2A/ARF* tumor suppressor gene, it is unclear if loss of *MTAP* plays a primary role in tumorigenesis or if it is lost simply due to proximity to *CDKN2A/ARF*. The purpose of this research project is to confirm that loss of *MTAP* directly affects tumorigenesis and to identify potential oncogenic mechanisms affected by loss of *MTAP* expression.
- Project Title: The ARF Tumor Suppressor and Autophagy
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: We have recently discovered that the ARF tumor suppressor (ARF) plays an integral role in a key survival pathway utilized by tumor cells called "autophagy". Autophagy is a self-catabolic process wherein cells exposed to metabolic or hypoxic stress use the lysosome to digest long-lived proteins and organelles in order to release free amino acids and thus survive. The importance of this pathway for cancer cell survival is epitomized by the fact that chloroquine, an autophagy inhibitor, can potently suppress the development of certain tumors. We propose to elucidate the role of ARF and an interacting protein, Hsp70, in autophagy. We will test the hypothesis that a novel autophagy inhibitor discovered in the laboratory of our collaborator, and found by our group to specifically target ARF-dependent autophagy, is an effective new chemotherapeutic agent.

- Project Title: Anti-Glucose Transporter-1 Antibodies as a Novel Treatment against Human Cancers
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Glucose fuels the rapid growth and metabolism of tumors. Glucose uptake by cells is facilitated by a family of transporter proteins called "Gluts". Tumors frequently over-express the high affinity glucose transporter protein, called Glut-1. Normal cells, on the other hand, require a slow and steady supply of glucose and therefore use lower affinity glucose transporters, Glut-4 or Glut-12. In the studies outlined here we will use antibodies against Glut-1 to decrease the uptake of glucose by the tumor, while sparing glucose uptake by normal cells. This novel and new therapeutic strategy could be applicable to a wide variety of human cancers, including lung cancer, breast cancer, and essentially any cancer that shows increased glucose uptake on a PET scan.
- Project Title: Regulation of Human Somatic Wee1 by Cyclin A/Cdk2 Complexes
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Mitosis is the process by which a cell divides into two daughter cells. This step is pivotal in the life of the cell and, potentially, the organism as a whole. If mitosis is performed before cellular DNA is completely duplicated or mutations are repaired, the progeny cells may die or sustain cancer-causing changes. Furthermore, uncontrolled cell division is a hallmark of cancer. Drugs that can preferentially block cell division in cancer cells or can drive their division in the face of lethal amounts of unreplicated or severely damaged DNA may provide effective therapy. Wee1 is a protein that inhibits entry into mitosis in human cells. We have recently identified a specific site through which an enzyme complex called cyclin A/Cdk2 binds Wee1 and inactivates it. This regulation involves Wee1 phosphorylation and export from the cell nucleus. This project will study this regulation. The long-term goal is cancer drug development.

Geisinger Clinic - Weis Center for Research ($95,564)

- Project Title: Genomics of Pregnancy-Related Complications
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Complications related to pregnancy are difficult to predict in advance, need better treatments, and are major causes of death or disability from pregnancy and/or delivery. Pregnancy-related complications include pre-eclampsia (high blood pressure and fluid retention caused by pregnancy) and pre-term or premature labor. Previous studies have shown that family history is a major risk factor for these complications, which indicates that they are influenced by inherited genetic factors. The goal of this study is to assemble a collection of blood and DNA samples from pregnant women and to use these in studies to identify genetic factors related to pre-eclampsia and pre-term labor. This information can then be used in follow-up studies to elucidate the biological factors associated with these conditions and to develop improved methods to diagnose and treat them.

Hepatitis B Foundation ($2,537)

- Project Title: Characterizing the Antiviral Activities of Small Interferon-Stimulated Genes against Hepatitis B Virus
  Type of Research: Biomedical

Focus: Immunology
Purpose: Interferon-alpha is currently used to treat people with chronic hepatitis B (HBV), to reduce viral activity and prevent liver damage and liver cancer. However, response rates are moderate, and there are many side effects. It is anticipated that this research will ultimately lead to development of more finely targeted Interferon therapy with improved long-term response rates and reduced side effects. The research will be conducted at the Hepatitis B Foundation and its research affiliates at the Pennsylvania Biotechnology Center of Bucks County, by select undergraduate students during a summer internship. In addition to studying promising new methods for treatment of chronic HBV, this project encourages Pennsylvania students to seek careers in biomedical research, increasing the future pool of biomedical researchers in the state.

Lankenau Institute for Medical Research ($223,613)

- Project Title: Arsenic Drugs and Hydroxyethyl Disulfide in the Control of Cancer Cell Growth and Response to Therapy
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The efficacy of arsenic trioxide (As_2O_3) as an anti cancer drug in leukemia and other cancer cells may be limited due to its detoxification by intracellular glutathione (GSH). Our preliminary results have demonstrated that hydroxyethyl disulfide (HEDS), a non-toxic oxidant, removes GSH and increases the response of glucose deprived cancer cells to radiation and chemotherapeutic agents. Increasing the susceptibility of the rest of the tumor cells containing glucose to HEDS is expected to improve the outcome of cancer therapy. In this project, we will determine the efficacy of combined treatment of HEDS and arsenic compounds (including but not limited to the FDA approved Trisenox) in increasing the response of human cancer cells to radiation and chemotherapeutic agents.
- Project Title: Role of IDO in B Cell-mediated Immunity and Autoimmunity
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation and destruction of the joints. RA patients have an elevation in the level of activity of an immunoregulatory enzyme called IDO. This elevation in IDO correlates with disease activity, suggesting that IDO may contribute to the disease process. In support of this, we have evidence that inhibiting IDO activity interferes with arthritis development in mice. In this project, we will investigate the mechanism by which IDO inhibition alleviates arthritis development. The overall goal of this project is to define the mechanism by which IDO modulates the immune response leading to arthritis and provide new insights into strategies that can be used to manipulate this pathway to reduce or prevent debilitating disease.

Lehigh University ($108,901)

- Project Title: Targeted Killing of Cancer Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Cancers harboring mutations in the tumor suppressor protein p53 are typically among the most difficult to treat and make up at least 50% of all human cancers. Tumor cells lacking a functional p53 are resistant to common chemotherapies, which induce a cell death process called apoptosis. These cancer

cells require a protein called stathmin for their survival, while normal cells live happily without stathmin. Future development of drugs to mimic stathmin depletion holds the promise to kill cancer cells without producing side effects in normal tissues. To take full advantage of stathmin as a drug target, we need to understand where and how it functions to promote cancer cell survival. This project examines how stathmin blocks apoptosis in cells lacking p53.

Magee Womens Research Institute ($1,194,952)

- Project Title: Roles of the Nuclear Receptor Cofactor LCOR in Placental Development and Gene Expression
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: The nuclear receptor PPARγ (Peroxisome Proliferator-Activated Receptor γ) is a transcription factor essential for placental development, and its deficiency results in early embryonic lethality due to placental failure. One of the key target genes of PPARγ in the placenta is Muc1. Our analyses of the transcriptional regulation of Muc1 by PPARγ identified the novel cofactor LCoR (Lignad-dependent nuclear receptor Co-Repressor) as a strong and specific co-activator of Muc1 transcription by PPARγ. Coupled with the observation that LCoR expression is enriched in the placenta, these findings underlie the hypothesis that LCoR is a key PPARγ-associated co-activator during placental development. This project will test this hypothesis by phenotypic and gene expression analyses of LCoR-deficient embryos in vivo and by biochemical dissection of the LCoR activity in vitro.
- Project Title: Establishment of an Animal Model for Respiratory Infection with Influenza during Pregnancy
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The purpose of the project is to develop and test a pregnant mouse model for respiratory challenge with influenza virus infection given the disproportionate morbidity and mortality seen among pregnant women during previous influenza pandemics and seasonal epidemics. Development of a pregnant animal model for respiratory challenge will also allow for future investigations to delineate more effectively the susceptibility to infection noted among pregnant women and their immunological response mechanisms. In addition, with the growing threat of bioterrorism and the fact that most of the category A bio-terror agents would be targeted for inhalational spread, development of a pregnant animal model will allow for ongoing research in countermeasures to current and evolving agents of high biological importance in this unique patient population.
- Project Title: Immune Responses to Herpes Simplex Virus Type 2 and Chlamydia Muridarum in a Murine Model of Co-infection
  Type of Research: Clinical
  Focus: Infectious Diseases and Microbiology
  Purpose: The number of individuals infected with genital Herpes Simplex Virus Type 2 (HSV-2) has reached epidemic proportions, and considerable evidence suggests that HSV-2 infection of the genital tract facilitates sexual transmission and acquisition of HIV. Recent clinical evidence also suggests that co-infection of the female genital tract with HSV-2 and *Chlamydia trachomatis* results in increased upper genital tract pathology including increased blockage of the Fallopian tubes. However, better elucidation of the immunologic response to HSV-2 is hindered by the lack of an acceptable animal model. We will first establish a female mouse model of genital HSV-2 infection and then use this model to determine the mechanisms used

to control vaginal HSV-2 infection and investigate how antecedent HSV-2 infection may modulate the immunologic response to subsequent infections with chlamydia.

- Project Title: Integration Study of the Target Genes of PPAR gamma in Human and Mouse Placenta
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The Peroxisome Proliferator Activated Receptor gamma (PPAR-gamma) is a transcription factor essential to placental development and function. The main purpose of this project is to identify genes that are affected by PPAR gamma in placenta. The results will lead to better understanding of the mechanism of PPAR gamma in human placenta, and potentially help to prevent or alleviate many pregnancy complications, such as intrauterine growth restriction (IUGR) and preeclampsia.
- Project Title: Soluble KIT Receptor in the Pathogenesis of Preeclampsia
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The purpose of this study is to learn more about what causes the human pregnancy-specific hypertensive disease called preeclampsia. Two factors belonging to a class of proteins known as soluble receptors have been identified in the circulation of women with preeclampsia that appear to damage to the mothers blood vessels and thus contribute to development of the disease. We have discovered that women with preeclampsia are distinguished by abnormally low circulating concentrations of a third soluble receptor s-kit (CD117). Evidence exists to suggest that this factor could adversely affect vascular function. We wish to see if s-kit increases in the blood early in pregnancy, heralding the development of preeclampsia, consistent with a causal role and/or disease prediction utility, and to study the expression and secretion of this factor by the placenta.
- Project Title: Post-Transcriptional Regulation of Fstl1 mRNA in Human Trophoblasts
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Our goal is to understand how cellular stress influences placental function, with its consequences on the developing fetus. Recently, we showed that oxygen deprivation alters the expression of many genes in the placenta, including genes that encode for microRNAs (miRNAs). The expression of one of these miRNAs, miR-198, is increased in hypoxia and is predicted to target the transcript for Fstl1. Suppression of Fstl1 could have important consequences for the placental function. In this project, we plan to investigate the influence of hypoxia on the post-transcriptional regulation of Fstl1 in the human placenta.
- Project Title: Analysis of Functional Domains within NDRG1
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Our research goal is to improve pregnancy outcome and allow the developing fetus to reach its full developmental potential. This project centers on the placenta, a "sole-source" provider of oxygen and nutrients to the developing fetus. Decreased supply of oxygen (hypoxia) is a common pathway for many injuries that may affect the placenta. We focus our research on a protein (NDRG1) that we have identified as a critical regulator of placental adaptation to hypoxia. While it is known that NDRG1 diminishes placental injury and cell death in response to hypoxia, we do not understand how NDRG1 works. We propose to dissect the mechanism of action of NDRG1 in placental cells. This will allow us to control the action of this protein,

which may pave the way to new tools designed to improve placental function, and consequently, fetal health.

- Project Title: Immunity to MUC1 Tumor Antigen in Conditional and Transplantable in vivo Models for Ovarian Cancer
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Ovarian cancer is the most lethal gynecologic cancer. Standard treatment for this disease begins with surgery followed by chemotherapy. However, these approaches are often ineffective, thus raising the need for new and improved therapies. The patient's immune system has the ability to recognize antigens on tumor cells and to eliminate them, making immune therapy with cancer vaccines an attractive approach for adjuvant therapy. The design and implementation of tumor antigen-based vaccines requires adequate in vivo animal models. In this project, we will generate two in vivo mouse models that express the tumor antigen MUC1, a cancer vaccine candidate. Using these complex models we will study how the immune system recognizes the antigen during ovarian cancer progression, with consequences on future cancer vaccine design.

Monell Chemical Senses Center ($217,894)

- Project Title: Effect of Genotype on Smoking, Taste and Obesity in Mothers and Children
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to explore the intereaction between behavior and genotype as it impacts human health, focusing on smoking and its relationship with taste, food preferences and obesity in mothers and their children. Previous work from our laboratory as well as others have indicated that alleles of a particular gene (a bitter receptor, *TAS2R38*) is associated with these behaviors (smoking, taste preferences and food choice). We will initiate a new study to determine how alleles of this gene and other candidate genes are related to smoking, bitter taste sensitivity and fat and sugar preference in mothers and their children. The information gleaned from this research may enable a better understanding of how individual differences in taste sensitivity contribues to health-promoting behaviors in the context of development.

MPC Corporation ($115,727)

- Project Title: Computational and Experimental Approaches for Predicting miRNAs and their Targets
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Micro ribonucleic acids (miRNAs) are small RNAs that have important roles in regulating gene expression by binding to other RNAs. Deleterious polymorphisms in either the miRNA or its target will have significant effects on development and cell differentiation and are, therefore, associated with disease and congenital birth defects. While datasets of known miRNAs are accumulating at a steady rate, very little is known of the targets, and hence function of these miRNAs. This project seeks to develop computational prediction algorithms to predict miRNAs and their targets in an experimentally tractable organism, the sea urchin. High throughput experimental technologies will be used to test these predictions and refine the algorithm. This computational tool can then be used to predict miRNAs and targets in other organisms, including humans.

- Project Title: High-Throughput Estimation and Modeling of Protein Filament Distributions from Microscope Images
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Proteins that form filamentous networks (e.g., microtubules, actin filaments) inside the cell play a crucial role in providing the cell its mechanical properties and, therefore, are related to many important biological processes, including wound healing and cancer metastases. Researchers who wish to characterize the effects of different drugs (or other alterations in the cell's environment) on these proteins are currently limited to performing qualitative studies because current imaging technology (including software) is insufficient for this task. Our goal in this project is to develop a software tool that can be used to extract the spatial distribution (structure) of these proteins directly from fluorescence microscopy images, thus facilitating future health sciences discoveries.
- Project Title: Computational Modeling of miRNA Involvement in Pulmonary Gene Networks
  Type of Research: Biomedical
  Focus: Respiratory Sciences
  Purpose: MicroRNA (miRNA) genes are small, non-coding RNAs that act as gene expression regulators. They have been associated with various diseases (pulmonary fibrosis, heart failure, cancer) and important biological processes (cell differentiation, development). This project will develop computational methods to study miRNA's involvement in complex eukaryotic gene networks. New and existing computational methods will be evaluated on publicly available data. Experimental high-throughput data collected from lung epithelial cells—following stimulation by a factor associated with idiopathic pulmonary fibrosis (IPF)—will be analyzed as a proof-of-principle. The analysis will identify miRNAs involved in critical networks in cells related to IPF. Our results will also enhance the understanding of basic principles in cells' response to stimuli.
- Project Title: Modeling the Interactions of Dual Specificity Phosphatases with Inhibitors
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Dual specificity phosphatases (DSPs) have become important targets for drug discovery, with the establishment of their deregulatory role in cancer and Alzheimer's disease. However, deficiencies in scoring protein-ligand interactions and inadequate consideration of protein conformational flexibility have limited the utility of computational approaches. Our purpose is to develop efficient computational models and methods to study the interactions of DSPs with small molecules toward developing selective and potent inhibitors. We will focus on the interactions of Cdc25B and MKP-1 with their inhibitors and substrates using elastic network models and various docking algorithms. Computational results will be analyzed in conjunction with experimental data from high throughput screening experiments conducted at the University of Pittsburgh Drug Discovery Institute.

National Disease Research Interchange ($58,338)

- Project Title: Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes
  Type of Research: Biomedical
  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. A previous project confirmed that genetic factors likely influence susceptibility to microvascular complications of diabetes, including retinopathy, kidney disease and neuropathy. We will test for associations between specific genes and the presence or absence of complications by using HBDI samples newly typed by the T1DGC (Type 1 Diabetes Genetic Consortium). To enhance our analyses and maintain the scientific value of our dataset, we will continue our program of administering follow-up questionnaires, begun in 2007. Finally, we will begin a SNP saturation study of statistically important genes. The additional information we collect will better define the genetic contribution to diabetes complications.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation ($1,288,794)

- Project Title: Development of Prognostic Index for Colon Cancer Patients Using Gene Expression Profiling
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Currently about a half of patients with a colon cancer diagnosis receive very toxic chemotherapy regimens containing oxaliplatin. However, we know that much milder chemotherapy that does not contain oxaliplatin may be effective in preventing recurrence in a considerable proportion of colon cancer patients. A test that can identify those who do not need oxaliplatin will help many patients avoid unnecessary, toxic therapy. We will utilize a whole genome expression analyses method to screen tumor specimens collected from already finished, large clinical trials conducted by the National Surgical Adjuvant Breast and Bowel Project to develop a prognostic test to achieve this goal. Statistical rigor will be exercised in the project to assure that the test we develop will be highly reliable for actual clinical use.

Oncology Nursing Society ($12,473)

- Project Title: The SEA Preparatory Intervention for Women with Metastatic Breast Cancer
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this pilot randomized controlled project is to provide information to women newly diagnosed with metastatic breast cancer (MBC) that they can use at diagnosis and across the illness continuum to maintain quality of life and reduce distress.

Pennsylvania State University ($7,628,852)

- Project Title: Vitamin D and Crohn's Disease: From the Bench to the Bedside
  Type of Research: Clinical
  Focus: Digestive Sciences
  Purpose: Decreased outdoor activity and increased pollution and diets that lack adequate vitamin D have combined to create large fluctuations in vitamin D status, especially in populations that experience winter. Since vitamin D regulates the development and function of the immune system, this may account for the increase in autoimmune diseases like inflammatory bowel disease (IBD). Changes in vitamin D status result in more severe forms of experimental IBD, but vitamin D supplementation completely blocks the development of experimental IBD. Our hypothesis is that Crohn's patients have low circulating levels of vitamin D, which

may exacerbate IBD. We propose to give Crohn's patients vitamin D and determine whether this dose is well tolerated, induces an increase in circulating vitamin D levels and/or improves health.

- Project Title: Epigenetic Regulation of Inactive X Chromosome Expression
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Personalized medicine, or the tailoring of pharmaceuticals and treatments to specific individuals, is an important goal of genomic medicine in the 21st century. It is increasingly apparent that even subtle gene differences may impact common traits. We are interested in evaluating gene differences that effect the female sex chromosome (X) where most, but not all, genes on the second X must be silenced. The goal of these experiments are to evaluate the variation in gene expression for genes on the X chromosome and to design an assay that can quickly and effectively assess inactive X expression for specific genes to assess their role in common diseases.
- Project Title: Role of UGT2B7 Genotype in Patient Response to Tamoxifen
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The glucuronidation phase II metabolic pathway is an important factor in breast cancer recurrence and toxicity associated with tamoxifen (TAM) treatment, and genetic mutations in the enzyme responsible for metabolizing TAM may play a key role in determining overall patient response to TAM. We propose to test this hypothesis by measuring levels of TAM metabolites in patients on TAM and correlating these levels with the presence of genetic mutations. Using detailed clinical questionnaires, we will also examine the potential association between the presence of mutations and patient toxicity and side effects (hot flashes, arthralgias, deep vein thrombosis and uterine cancer). Long-term goals will include studies examining whether these genetic mutations impact breast cancer recurrence and metastasis.
- Project Title: Functional Brain Imaging of Memory and Language for Epilepsy Surgery
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: The purpose of this project is to translate procedures and findings in experimental functional MRI (fMRI) into clinically validated techniques for localizing language and memory systems in the brain of patients undergoing surgery for epilepsy (i.e., temporal lobectomy). The current Wada procedure, which is used to localize systems in the brain, was developed over 50 years ago and is highly invasive, and does not always provide interpretable data. We propose to investigate the feasibility of using fMRI procedures as reliable indicators of language and memory localization to replace the Wada Test.
- Project Title: Molecular Targets for Preventing Loss of Skeletal Muscle Mass
  Type of Research: Biomedical and Clinical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The loss of skeletal muscle mass that occurs in a number of physiological and pathological conditions has adverse effects on functional strength and mobility, and in many conditions is associated with an increase in morbidity and mortality (e.g., aging, sepsis, cancer). In order to design appropriate therapeutic interventions to ameliorate skeletal muscle atrophy, the molecular mechanisms that regulate skeletal muscle size must be thoroughly understood. Significant strides have been

made recently with regard to elucidating the pathways involved in the regulation of both protein synthesis and degradation in muscle, but many gaps still remain in our understanding of the complex processes regulating muscle growth in adults. The purpose of this project is to more fully characterize a molecular target identified as key in the regulation of protein synthesis.

- Project Title: Research Infrastructure - Biological Research Laboratory Construction
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to design and build an Animal Biosafety Level three (ABSL-3) research laboratory for the study of immunology and infectious diseases requiring high level Biocontainment. This project is a continuation of the project funded by the 2007-08 formula grant.
- Project Title: Regulation of Nutrient Sensing and Muscle Wasting by Alcohol
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Metabolic balance is maintained at the cellular and whole-body level by responding to signals from the environment and from inside the body, namely growth factors, hormones, and stress signals. Chronic consumption and acute ingestion of alcohol reduces the muscle mass of those abusing this drug by changing the body's ability to respond to some of these signals. The purpose of the project is to elucidate how alcohol decreases the ability of the amino acid leucine to increase the synthesis of muscle proteins. If we can determine this mechanism, therapeutic interventions can potentially be developed which prevent the loss of muscle under this condition and as a result of other stress conditions, such as immobilization, trauma, infection, which have similar effects on muscle protein balance.
- Project Title: Murine Induced Pluripotent Stem Cells: Differentiation and Bone Formation
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: The goals of the project are to assess the potential of stem like cells called induced pluripotent stem cells (iPS) to differentiate toward mesenchymal stem cells (MSCs) and to make bone and cartilage in vivo, thus to understand the future application of the cells for the repair and regeneration of musculoskeletal tissues.
- Project Title: Evaluation of mTOR as a Chemoprevention Target in Skin Cancer
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The object of these studies is to validate the mammalian target of rapamycin (mTOR) as a target for chemoprevention of non-melanoma skin cancer. Since skin cancers are the most common form of malignancies, with increasing numbers world-wide, identification of possible targets for their prevention are particularly relevant to public health.
- Project Title: IRES-Mediated Synthesis of Proteins Integral to Adaptation to Hyperoxia
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is determine if exposure of human lung cells to high concentrations of oxygen alters the processes responsible for synthesis of specific proteins. In particular, our goal is to understand how high ambient oxygen concentrations increase the synthesis of some proteins while decreasing the synthesis of others. We believe, that oxygen "uncovers" alternative synthetic

processes inherent in some protein templates, thereby enabling increased synthesis during periods of stress.

- Project Title: Stroke Recovery in Type II Diabetes
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The overall objective of this project is to determine the role anti-diabetic agents have on stroke outcome. Although it is well established that diabetics are at an increased risk of mortality and morbidity following an ischemic stroke there are no known therapies that are specifically targeted at diabetics to improve stroke recovery. This is a significant public health problem considering that the worldwide diabetic population is growing at an alarming rate and thus the incidence of strokes is undergoing the same dramatic increase. This project will test both the chronic and acute effect of several anti-diabetic agents on stroke outcome with the specific objectives of determining which are the most efficacious in promoting recovery in the diabetic animals and the mechanism(s) by which the respective agents elicit their actions.
- Project Title: Modulation of Basal Ganglia Electrophysiology by Dopaminergic Cell Transplant
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Cell transplants have been shown to provide symptomatic relief for Parkinson's disease patients and in parkinsonian animal models. Separately, researchers have highlighted abnormal brain electrical patterns that occur in Parkinson's disease and are partially reversed with levodopa treatment. This project looks at a crucial related question which has not yet been examined: whether cell transplants change the electrical patterns in the brain. The results of the project will shed crucial light on the utility of cell transplants compared to levodopa treatment and the potential to reduce dyskinesias (a major side effect of prolonged levodopa treatment). The results will also shed light on basic neuroscience questions underlying Parkinson's disease pathology.
- Project Title: Identification and Analysis of Arterial Blood Pressure Noise in Baroreceptor Denervated Rats
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The arterial baroreceptor reflex rapidly and effectively stabilizes blood pressure. A prominent finding, across many species, is that eliminating the baroreceptor input by sinoaortic denervation (SAD) more than doubles arterial pressure variability (APV). Understanding the sources and basic mechanisms of APV is of clinical importance. Using neuromuscular blocked (NMB) rat preparation, we will specifically examine the obligate roles of the baroreflex key way stations, e.g., the rostral ventral lateral medulla (RVLM), in producing the large post-SAD APV. The funds will be used to collect preliminary data for our NIH R03 2nd re-submission. Our long-term goal is to develop APV analysis into a non-invasive and economical tool for clinical prognosis and diagnosis of cardiovascular diseases.
- Project Title: Myocardial Protein Synthesis after Alcohol Intoxication
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Although the risk of cardiovascular diseases is reduced with moderate alcohol consumption, chronic alcohol abuse leads to heart dysfunction and potentially heart failure. Excessive use of alcohol has a direct toxic effect on the heart demonstrated by a weakening of the heart muscle and the inability to pump blood efficiently. The degree of dysfunction is proportional to the duration and severity of

alcohol consumption, with continued heavy drinking leading to an enlarged heart. The purpose of this project is to understand how excessive, chronic alcohol consumption causes structural and functional damage to the heart at the molecular level. Detailed understanding of the defects caused by alcohol will allow for a better understanding of the molecular events surrounding the onset of alcohol-induced heart disease and may allow for the development of targeted therapies.

- Project Title: Development of Nanoliposomal Therapeutics for Leukemia
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Leukemia is a cancer of the blood which is expected to cause 21,710 deaths in 2008 in the United States. Research continues to find mutations that cause leukemia. Inhibitory RNA (RNAi) is a silencing mechanism that turns off a gene. RNAi directed at a cancer-causing mutation can specifically kill cancer cells. However, RNAi must be delivered to cells and protected from degradation in order to work. Small vesicles called nanoliposomes create an efficient and non-toxic delivery vehicle for RNAi as well as other drugs. Another drug that selectively kills cancer cells is ceramide. Ceramide is a lipid produced in the body during many chemotherapy treatments that is partly responsible for the action of these drugs. This project seeks to test anti-leukemia treatment with nanoliposomes containing ceramide, RNAi, or both, initially in mouse and ultimately in future projects in human leukemia.
- Project Title: P16 Alteration and BRAF Mutation and Patient Outcomes in Papillary Thyroid Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Thyroid cancer represents the most common endocrine malignancy, with papillary thyroid cancer (PTC) accounting for 90% of malignant thyroid tumors. Although outcome is generally favorable, a group of patients develop local recurrence and/or distant metastases and ultimately die of their disease. For these patients with aggressive disease, better diagnostic and prognostic tools are clearly needed. Molecular markers that accurately predict tumor behavior are lacking. In the past, p16 gene alterations and BRAF mutations have individually been implicated in tumor aggressiveness in PTC. We hypothesize that presence of these mutations simultaneously in patients with PTC is a predictor of worse clinical outcomes and tumor aggressiveness.
- Project Title: The Interaction of Environmental Agents and LDL-Cholesterol in Parkinson's Disease
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: This project seeks to characterize the apparently paradoxical observation that low cholesterol (LDL-C) is a risk factor for Parkinson's disease (PD), and to examine some of the possible underlying mechanisms. One aim is to collect pilot data and support the planning of testing the association between low LDL-C and PD further via a prospective study in the "Atherosclerosis Risk in the Communities" (ARIC) cohort. The second aim is to test the idea that lower LDL-C is etiologically-linked to PD because it affects the distribution or toxicity of trace environmental toxicants. The data provided by this pilot study will set the stage for more detailed examination of the health consequences of these findings and their underlying mechanisms with the collaboration of a PD clinician, epidemiologist, and basic neuroscientist.
- Project Title: Moving Experimental Cancer Therapeutics from the Research Bench to the Clinic

Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The Penn State Melanoma Therapeutics Program has a Therapeutic Drug Portfolio of ~20 experimental therapeutic compounds at various stages of development. Unfortunately, agents proceed through preclinical development at which point progress halts. The purpose of this project is to establish the necessary expertise and infrastructure to more rapidly move these compounds to the clinic. This involves developing interactions with companies to make clinical grade compound for testing in patients; undertaking necessary toxicological and pharmacological evaluation for an Investigational New Drug (IND) application; and interacting with the Food and Drug Administration (FDA) to enable experimental agents to obtain IND status so that they can be evaluated in the Pennsylvania State University (PSU) Cancer Institute Clinics in phase I trials. Accomplishing these objectives for one of the compounds from the current melanoma drug portfolio is the objective of this project.

- Project title: Changes in Oxygen-induced Proliferative Retinopathy in 4E-BP1/2 Knockout Mice
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this project is to determine if dysregulation of protein synthetic pathways contributes to the aberrant development of retinal blood vessels in oxygen-exposed newborn rodents. Using newborn mice deficient in proteins (4E-BP1/2) regulating the initiation phase of protein synthesis, we seek to determine the impact of high concentrations of oxygen to retinal blood vessel growth and vascular endothelial growth factor expression. We believe that the findings from this project will provide a useful framework from which to develop clinical and therapeutic interventions to protect premature newborns from the detrimental effects of oxygen exposure.
- Project title: Molecular Mechanisms of Uninfected Red Cell Phagocytosis in Severe Malarial Anemia (SMA)
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this study is to determine how uninfected red cells are destroyed by macrophages of malaria-infected mice.
- Project Title: In Vivo Anti Tumoral Properties of Ceramide Nano-Liposome in Murine Hepatocellular Cancer
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Through the use of nanotechnology, ceramide has been encapsulated in tiny bundles called liposomes. Ceramide is a sphingolipid, and is not soluble in blood. However encapsulation of ceramide into nanoliposome allows ceramide to travel in the bloodstream without any toxicity and thus allows it to target the tumor. Previous studies in murine breast cancer models showed that ceramide preferentially induced apoptosis of breast cancer cells, sparing the surrounding healthy tissue and found that very high doses of ceramide was non-toxic to the animals. In this study we will apply ceramide liposome treatments for cancer therapy using a SV40 T- antigen murine model system aimed at the inhibition of the solid tumor of hepatocellular cancer (HCC). These studies are critical in understanding the importance of the liposomal drug therapy, and may be unique for the experimental model.
- Project Title: The Use of Biomarkers to Predict the Onset of Vasospasm in Aneurysmal Subarachnoid Hemorrhage
  Type of Research: Biomedical and Clinical

Focus: Neurosciences
Purpose: The purpose is to create a panel of key molecular markers that can be used as a diagnostic test to predict the occurrence of cerebral vasospasm in the setting of aneurysmal subarachnoid hemorrhage (SAH).

- Project Title: Tim-2 Expression on Oligodendrocytes: A New Immune System Target
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Recently, we have made a novel and exciting discovery that Tim-2 receptor is selectively expressed on oligodendrocytes. One of the ligands for Tim-2 is Sema4A, which is highly expressed in the immune system, and is critical in regulating immune attacks on the myelin in animal models of multiple sclerosis (MS). We have shown that when oligodendrocytes are exposed to Sema4A in a cell culture model they die. This is an exciting and new finding suggesting that the Sema4A/Tim-2 interaction may be the deleterious relationship between oligodendrocytes and immune cells that scientists have been seeking. Therefore, in this project, we want to investigate mechanism of Sema4A-induced oligodendrocyte death.
- Project Title: Mechanisms of Microsatellite Mutagenesis in Human Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Short, repetitive DNA sequences, called microsatellites, are a characteristic feature of the human genome. Mutations within microsatellite sequences are causally linked to the development of several human diseases, including cancer and cardiovascular illness. We have created a new, interdisciplinary program among computational and experimental investigators at Penn State University to elucidate the mechanisms whereby microsatellites arise, mutate, and disappear within individual human genomes. The purpose of this project is to provide direct experimental evidence in support of our new collaborative model in order to improve the competitiveness of our NIH-R01 application.
- Project Title: Epigenetic Therapy of Human B Cell Malignancies
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: Cancers of B cells including leukemia and lymphoma are common and mostly incurable. We have used a unique combination of chemotherapy and immunotherapy to achieve durable complete response in B cell malignancies like mantle cell lymphoma. Clinical trials have been initiated to test these hypotheses. Clinical samples will be available from these trials for correlative science studies. The purpose of this project is to use these samples to determine the silenced target genes activated by our treatment regimen and to further study these genes in vitro.
- Project Title: Novel Multielectrode Recording Techniques for Assessment of Taste Functions in the Brain
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Obesity contributes to a number of life threatening health problems such as non-insulin dependent diabetes, hypertension, and coronary heart disease. The causes of obesity are complex but overconsumption motivated by palatable foods may be an important factor in the etiology of obesity. Since meal size is controlled by sensation originating in the oral cavity, the contribution of oral sensation will potentially provide significant data on ways to control obesity. The present application seeks support to develop novel multielectrode recording techniques necessary to obtain critical pilot data for a future NIH R01 grant application. Specifically, the project will record activity of gustatory-sensory neurons of the

hindbrain in high caloric high fat diet-induced obese (DIO) and lean male rats to compare taste responses to palatable sucrose solutions in hungry and sated states.

- Project Title: Glycosphingolipids and Diabetic Retinopathy
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Diabetic retinopathy is the leading cause of blindness among working age adults. We have found that a class of lipids, glycosphingolipids, is elevated in the diabetic retina. The purpose of this study is to understand the consequences of elevated glycosphingolipids within the retina and determine if systemic inhibition of glycosphingolipid accumulation is therapeutic for diabetic complications.
- Project Title: Epithelial/Dendritic Cell Crosstalk in Acute Kidney Injury
  Type of Research: Biomedical
  Focus: Renal and Urological Sciences
  Purpose: The purpose of these studies is to evaluate the interactions between cells of the immune system and kidney cells in causing drug-induced damage in the kidney.
- Project Title: Synergistically Acting Targeted Therapeutics for Melanoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Malignant melanoma remains the most deadly skin cancer with no effective drugs available for the long-term treatment of patients. The melanoma community believes that targeting Akt3, ^{V600E}B-Raf and other key kinases deregulated in melanoma is needed to effectively treat this disease. However, the identity of kinases to target using siRNA for synergistically acting tumor inhibition remains unknown and delivery of siRNA in animals remains a challenge. Therefore, the purpose of this project is to develop therapeutic agents inhibiting proteins deregulated in melanoma to shrink tumors in a synergistically acting manner. To accomplish this nanoliposomes containing siRNA designed to target ^{V600E}B-Raf, Akt3 and other key kinases in melanoma will be developed and efficacy for synergistically inhibiting melanoma development in skin and animals evaluated. Accomplishing these objectives not only identifies key kinases to synergistically inhibit melanoma development but also validates the utility of siRNA-loaded liposomes for treating melanoma patients.
- Project Title: Diabetic Changes in Contractile Proteins and Contractility in Arterial versus Venous Grafts
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Coronary artery disease is the leading cause of death and disability in patients with diabetes mellitus. Because of this, more than 300,000 patients with diabetes undergo coronary revascularization procedures annually in the U.S. to clear coronary blockages. Unfortunately, the benefit of percutaneous coronary intervention in diabetic patients is limited by their tendency to develop coronary restenosis by nearly 2- to 4-fold compared with nondiabetic patients. To date, the extent of alterations in contractile protein levels and the contractile responses in arterial *vs.* venous grafts remain unclear. Hence, the current project will compare diabetic *vs.* nondiabetic alterations in contractile proteins that regulate smooth muscle contractility in arterial and venous grafts, which will be obtained from patients undergoing coronary artery bypass grafting surgery.
- Project Title: Autism Indicators: Erythrocyte Membrane Fluidity and/or Lipid Composition
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: To determine whether fluidity and/or lipid composition of isolated red blood cell membranes differ in children with autism compared to age and gender matched children who are developing normally. If consistent differences are observed, funding to determine whether they are of diagnostic value will be sought.

- Project Title: Efficacy of Gemcitabine for Pancreatic Cancer: Role of DNA Polymerases
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: Pancreatic ductal adenocarcinoma is a very aggressive malignancy that is treated by gemcitabine. Its efficacy is thought to be due to inhibition of DNA synthesis. It is our hypothesis that newly discovered DNA polymerases modulate gemcitabine toxicity and thereby decrease its efficacy. The purpose of the present experiments is to test the hypothesis that inter-individual differences in the levels of these polymerases affect incorporation of gemcitabine into the DNA and its efficacy in pancreatic cancer patients receiving gemcitabine.
- Project Title: Embedded Rural Clinical Research Infrastructure: Utilization of Community Based Nurses and Paramedics
  Type of Research: Health Service
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project establishes the foundation for a research and community health approach that will be applicable to rural Americans nationwide. Rural Pennsylvanians are an underserved and aging population who suffer from an increased rate of elder falls and poor rates of influenza immunization. This project will deploy an innovative strategy to engage this community by using Penn State Cooperative Extension agents working together with newly trained and embedded health assessment staff. Embedded nurses and emergency medical technicians may offer an effective solution to furthering community assessment, improving important health measures, and creating new employment opportunities for these providers. Home safety assessment recommendations will be collected and recommendations for aging in place re-construction will be made with preferred local contractors.
- Title: Cytoadherence in Maternal Malaria
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Infection by malaria parasite Plasmodium falciparum during pregnancy, especially during the first pregnancy, results in several pathological conditions, including low birth weight, spontaneous abortion, still birth, and maternal morbidity and mortality. The pathology is caused by the accumulation of parasite-infected red blood cells in the placenta by the binding of a parasite adhesive protein expressed on the infected red blood cell surface to chondroitin 4-sulfate receptor in the placenta. Knowledge of the structural interactions involved in this adherence process will be valuable for the development of a vaccine and/or therapeutics for pregnancy-associated malaria.
- Title: Impact of iPS Cell-derived Highly Reactive Immune Cells on Cancer
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Adoptive cell transfer (ACT) of tumor-specific T killer cells that are able to directly or indirectly kill or suppress cancer cells is a promising treatment for cancer. It is known that highly avid T killer cells are the optimal population for ACT-based immunotherapy. However, ACT with such T killer cells is often not feasible due to difficulties in generating large numbers of these cells from patients. Finding a new mechanism to generate these cells is critical for the success of ACT-based cancer immunotherapy. Using a series of complementary approaches, including the

combination of genetic modification and in vitro development, we will generate and characterize highly avid melanoma-reactive T killer cells from induced pluripotent stem (iPS) cells, and study the impact of iPS cell-derived T killer cells on cancer.

- Title: Cannula Development and In Vivo Testing for Pediatric VAD Development
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: – The purpose of this research is to take the Penn State Pediatric Ventricular Assist Device (VAD) to the next stage of development. The Pediatric VAD is a blood pump, which is intended for infants less than 9 months of age and can take over the work of the heart in cases where the heart function is weakened by disease or congenital defects. The VAD is designed to function for many months, as a bridge to heart transplantation, or as support leading to recovery of native heart function. The specific objectives of this project are to develop cannulae, which are specially designed tubes that connect the VAD to the patient's heart and blood vessels, and to test the VAD/cannulae system in animal studies for 8 weeks in duration. The goal of these studies is to demonstrate minimal risk of clot formation and stroke, leading to pre-clinical studies and eventual clinical trials.
- Title: Role of Leucine Metabolism in Leucine Signaling
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: There are three major purposes for the project. First, we will determine whether branched chain amino acids (BCAA) or branched chain keto acids (BCKA) regulate protein synthesis and breakdown and how altered BCAA catabolism controls protein turnover and energy expenditure in three lines of gene knockout mice targeting BCAA catabolism. Second, we will determine the mechanisms underlying elevated plasma BCAA in obesity. These studies will provide a better understanding of how BCAA catabolism regulates energy expenditure in normal and obese rodents and therefore will clarify some of the confusion regarding the role of BCAA in obesity. Third, these studies will result in at least two manuscripts for publication, therefore addressing one major concern from the reviewers of our R01 application for resubmission of the grant.

Philadelphia College of Osteopathic Medicine ($17,036)

- Project Title: Dissecting the Apoptosis Pathway Affected by *C. pneumoniae* in Alzheimer's Disease
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Alzheimer's disease (AD) is thought to be the leading cause of dementia in the elderly population, and is recognized clinically in early-onset (familial) and more prevalent late-onset forms, both of which manifest similar neuropathologies. This project will examine the detailed events that lead to neuronal cell death in late-onset AD, specifically the role in initiating these events played by the bacterium Chlamydia pneumoniae (Cpn), a common pathogen that infects the respiratory system and has been found in the autopsied brains of late-onset AD patients. We focus on the apoptotic process that has been implicated in the death of neurons in AD. Understanding these mechanisms may lead to treatment strategies for the growing numbers of AD patients.

Pittsburgh Tissue Engineering Initiative ($15,697)

- Project Title: Novel Biofuel Cell Based on High Surface Area Enzymatic Microelectrodes
  Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of this project is to develop a miniaturized biofuel cell, a device that can turn available substances like glucose to energy, by using an assembly of biocatalysts and a special high surface area electrode. The device will be designed to utilize glucose as the only fuel, and turn this into energy by a series of enzymatic reactions, using commercial enzymes as the combustion elements. The process will be carried out on the surface of a new type of electrodes, comprised of extremely high surface area gold microfibers, which will be developed. The high surface area will enable immobilization of a high concentration of enzymes and better diffusion of glucose and oxygen to and from the electrode. The final size of the device is expected to be small, i.e. less than 0.1 cm^3, and could be implanted in the body to power devices like insulin pumps or pace makers.

Public Health Management Corporation ($20,369)

- Project Title: The Association of Drug Use and Sexual Risk for HIV Infection Among Black Men Who Have Sex with Men
  Type of Research: Health Services
  Focus: AIDS and Related Research
  Purpose: The overall purpose of this project is to increase the current understanding of the factors that contribute to the disparate rates of HIV infection among Black men who have sex with men (MSM). Urban Black MSM are the single population most heavily impacted by the HIV epidemic in the United States, with HIV infection rates rivaling those found in many sub-Saharan African nations. This project will utilize existing data gathered from a sample of 540 Black MSM in Philadelphia to examine the link between drug use and sexual risk behaviors that may result in HIV infection (including acquisition or transmission). Moreover, this project will examine the link between drug use and HIV sexual risk for different subgroups of Black MSM, including HIV-negative and HIV-positive MSM, men who use different types of substances, and MSM who are gay- and non-gay identified.

Salus University ($60,332)

- Project Title: Molecular Mechanisms of Leber's Congenital Amaurosis
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Leber's congenital amaurosis (LCA) is an early-onset loss of vision that constitutes a group of genetically diverse inherited retinal disorders, often resulting in complete blindness. Severe forms of LCA result from mutations in an enzyme called retinal guanylyl cyclase 1 (RetGC1). Two new mutations in RetGC1 were recently found in patients diagnosed with LCA, and the preliminary biochemical characterization of the mutant enzyme revealed strong abnormalities in its activity and regulation. The purpose of this project is to conduct a pilot short-term study of the possible physiological implications of these two mutations using transgenic mice in order to establish their relevance to the onset of LCA.

Temple University ($2,005,437)

- Project Title: Resolving Inflammation in Arthritis
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Conventionally, inflammation has been perceived as a progressive reaction that gradually dissipates, so the therapeutic approach has been to block activation of inflammation. COX-2 inhibitors, which inhibit production of the pro-inflammatory prostaglandin E_2 (PGE_2) and reduce pain, have been widely prescribed. However, a

new concept that views inflammation as an active, orderly process with phases, induction-progression- resolution, and considers chronic inflammation as "failure to resolve" has emerged. In an animal model of arthritis, collagen-induced arthritis, we found that inhibiting COX-2 during resolution exacerbated inflammation. Thus, the purpose of this project is to investigate how the resolution works, and what molecules control the machinery. This is imperative for safety as well as for designing better therapy.

- Project Title: Identification of the Role of TULA-2 a Novel Phosphatase in Osteoclast Differentiation and Function
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Osteoporosis and other bone-related maladies afflict 150 million Americans and constitute a significant burden to ever-rising health care cost. This project will evaluate the role of TULA-2, a novel phosphatase in bone remodeling in mouse skeleton. In addition, ex vivo experiments will be performed to investigate the role of TULA-2 in differentiation and function of osteoclasts. The research proposed here will help in understanding the basic biology behind bone resorption and will help identify targets for therapeutic interventions to control bone loss.
- Project Title: C/EBP(s) and the Transcription of Dihydrodiol Dehydrogenase 1 in Human Ovarian Cancer Cells
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Transcription factors (TFs) induce the expression of the target gene by binding regulatory sequences on the target gene's promoter region. CCAAT/enhancer binding proteins (C/EBPs) are a family of TFs that are important for cellular differentiation and proliferation. The expression levels of C/EBPs transcription factors have been found to change during pathophysiological conditions of the cell. Preliminary studies have identified potential C/EBP binding sites on the dihydrodiol dehydrogenase gene 1 (DDH1) promoter in ovarian cancer cells. DDH are a family of aldo-keto reductases involved in the de novo detoxification of xenobiotics. This study aims to clarify the role of C/EBP TFs in regulating the transcription of DDH1 in ovarian cancer cells.
- Project Title: Development of a Microvascular Network on a Chip
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Recognition of drastically altered endothelial surfaces in various pathologies (e.g., tumors) has led to the concept of endothelial cell adhesion molecule mediated targeted delivery using nanoparticles as drug carriers. However, currently there are no realistic test beds for preclinical testing and optimization of these nanoparticles in a realistic environment. Development of more complex, realistic in vitro flow chambers will not only advance our knowledge in targeted drug delivery but may also reduce the need for animal experimentation. In this project we will design an anatomically realistic in vitro microfluidic chip for testing and optimization of drug carriers and develop protocols for successful growth of cells on the chips to study drug carrier-cell interaction.
- Project Title: CB1 Antagonists as Neuroprotective Drugs
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this project is to improve our understanding of how a drug that was designed to block the effect of chemicals produced by the brain called cannabinoids might be used to protect the central nervous system from injury following trauma or an interruption in blood flow.

- Project Title: The Role of GSK3 in Psychostimulant-Induced Behaviors
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Abuse of psychostimulants including cocaine and amphetamine continues to be a major public health problem that leads to loss of employment productivity, breakdown of families and communities, increases in crime and violence, and a variety of health issues not only for the individual but also for their children. Treatments for addiction to psychostimulants are lacking. As such, identification of potential novel targets for treatment of psychostimulant abuse is needed. This project will examine a novel cellular pathway that mediates some of the behavioral effects of cocaine and amphetamine. The role of the Akt-GSK3 pathway in psychostimulant-induced behaviors will be investigated, as will methods to regulate its function in order to reduce the addictive properties of these drugs.
- Project Title: Biomimetic Composite Design
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this project is to refine analytical models of novel composites intended for use as dental restorative materials. The novelty of the composites lies in borrowing strengthening and toughening strategies from naturally occurring composites, i.e., seashells. The refined models will be useful for designing the new composites.
- Project Title: Interactions Between Cytotoxic and Antiangiogenic Drugs
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Combination anticancer drug therapy is standard for most cancer types, yet the types of drugs that are combined in therapeutic regimens is changing. Rather than combining toxic drugs with severe and overlapping toxicities, new efforts seek to combine drugs not only with different and less severe toxicities, but also drugs with different cell and molecular targets or mechanisms of action. Antiangiogenic drugs are among a new portfolio of agents that may be referred to as targeted drugs that can interfere with the growth and spread of tumors by various mechanisms, and may compliment the action of more traditional cytotoxic drugs. The purpose of this project is to understand how two targeted drugs can be optimally combined with a cytotoxic drug in a preclinical brain tumor model.
- Project Title: Control of Cellular and HIV-1 Gene Expression by Cellular CDK9, A Potential Target for HIV Therapeutics
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: HIV is the causative agent of AIDS (Acquired Immunodeficiency Syndrome). Highly Active AntiRetroviral Therapy (HAART) is a drug combination currently used to reduce viral loads by neutralizing at least two different HIV proteins. However, because HIV mutates, viral strains resistant to current HAART drug combinations arise. It is believed that anti-HIV drugs directed to host cellular proteins that are essential for HIV replication may be a solution to this problem. Therefore, there is an urgent need for identification and validation of such cellular targets and the development of new high throughput assays to identify drugs against them. This project aims at both further characterizing a cellular kinase complex that is hijacked by an HIV-1 viral protein and to design strategies to identify drugs targeting this essential step on the HIV life cycle.
- Project Title: Data Analysis of Cognitive-Behavioral Therapy as an Augmentation Strategy for Social Anxiety Disorder
  Type of Research: Biomedical

Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: We have completed a study of the efficacy of cognitive-behavioral therapy in the augmentation of response to the antidepressant paroxetine for patients with social anxiety disorder. The study was conducted at two sites (Temple University and the New York State Psychiatric Institute). Data files have been constructed at each site but funding expired prior to the initiation of formal data analysis suitable for professional publication. Therefore, the purpose of this project will be the construction of the final merged and cleaned dataset and the conduct of the statistical analysis for this project.

- Project Title: RAD51 Causes Genomic Instability in Chronic Myeloid Leukemia
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: BCR/ABL kinase-positive leukemia cells display genomic instability leading to the resistance to imatinib mesylate and malignant progression of the disease to fatal blast crisis. We reported previously that BCR/ABL enhances homologous recombination repair (HRR) of DNA double strand breaks (DSBs) due to stimulation of expression and tyrosine phosphorylation of RAD51. However, the fidelity of HRR is compromised in leukemia cells. We will investigate in depth the role of unfaithful DNA polymerase beta, BCR/ABL-RAD51 interaction, and constitutive tyrosine phosphorylation of RAD51 in compromising the fidelity of HRR eventually leading to genomic instability in leukemia cells.
- Project Title: Enhancing Diabetic Foot Education by Viewing Personal Plantar Pressures
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to examine the efficacy of a novel patient education strategy, compared to a standard diabetic foot education. The proposed diabetic foot care education uses personal computer-animated plantar pressure data to educate patients on why and how they should care for their feet. The effectiveness of the diabetic foot education will be examined by looking at the following: (1) personal daily foot care as measured by foot-self care behavior scores; (2) subject understanding of peripheral neuropathy as assessed by the Patient Interpretation of Neuropathy Questionnaire; (3) occurrence of foot complications; and (4) peak barefoot plantar pressures.
- Project Title: Tactile Imaging Sensor and Hyperspectral Data for Early Breast Cancer Detection
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to investigate the feasibility of a novel portable tactile and hyperspectral system for the early breast cancer detection. A portable system would dramatically increase the probability of detecting breast cancer early, especially in remote areas. We propose to develop a tactile imaging sensor for breast cancer detection. When an object touches the sensor, the light will be diffused in varying amounts, which can be captured with a camera. Furthermore, we propose to integrate the tactile sensor image with the hyperspectral camera image to generate more accurate diagnosis of the breast cancer. Hyperspectral camera images allow health care providers to see in "different" colors—bands. The material composition of an object can be identified using a hyperspectral camera. This system will allow minimally trained health care provides to detect breast cancer.
- Project Title: Small Animal Model of Medulloblastoma for Translational MR Neuroimaging at 3 Tesla
  Type of Research: Biomedical

Focus: Neurosciences
Purpose: This project will support the acquisition of a customized mouse brain coil which will allow us to adapt our brand new state-of-the-art human 3 Tesla MRI scanner for small animal neuroimaging. We will utilize the mouse brain coil for imaging of our transgenic mouse brain tumor model of medulloblastoma. The ability to perform high resolution neuroimaging and longitudinal studies of our mouse model of medulloblastoma on a human 3 Tesla magnet will give us the ability to directly translate our findings to non-invasive diagnostic, molecular, and therapeutic neuroimaging in the clinical setting.

- Project Title: Developing Radiological Risk Communication for Low-literacy Populations
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Radiological exposure from a terror event has been identified by the Centers for Disease Control and Prevention (CDC) and the Office of Homeland Security as a potential threat worthy of significant national preparedness. Little research has been done, however, to develop risk communication strategies for those with limited literacy. The purpose of this project is to assess whether new approaches to designing risk communication are valid methods to develop emergency preparedness materials for people with low literacy. The project will pilot the use of health literacy measures as well as physiological measure tools (i.e., skin response, eye tracking and respiration) with General Internal Medicine Clinic patients at Temple University Hospital. These pilots will enable us to effectively use these evaluative tools with individuals with low levels of literacy.
- Project Title: Using a Telemedicine System to Promote Patient Care Among Underserved Individuals
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Hypertension (high blood pressure) affects more than 65 million people in the US with African Americans disproportionably affected. Untreated hypertension is associated with an increased risk for heart attacks, sudden death, stroke, and kidney failure. Home-measured blood pressure has become an important method of managing hypertension. This study will test the effectiveness of an Internet-based telemedicine system coupled with home-measured blood pressure to strengthen the patient-provider relationship and to educate and empower individuals with hypertension to take a more active role in their own health care.
- Project Title: Control of Calcium Entry Mechanisms in Smooth Muscle
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: An understanding of the molecular mechanisms of store-operated channels and the coupling interactions between Stim sensors and Orai channels has important implications in vascular SMC function and the development of therapies to treat contractile and growth diseases, including hypertension and atherosclerosis. The purpose of this project is to understand and clarify the basic pharmacology of the activation of these channels which may provide crucial new methods to control Ca2+ in vascular smooth muscle cells.
- Project Title: Assays to Identify Inhibitors of Cellular and HIV Transcription in Human Cells
  Type of Research: Biomedical
  Focus: AIDS and Related Research

Purpose: To develop assays to monitor inhibition of RNA polymerase II (RNAPII) activity and/or phosphorylation or other markers of transcriptional activity in human cells. Identification of compounds with the ability to inhibit particular events during a transcription cycle by RNAPII will generate tools to study the control of gene expression in vivo and in vitro. Further characterization of the selectivity of these compounds as C-terminal domain (CTD) kinase inhibitors in vitro will allow identification of their direct targets. Compounds with enhanced selectivity towards particular cyclin/CDK complexes, or with defined inhibitory potency towards a subset of CDKs may have enormous potential in the clinic for the therapeutic treatment of HIV, cardiac hypertrophy or even certain cancers.

- Project Title: Smoking Cessation in Homeless Shelters: Benefits of Physical Activity and Support
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to pilot test protocols for a future trial that will provide evidence of the efficacy of delivering a smoking cessation intervention in conjunction with an existing physical activity program vs. cessation alone with the homeless population. Further, this project will examine whether any differences between the two interventions are mediated by social support to inform intervention components for the future trial. To date, this project represents a first attempt at examining the efficacy of smoking cessation intervention combined with physical activity with a sample of homeless individuals. Findings from this project will advance knowledge and understanding of tobacco use behaviors among the homeless, a population that smokes at a rate three times greater than the general population yet is generally overlooked in tobacco related research.
- Project Title: Cellular Transformation and Transcriptional Regulation of JC Virus in a Human Brain Tumor Model
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Human medulloblastoma is a malignant pediatric brain tumor that is refractory to treatment. Our model of medulloblastoma induced by the human polyomavirus, JC virus, will allow us to study the mechanisms involved in transcriptional regulation of JC virus and investigate a novel splicing pathway which may play a role in cellular transformation and tumor progression.
- Project Title: The Role of Mucin in Promoting Survival of CA-MRSA and *Streptococcus mutans*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The purpose of these studies is to understand the role of mucin in survival of Community-Associated/Acquired Methicillin Resistant *Staphylococcus aureus* (CA-MRSA) and *Streptococcus mutans*. Mucin is found in saliva and on mucosal surfaces such as the inside of the nose and throat. We found survival of both CA-MRSA and *S. mutans* requires nutrients. *S. mutans* is the major agent of dental caries (cavities) and mucin found in saliva prolongs its survival from days to months. CA-MRSA is the cause of lethal infections in young, healthy student athletes. We found mucin allows for survival of CA-MRSA on artificial turf, suggesting "snotting" by CA-MRSA carriers could deposit CA-MRSA on the artificial turf, where it remains alive for >60 days serving as a reservoir of CA-MRSA for subsequent athlete infections. The goal of these studies is to determine if mucin is providing sugars necessary for the survival of these pathogens.
- Project Title: Active Owls: Promoting Active Commuting and Physical Activity at Temple University

Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The Active Owls project seeks to evaluate a multi-pronged project aimed at promoting physical activity, primarily via cycling. Phase I will assess a social marketing campaign ("Bike Temple") designed to promote active commuting via cycling among Temple University community members. Phase II will evaluate an intervention aimed at college students using an adapted web-based program that includes both online gaming and social networking through the use of Facebook ("social gaming"). Finally, Phase III will assess child participant and college student perceptions (using focus groups) of a local non-profit neighborhood program designed to promote cycling ("Earn-a-Bike").

- Project Title: The Role of Osteoactivin (OA) as a Downstream Mediator of Osteoblast Differentiation Induced by BMP2
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Osteoactivin (OA) is a downstream mediator of osteoblast differentiation induced by BMP2. OA expression is regulated by BMP2 through the Smad1 signaling pathway, we hypothesize that OA acts a downstream mediator of BMP2-induced osteoblast differentiation and function, and this effect is mediated by the recruitment of Smad1, homeodomain proteins, and the CBP co-activator to the OA promoter to modulate the induction of its activity during osteoblast differentiation. We will determine whether OA acts as a downstream mediator of BMP2-induced osteoblast differentiation using primary osteoblasts derived from WT, OA KO and OA Tg mice and examine BMP2 responsiveness and Smad signaling. Subsequent analysis to examine the mechanism of activation and regulation of OA transcription by Smad1, Dlx3, Dlx5 and CBP during osteoblastogenesis.
- Project Title: Defining a Typology of Low-Literacy African Americans for Colorectal Cancer Screening
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: To conduct specialized cluster analyses of data collected under a current NCI R21 grant. The cluster analyses will result in a typology of low-literacy African Americans that will provide the foundation for development of communication for minority populations as well as expanded future research and grant applications.
- Project Title: Understanding Drug Binding to the M2 Channel of the Influenza A Virus
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Funds will be used to support research at the new Institute for Computational Molecular Science (ICMS) in the Temple University College of Science & Technology (CST). The research in question will use computational methods to understand how the so-called M2 proton channel on the surface of the influenza A virus is able to acidify the virus interior as a prelude to replication. The research will also help understand how traditional drugs such as rimantadine act to inhibit the replication cycle of the virus. Importantly, the research will also address the question of how mutations of the flu virus that are involved in the bird flu (so called H5N1) and swine flu (H1N1) enable the flu virus M2 to function in the presence of drugs such as rimantadine. The aim of the computational studies is to inform the rational design of new drugs.
- Project Title: Improving Cell Therapy for the Damaged Heart
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences

Purpose: Loss of cardiomyocytes associated with either longstanding heart failure or acute myocardial infarction could be therapeutically addressed by a treatment that specifically replaces lost myocytes. Currently, a number of clinical trials to test the efficacy of injecting different types of stem cells into the damaged heart are ongoing. Our research is basic in nature and explores the idea that there are already cells within the heart that have the capacity to repair it if it is damaged. The purpose of our research is to modify adult stem cells so that they will repair the damage of the heart after a myocardial infarction.

- Project Title: Determining the Role of c-Abl in Nongenomic Hormone Signaling of Estrogen Receptor Alpha
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this work will be to determine if the nongenomic signaling of the nuclear hormone receptors contributes to tumorigenesis via activation of both cytoplasmic tyrosine kinases c-Src and c-Abl. The project will deal with the activation of c-Src via nongenomic signaling of nuclear hormone receptors which in turn could cause the activation of c-Abl. This would perhaps define a role for c-Abl in solid tumorigenesis.
- Project Title: Protection from Atherosclerosis in IL-19 Transgenic Mice
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Cardiovascular disease is the number one killer of Americans. Vascular diseases such as atherosclerosis, hypertension, restenosis, and transplant vasculopathy are inflammatory in nature. Very little has been reported on the potential protective effects of anti-inflammatory cytokines on development of vascular disease. We have novel preliminary data which shows that the naturally occurring anti-inflammatory compound, Interleukin-19 (IL-19) can have protective effects on vascular cells grown in culture. The purpose of this project is to determine if IL-19 can reduce atherosclerosis in an important animal model of this disease.
- Project Title: Biology Department Core Facility Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: Temple University's Department of Biology is undergoing a significant expansion to invigorate its research environment and to improve the education of the next generation of biological scientists. To advance biomedical research, two new animal facilities were built and opened: a Biosafety Level 1 Zebrafish Facility and a Biosafety level 3 Mouse Facility. While these improvements have strongly advanced Temple's research capabilities, we still require various new instrumentation as well as updates to our current research inventory. The proposed infrastructure project includes the renovations necessary to accommodate new equipment to be used by faculty from the Department as well as the larger College of Science and Technology.

Thomas Jefferson University ($3,455,597)

- Project Title: Role and Regulation of Focal Adhesion Kinase in Melanoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Malignant melanoma is the deadliest form of skin cancer. Currently, the spreading of melanoma, known as metastasis, is only preventable by early detection and surgical excision of primary tumors. Therefore, it is critical that we understand the mechanisms underlying melanoma initiation and progression. The depth of invasion of a melanoma into the skin (dermis) is a determinant of treatment outcome. A gene, labeled B-RAF, is mutated in two-thirds of melanomas. This

project has identified a target of the B-RAF gene known as focal adhesion kinase (FAK). This study will test whether B-RAF regulates FAK, which in turn promotes melanoma cell invasion into the dermis. Ultimately, the focus of this project is to identify why melanomas display invasive growth and, in doing so, identify novel targets for therapeutic intervention.

- Project Title: Prolactin and Growth Factor Signaling in Breast Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Progression of breast cancer from early solitary lesions to advanced metastatic disease requires loss of cellular differentiation and epithelial-to-mesenchymal transition (EMT). While extensive efforts have been devoted to understanding the factors that allow this transition to occur in breast cancer, little work has focused on factors that prevent EMT, or on molecular strategies to reverse EMT for use in differentiation therapy. The long-range goal of this laboratory is to identify molecular mechanisms that govern growth and cellular differentiation of human breast cancer to improve therapies, and to use this knowledge to improve drug responsiveness of individual tumors, so that more effective, personalized medical treatment can be realized for cancer patients.
- Project Title: Stat5 and ErbB2 in Prostate Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Organ-confined primary prostate cancer is typically treated by surgery, radiation, hormone therapy, or different combinations of these three treatment modalities, depending on the age and operability of the patient. If prostate cancer has already invaded the neighboring tissues or metastasized to distant sites by the time of the diagnosis, the main treatment options include radiation, hormone therapy and/or chemotherapy (docetaxel) combined with (neo) adjuvant therapies. However, the existing pharmacological therapies for prostate cancer only provide a temporary relief of the symptoms and the cancer growth, while the hormone-refractory form of prostate cancer develops. Moreover, no effective therapies for metastatic prostate cancer currently exist. In this project, the molecular basis of why positive activation status of transcription factor Stat5a/b may provide a biomarker for sensitivity of prostate cancer to ErbB2-inhibitors as a therapy will be examined.
- Project Title: Targeting the IGF-I Receptor in Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project proposes to determine conditions which will maximize the therapeutic effect of antibodies to the insulin growth factor I (IGF-I) receptor (a receptor for a growth factor) in cancerous tumors. Many cancers (including lung, colon and breast cancers), have already shown susceptibility to this treatment, and these antibodies are currently being used in clinical trials. Clinicians are now anxious to know which human tumors are most sensitive to the antibodies to the IGF-I receptor. There are intra- and extra-cellular factors that condition the response of tumor cells to treatment and the purpose of this project is to identify these conditions.
- Project Title: The Role of MicroRNA Gene Expression in Therapy Resistance of Human Breast Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This year breast cancer will kill over 40,000 women in the United States, and there will be over 210,000 new cases, according to statistics from the American Cancer Society and Centers for Disease Control. Since the risk of developing breast

cancer increases with age, the prevalence of this disease can be expected to increase as the overall population continues to age. However, studies on the underlying genesis and progression of breast cancer, utilizing the latest techniques of molecular biology, offer hope of finding more effective treatments. Studies over the last two years have demonstrated that the presence of "stem cells" which are found within human breast cancer, contribute to therapy resistance. This project will focus on a class of genes called the microRNA (miRNA) found in breast cancer stem cells, and their role in therapy resistance and breast cancer metastasis.

- Project Title: Mechanisms for Metastasis Suppression through Kisspeptin Regulation of the Microenvironment
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Metastasis (spreading) is an unfavorable milestone in the clinical course of cancer. The ability of tumor cells to spread from the primary site and invade normal tissues requires a specific set of properties enabling them to proliferate and migrate. It is also critical that these malignant cells have a supportive niche within which they can expand. The KiSS1 gene was discovered based on its ability to block metastasis of human cells in mouse models of melanoma. Current evidence suggests that the product of this gene is secreted by tumor cells and prevents the migrating cells from developing a niche. These experiments, which will elucidate the mechanisms of action, may provide novel, non-toxic approaches for the treatment and prevention of tumor metastasis.

Treatment Research Institute ($158,950)

- Project Title: Program Quality Measures for a Consumer Guide to Adolescent Addiction Treatment
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Parents of adolescents needing treatment for substance abuse have few resources to describe available options. A Consumer Guide could educate parents about evidence-based clinical practices available in treatment programs. In turn, educated parents could demand better care and improve overall quality. Toward this end, the purpose of this project is the development of three measures to collect and report on quality features (evidence based practices) within adolescent programs. This project will create and test interviews with program directors regarding available evidence based practices and a parallel patient interview will measure the evidence based practices actually received during treatment. Finally, parents will be interviewed regarding their experiences and needs in seeking treatment for their adolescent.

University of Pennsylvania ($8,975,120)

- Project Title: Molecular Mechanisms Involved in Reprogramming Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The reprogramming of adult cells to a pluripotent state resembling embryonic stem cells is one of the most exciting advances in stem cell biology over the past decade. These induced pluripotential stem (iPS) cells offer the potential for patient-specific regenerative therapies, new sources of cells to understand disease and for drug discovery. This project is fundamental research that will help to elucidate the process by which adult cells are converted to pluripotent cells and

provide information that can be used in efforts to make the generation of iPS more efficient and safe for clinical use.

- Project Title: Nanofabrication Lab for Biosensors and Biomeasurements – Research Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: This research infrastructure project renovates Penn's Wolf Nanofabrication Facility, expanding the cleanroom (filtered air) space which is required for micron and nanoscale technology and medical research. This facility addresses key needs that are shared by Penn, the NIH Roadmap, and the Commonwealth of Pennsylvania: it provides tooling that allows test beds to be fabricated to measure properties of cells and to create devices which can change them. Renovation of space in the Moore Building is essential to Penn's efforts to create an interactive environment that both promotes the research initiatives and enables the recruitment of new faculty with expertise in micromedical devices. With these new collaborators and resources, Penn's researchers will create micron and nanoscale biomedical devices for the benefit of the citizens of the Commonwealth.
- Project Title: Effects of Nicotine on Mu Opioid Receptor Binding
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: We will evaluate whether there are different effects of nicotine on mu opioid receptors in smokers with different genetic backgrounds. This will help us to understand the brain related mechanisms that explain why smokers with a particular gene variant for this brain receptor are at higher risk for smoking relapse.
- Project Title: Validation of Imaging Markers for Use in Cancer Clinical Trials
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Biomarkers to identify appropriate patient populations and detect early response represent a significant opportunity to bring cancer drugs to the clinic more expeditiously and at a reduced cost. Advances in medical imaging already can provide quantitative in vivo assays of tumor anatomy and function in cancer patients. Support of quantitative imaging in cancer clinical trials has been limited by the lack of coordinated efforts between clinical imaging specialists and clinical cancer researchers. This project will establish a collaboration between the oncology investigators engaged in clinical trials of cancer therapy and imaging investigators to develop and validate imaging biomarkers to predict and monitor the response to therapy. This will impact our ability to develop and evaluate new therapies for cancer.
- Project Title: Understanding the Biology of Residual Neoplastic Disease
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: A cardinal feature of human breast cancers is the survival and persistence of residual neoplastic cells in a presumed quiescent state following the apparently successful treatment of the initial tumor. Ultimately, these residual cells re-emerge from their dormant state and resume growth, leading to cancer recurrence. Indeed, analyses of bone marrow samples show that disseminated cells are present in 20-40% of primary breast cancer patients without any clinical or histopathological signs of metastasis. As such, residual neoplastic disease is a major obstacle to the successful treatment of breast cancer and other human cancers. Accordingly, the purpose of this project is to investigate the biological properties of residual neoplastic cells, since these cells represent the reservoir from which tumor recurrences invariably arise.

- Project Title: Individualizing Breast Cancer Prevention in Primary Care
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The overarching objective of this project is to develop and test a multi-faceted strategy for optimizing the adoption of individualized breast cancer prevention in primary care. Specifically, we will determine whether the use of breast cancer risk reduction strategies among high risk women can be increased by providing the women targeted information and by incorporating breast cancer risk assessment and prevention into the electronic medical record of their primary care providers, and that the combination of these interventions is more effective than either intervention alone.
- Project Title: Clinical and Molecular Predictors of Responsiveness to Angiogenesis Inhibition in Advanced NSCLC
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Bevacizumab is a monoclonal antibody targeting VEGF (vascular endothelial growth factor), a humoral protein that stimulates the growth of tumor vasculature (blood vessels), which, in turn, fuels the growth and spread of cancer. This agent in combination with chemotherapy, has been approved for use in "selected" patients with metastatic non-small cell lung cancer; but it is not been determined *a priori* who actually benefits from this costly, potentially toxic agent. This study will evaluate serum, tissue and radiological correlates to help determine who is likely to benefit from Bevacizumab.
- Project Title: Reprogramming Cells in Studies of Heart and Lung Development and Repair
  Type of Research: Clinical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Heart and lung disease are the number one and three causes of death and illness in the United States. The ability of the heart and lungs to repair themselves is very limited and poorly understood. Research into how these two organ systems respond to injury as well as try to affect repair will have a dramatic impact on both human and financial costs of these illnesses. Our project will investigate whether non-heart and lung cells can be differentiated into heart and lung cells which would provide a potential source for heart and lung repair. Such discoveries would greatly improve the outcomes of people with cardiac and lung disease.
- Project Title: Genome-based Bio-marker Discovery and Systems Biology Engineering
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Biomarkers allow for convenient diagnosis of particular states of an organism. A robust diagnostic marker is not only important for clinical treatment regimes; it also helps us understand the molecular mechanisms of diseases. For example, many mental diseases like autism are considered psychiatric diseases mainly because neural correlates have not been found. A biomarker, once established, points to possible mechanisms that ultimately might suggest potential therapeutic approaches. Thus, establishment of biomarkers for all organismal normal and abnormal processes is of great significance to both basic and clinical studies. This project aims to develop novel biomarkers using genome-scale data, through the development of novel reagents, computational modeling and analysis, and micro- and nano-engineering.

- Project Title: Expansion and Enhancement of Rodent Housing Space – Research Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this research infrastructure project is to support NIH-funded research in diabetes and other diseases, as well as basic research in genetics through modification of the Clinical Research Building (CRB) animal facility. Renovation of the CRB animal facility is a critical ingredient of an institutional plan to advance Penn's mission to develop new cures through a combination of basic and clinical research. This project will allow us to achieve this goal by: (1) Renovating space to maximize cage capacity in the CRB animal facility; (2) Upgrading the ventilation system and expanding the "barrier" to reduce the spread of infectious diseases; and (3) Renovating the staff support facilities to modern standards.
- Project Title: Development and Validation of a Tool to Assess Perceived Nutrition Environments
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Obesity prevalence has reached pandemic proportions in the United States. The availability and distribution of food within a neighborhood has been related to the food intake and obesity prevalence of people living in that neighborhood. To improve our understanding of the relationship between neighborhood food environment and food intake, we need to know more about how people living in the neighborhood perceive what foods are available to them. To address this gap in the literature, the purpose of the current study is to develop a standardized measure of perceived food environment. Development of such a measure will go toward fulfilling one of the research priorities recently identified by a panel of experts for this area of work.

University of Pittsburgh ($8,975,120)

- Project Title: Small Molecule Inhibitors of HIV Nef Signaling
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: The project focuses on discovery of small molecules to target a unique human immunodeficiency virus type 1 (HIV-1) protein, called Nef, which is essential for progression from a state of HIV infection to full-blown acquired immune deficiency syndrome (AIDS). Using in vitro and cell-based screens, the investigators aim to identify two classes of drug-like compounds with potent activity against HIV replication. These studies could eventually provide new tools for understanding Nef interactions with host cell proteins and identify novel lead compounds for anti-HIV therapeutics.
- Project Title: Alterations in Bioenergetics and Mitochondrial Function in Tumor Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Cells generate the energy they need to function and divide through two different metabolic pathways, mitochondrial oxidative phosphorylation and glycolysis. Due to their rapid growth, tumor cells have unique energy demands. However, the mechanism by which tumor cells regulate energy production is poorly understood. This project will examine the balance between these two energy producing pathways in tumor cells. The cells to be examined are associated with specific genetic alterations in critical genes (oncogenes, like Myc and Ras) or include critical genes that have been mutated (tumor suppressor genes, like p53). This project also

addresses how shifts in energy demands can increase genome instabilities like mutations. Understanding bioenergetic shifts of specific tumor types may improve therapeutic approaches.

- Project Title: Clinical Trials in Melanoma
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The University of Pittsburgh Cancer Institute's (UPCI) Clinical Research Service (CRS) provides valuable resources for researchers and clinicians seeking to improve clinical research as a means to elevate patient care standards and treatment efficacy. This project will evaluate the clinical response of melanoma patients at various disease stages to novel therapeutic regimens designed to be specific to their treatment needs.
- Project Title: Therapeutic Vaccine Trials in Recurrent Prostate Cancer
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The University of Pittsburgh Cancer Institute's (UPCI) Clinical Research Service (CRS) provides valuable resources for researchers and clinicians seeking to improve clinical research to elevate patient care standards and treatment efficacy. This project will conduct two novel vaccine trials in patients with recurrent prostate cancer: (1) a safety and efficacy study of a new vaccine targeted against mucin-1 (MUC-1) in conjunction with poly-ICLC (polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose) in patients with recurrent and/or advanced prostate cancer and (2) a safety and efficacy evaluation of alpha-type-1 dendritic cell (DC)-based vaccines loaded with allogeneic prostate tumor cells in combination with androgen ablation in patients with recurrent prostate cancer.
- Project Title: Research Infrastructure: Bridgeside Point II Building Renovations
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: Bridgeside Point II (BPII), the University of Pittsburgh's newest research facility, is nearing completion. This project will address final construction and laboratory fit-out in the building. By establishing this additional space, the Department of Orthopaedic Surgery, the Department of Microbiology and Molecular Genetics, and the McGowan Institute for Regenerative Medicine will be able to expand their research programs, recruit additional faculty members, and accommodate researchers' changing needs.
- Project Title: Estrogen Receptor Genetics in Breast Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Breast cancer remains a major health issue in the United States, with approximately 210,000 new cases and 40,000 deaths per year. Breast cancer can be subdivided into estrogen receptor (ER) positive and negative disease. Breast cancers that express ER are often less aggressive and respond to anti-hormone therapy; however, a significant fraction of patients with ER positive disease do not respond to therapy. New sequencing technologies have recently allowed an unprecedented view of ER action in breast cancer. This project will investigate how genetic alterations in ER and the ER pathway affect response to the hormone and whether the ER itself is involved in generating genetic changes in breast cancer. Better knowledge of ER action should translate into improved treatment of ER positive breast cancer.

UPMC McKeesport ($53,071)

- Project Title: Analysis of Emergency Department Elopements Over Time

Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of the analysis is to measure the effectiveness of a newly initiated program as it relates to Emergency Department elopements. This analysis is not part of the new initiative but we anticipate that it will have an effect on elopements and therefore measure an unanticipated benefit that may be replicated in other community settings.

Wistar Institute ($1,461,800)

- Project Title: Critical Roles of Transcription Factor Foxp1 in Thymocyte Development and Peripheral T Cell Function
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: T lymphocytes are one of the two main components of adaptive immunity. Effective immune responses against various infectious diseases require the successful generation of competent T cells, whereas inappropriate differentiation (unsuccessful generation) of T cells can lead to diseases such as those of the autoimmune system. Transcription factors are proteins involved in the regulation of gene expression. We recently demonstrated that transcription factor Foxp1 is essential for T cell development. In the absence of Foxp1, even without an overt antigen challenge, all of the generated T cells have the activated phenotype and have acquired effector functions. Our study of Foxp1 provides a new mouse model to investigate the molecular mechanism(s) underlying T cell development, activation and autoimmunity.
- Project Title: Impact of Latent Cytomegalovirus Immediate Early Protein Expression on Embryonic Development
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Development of the human fetus can be severely affected by infection with human cytomegalovirus during pregnancy, resulting in mental retardation, vision loss and deafness. To test the hypothesis that proteins produced by latent virus are responsible for the abnormal embryonic development, we will establish and investigate a mouse model system. The work will eventually allow screening in a mouse model for small molecules that can prevent the functions of major immediate early proteins and testing of interference strategies during development.
- Project Title: Frequency, Fate and Significance of MicroRNA Editing
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Within the last decade a new type of ribonucleic acid (RNA) was discovered, microRNA (miRNA), which plays a major role in the regulation of gene expression. miRNAs are produced as larger gene transcripts (pri-miRNA) which are subsequently processed to mature miRNA. We found that pri-miRNAs are subject to editing by conversion of adenosine residues to inosine residues ($A \rightarrow I$ editing). Editing of pri-miRNAs results in inhibition of their processing and alters the genes targeted by the unedited miRNAs, resulting in naturally occurring "off-targeting effects". The overall goal of this project is to gain a better understanding of the biological significance of miRNA editing.
- Project Title: Diagnosis of Lung Cancer from Peripheral Blood Using Genomics
  Type of Research: Biomedical
  Focus: Oncological Sciences

Purpose: Lung cancer is the most common worldwide cause of cancer mortality. It is the second most prevalent cancer in both men and women and will account for more than 162,000 cancer deaths in the United States per year – more than from breast, prostate and colorectal cancers combined. Treatment for lung cancer remains very limited and the prognosis is strongly correlated to the stage of disease at presentation. Unfortunately, at the time of diagnosis only 15% of patients with lung cancer have localized disease. Given these facts, one of the most important long-term goals in improving lung cancer survival is to detect malignant tumors in high-risk patients (i.e., smokers and ex-smokers) who represent the majority of all lung cancer cases, at an early stage, while they are still surgically resectable.