Health Research Formula Grants - State Fiscal Year 2007-08

Thirty-three organizations received health research formula grants for the state fiscal year 2007-08. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2008 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 ($141,075)

Research Projects:

• Title: Feasibility of Adopting the Mediterranean Diet to Modify Risk Factors Associated with Metabolic Syndrome in Older African American Women
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The Metabolic Syndrome (MSY) is a mosaic of coronary heart disease and diabetes risk factors, including glucose impairment. Persons with MSY have an increased chance of developing type 2 diabetes and/or coronary heart disease (CHD). The purpose of this pilot study is to test a 6-month intervention teaching self-management skills that will include improving lifestyle and diet among older African American women who have risk factors associated with MSY. The Mediterranean diet (MED) has been shown to positively impact MSY in European and Mediterranean populations, but it has not been tested among an African American population who are at a high risk for MSY, diabetes, and CHD. This project is unique since it will be examining the adoption of MED in a low-income African American population.

• Title: Visual Attention and Cognition in Action: Anticipatory Grip Force Production Deficits in Stroke
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: Hemiparesis (weakness) of the contralesional hand is one of the most disabling consequences of stroke, resulting in considerable difficulty with grasping and manipulating objects. Impairments in hand function in stroke are typically treated as motor deficits resulting from weakness, spasticity, and abnormal muscle synergies. However, sensitive kinematic testing has suggested the contribution of a problem in higher-order processing, such as motor planning or learning, which may prevent recovery of motor capacity in the hand. This project seeks to assess anticipatory hand shaping to increase our understanding of the role of motor planning and learning in object manipulation deficits, and is therefore critical to improvements in the design of targeted rehabilitation interventions.

• Title: Real-life Use of Portable Assistive Technology for Aphasic Language Disability
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: The purpose is to conduct pilot research on real-life use of augmentative-assistive communication (AAC) technology designed for persons with acquired aphasia. Aphasia is a stroke-related disability that features poor recall of words and grammatical structure due to slowed processing and reduced working memory. This project investigates an AAC system that greatly reduces the processing demands of spoken language production, enabling the user with aphasia to produce and record speech that is enhanced, grammatically and informationally, relative to his spontaneous speech. Recent laboratory tests of the system’s newly added portable functionality produced encouraging results. This project aims to reproduce those
results in a real-life situation chosen by the participant. This constitutes critical pilot
data for a planned federal grant.

Allegheny-Singer Research Institute ($237,838)
Research Projects:
- **Title:** Expressomic Approach to Enhanced Wound Healing  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Cigarette smoking and tobacco use are known to significantly interfere with the body’s ability to heal its wounds. In a wide variety of circumstances smokers are known to have significantly higher rates of complications following surgery than non-smokers, including after breast surgery, abdominal surgery, oral surgery etc., due to impaired wound healing. This poor wound healing results from a variety of causes which are still incompletely understood. In contrast, during developmental life all mammalian species (including humans) are able to heal their wounds flawlessly and without scar. It is likely that different genes are used by the body to heal itself during development than in adult life, that is, the developing organism uses a different “expressome” than an adult. This project seeks to better understand the genes in the “expressome” of developing mammals in the hopes that they may one day be used to improve wound healing in adult tissues.

American Aging Association ($1,809)
Research Project:
- **Title:** Effects of Antioxidants on the Growth and Proliferative Capacity of Adult Adipose Stem Cells  
  **Type of Research:** Biomedical  
  **Focus:** Biology of Development and Aging  
  **Purpose:** A mixture of antioxidants exerts profoundly different effects on fully differentiated mortal human cells than on immortal cells that have an aberrant state of differentiation; i.e., cancer cells. Antioxidants promote growth in normal cells but tend to inhibit growth of immortal cells. The purpose of this study is to determine the effects of antioxidants on the growth and proliferative capacity of adult adipose stem cells. These cells were obtained from liposuction fat; they are not fully differentiated, but unlike fetal stem cells that are immortal, adult adipose stem cells exhibit limited proliferative capacity. An examination of antioxidant effects in these cells will aid in understanding if the differences observed in normal and cancer cells are the result of differentiation or effects on factors that control cell mortality.
**American College of Radiology ($2,433,581)**

**Research Projects:**
- **Title:** Emerging Imaging Technology Clinical Trials in PA: Coronary CT for Rapid Discharge of Low Risk Patients with Potential Acute Coronary Syndrome
  
  **Type of Research:** Clinical
  
  **Focus:** Cardiovascular Sciences
  
  **Purpose:** The purpose of this multi-center study in five academic medical centers in Pennsylvania is to evaluate the safety of using coronary CTA (computerized tomography angiography) for rapid disposition of low risk patients who present with chest pain to emergency departments and to further evaluate the effect of a coronary CTA strategy on cost and efficiency of care, as well as on emergency department and inpatient resource utilization.

- **Title:** Controlling Patient Dose Resulting from the Use of Frequent Image Guidance in RTOG Protocols
  
  **Type of Research:** Clinical
  
  **Focus:** Oncological Sciences
  
  **Purpose:** The use of Image Guided Radiation Therapy (IGRT) in clinical trials can increase the dose prescribed in cooperative group protocols. Additionally, the imaging can increase the dose to healthy sensitive structures that are positioned near the target region. The purpose of this study is to quantify the radiation dose the patient receives to various parts of the body as a result of the frequent use of image guidance and to devise techniques that will limit the imaging dose the patient receives.

**Bryn Mawr College ($11,524)**

**Research Project:**
- **Title:** Synaptic Proteins and Neurite Outgrowth
  
  **Type of Research:** Biomedical
  
  **Focus:** Neurosciences
  
  **Purpose:** Proteins involved in communication between nerve cells may also influence the growth of processes that connect nerve cells during nervous system development. This project investigates these roles by manipulating the levels of proteins in neurons growing in cell culture and examines the effects on the patterns of nerve processes. Altering the levels of protein may result in shorter or longer processes and changes in branching of processes when compared with control cultures.

**Carnegie Mellon University ($710,806)**

**Research Projects:**
- **Title:** Toward Automated Collection of Falls Risk Data in Elder Care Environments
  
  **Type of Research:** Biomedical
  
  **Focus:** Bioengineering, Surgical Sciences and Technology
  
  **Purpose:** The purpose of this project is to develop an integrated system of computer-based instrumentation for collecting datasets of vital signs and biomechanical parameters in older adults. Through creation and deployment of a prototype, we will also explore usability and acceptance of such a measurement approach to older adults and clinicians who work in long term care settings. This project supports a pilot study, the goal of which is to study health reporting mechanisms of independent living campus and assisted living facility residents.

- **Title:** Computational and Neural Mechanisms of Lexical Processing
  
  **Type of Research:** Biomedical
  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to use computational modeling with artificial neural networks, combined with coordinated behavioral studies, to elucidate the cognitive and neural mechanisms underlying how written and spoken words are understood and produced by the brain. The research examines and attempts to explain how reading and language skills develop in children both normally and in those failing to achieve age-appropriate skills; how they operate in neurologically intact adults and how they may be impaired as a result of brain damage; and, when impaired, how they might best be remediated. The results should lead to improvements in both educational and clinical practice.

- **Title:** Testing the Impact of Sexual Frequency on Health and Wellbeing
  - **Type of Research:** Biomedical
  - **Focus:** Health of Populations, Behavioral and Biobehavioral Processes
  - **Purpose:** This study will test whether the frequency of sexual activity in a relationship has a positive impact on self-reported health and well-being among marital partners. We propose to test two possible mechanisms by which frequency of intercourse may improve health, as measured by self-reported physical symptoms. These are 1) increased positive affect, including positive affect due to partner closeness and 2) improved health behaviors. Participants will be monogamous married couples aged 40-65 years, in good health, with no chronic illnesses and no regular medication regime. We will use a between-subjects randomized controlled trial (RCT) to evaluate the impact of sexual frequency in a monogamous relationship.

**Children’s Hospital of Philadelphia ($3,499,480)**

**Research Projects:**

- **Title:** MRI Studies of System Level Brain Dysfunction in Autism Spectrum Disorders
  - **Type of Research:** Clinical Research
  - **Focus:** Neurosciences
  - **Purpose:** Neuroimaging research is beginning to characterize several important ways in which the brains of persons with an Autism Spectrum Disorder (ASD) develop and function differently. Magnetic resonance imaging (MRI) has been particularly important in this regard. It is also now widely recognized that ASD is a heterogeneous disorder, with individual differences in severity of symptoms, other aspects of behavior and cognitive functioning. This project will use MRI to study the brain anatomy and function, and will correlate neuroanatomy and function with differences in symptomatology and behavior, in order to enhance our understanding of the brain-bases of the ASDs. This research is guided by the belief that understanding the fundamental mechanisms that cause ASDs will allow for the development of better interventions and treatments.

- **Title:** Ethnic Diversity and Gene-Environment Interactions in Childhood Asthma
  - **Type of Research:** Biomedical
  - **Focus:** Respiratory Sciences
  - **Purpose:** The purpose of this research is to use a genome-wide association (GWA) approach to uncover the genetic factors that predispose to asthma, the most common chronic disease in children, and to thoroughly examine gene-environment interaction in asthma patients of different ethnic background. The utilization of the GWA approach has excellent potential of identifying the genetic determinants of asthma predisposition and to subsequently dissect out the role of second hand smoke and potentially other specific environmental exposures in the pathogenesis of asthma in subjects from different ethnic background, including Caucasian, African-American and Hispanic Caucasian decent. The study will utilize a well-characterized pediatric asthma cohort from the Children’s Hospital of Philadelphia (CHOP) to drive the discovery phase.
Children's Hospital of Pittsburgh ($879,637)
Research Project:
- Title: Immunopathogenesis of Chlamydial Genital Tract Disease
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Chlamydia trachomatis is the leading cause of bacterial sexually transmitted diseases worldwide. In women, infection may ascend from the cervix into the upper genital tract and lead to the sequelae of ectopic pregnancy, premature delivery, and infertility. The mechanisms by which chlamydiae induce disease are not clear. Chlamydia do not make potent toxins or tissue-damaging products; instead, it appears to induce an immune response that in the process of clearing away the bacteria results in collateral damage with inadvertent tissue destruction beyond what is needed to kill the pathogen. This project is designed to determine mechanisms responsible for oviduct pathology associated with Chlamydial infection. An understanding of the immunopathogenic mechanisms will promote rational design of a vaccine.

Drexel University ($1,138,730)
Research Projects:
- Title: Imaging Amyloid Therapy In Vivo Using Two-Photon Microscopy
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The goal of this project is to develop a drug specifically targeted to the amyloid-beta plaques involved in Alzheimer’s disease (AD). AD is the most common age-related neurodegenerative disorder and cause of dementia amongst the elderly. AD was discovered exactly 100 years ago. At that time autopsy of patients showed a characteristic biochemical hallmark in the diseased brain: the amyloid-beta (or simply “Aβ”) plaques. Surprisingly, the exact relationship between neuronal loss, dementia and plaque deposition is not yet understood. However, it is well established that the Aβ plaques destroy neurons. The goal of this project is to use synthetic organic chemistry to make an Aβ-specific drug by linking a plaque-targeting fluorescent tag to an artificial peptidase which will then destroy the harmful plaques in the diseased brain.
- Title: Genetic and Immunological Analysis of Resistance to HSV-1 Infections
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this study is to understand the host genetic components associated with restricting the entry of the neurotropic enveloped viral pathogen, herpes simplex virus type 1 (HSV-1), into the peripheral and central nervous systems from peripheral sites of infection. The importance of these studies lies in determining how the body limits neuronal infection, which, in humans, is related to the frequency of reactivation from latent infection, the frequency and severity of recrudescent disease, the frequency and duration of viral shedding for transmission to other susceptible individuals, and the potential for the development of life-threatening herpes encephalitis. The identification of immune-associated genes involved in this process will facilitate the design of more effective anti-HSV-1 vaccines and therapeutics in the future.
- Title: Identification of Biomarkers and Therapeutic Targets in 3D 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.

- **Title:** Therapeutic Magnetic Nanoparticles for Targeted Delivery to Stents  
  **Type of Research:** Biomedical  
  **Focus:** Bioengineering, Surgical Sciences and Technology  
  **Purpose:** Stent angioplasty, including use of drug eluting stents (DES), has led to a major paradigm shift in the care of coronary disease. Although the efficacy of the DES platform has been well validated in large clinical trials across various population and lesion subsets, there are still remaining concerns regarding the long term safety and efficacy of these devices. Under this program, a novel method of magnetically-mediated drug delivery to stents will be developed. This approach will allow redosing of drug by additional delivery if needed and will enable us to tailor the drug dose specifically for the patient, which will result in a more effective treatment of a coronary disease.

- **Title:** Modeling L-Selectin Mediated Attachment Strength During Embryo Implantation  
  **Type of Research:** Biomedical  
  **Focus:** Bioengineering, Surgical Sciences and Technology  
  **Purpose:** The main challenge in understanding the fundamental mechanisms associated with primary implantation lies in an understanding of the mechanism of "braking" required to stop the blastocyst rolling and to begin the complex biochemical pathways that result in embryo attachment. Our strategy is to develop an in vitro cell model that can be used to study the attachment of trophoblast-like cells and a human endometrial epithelial 3D model. Through this work, we will for the first time, quantify attachment strength providing a functional assessment of the L-selectin adhesion system. The functional assay will bring us closer to understanding the importance of L-selectin expression in achieving adequate strength to slow and stop the blastocyst in the uterus as the key initial step toward implantation.

- **Title:** Small Molecule Inhibitors of Parasite Invasion  
  **Type of Research:** Biomedical  
  **Focus:** Infectious Diseases and Microbiology  
  **Purpose:** Malaria is a disease caused by parasites that take huge toll on human populations: estimated 500,000,000 cases and 1-3 million deaths per year. The parasites that cause malaria have become resistant to most widely used drugs, and our arsenal against this disease is becoming limited. Thus, there is an urgent need to find alternative drugs to treat malaria. The malaria parasites live within human red blood cells and to do this, they have evolved sophisticated machinery to invade our cells. We have discovered components of this invasion machinery and have derived a detailed structure of some of these components. Our purpose is to use this detailed structure to discover small molecules that can inhibit the invasion machinery. We have already identified a few drug-like molecules that appear to have this property, and our purpose is to develop these into potential drugs.
• Title: Pharmacology, Physiology and Behavioral Testing of Drugs Used to Treat Cognitive and Attentional Disorders  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: The purpose of this project is to develop a novel set of neurophysiological and behavioral assays that will rigorously and quantitatively measure the effects of attention deficit, hyperactivity disorder (ADHD)-medications on brain information processing in laboratory rats and then use that information to compare and interpret drug efficacy in patient populations. The central idea is that, once developed, a standard set of sophisticated assays will establish screening criteria for new ADHD medications that are based upon clinically relevant information and specific drug attributes. Such analyses are proposed for ADHD medications as prototypes but similar principles of evaluation and comparable assays can be extended to many additional classes of psychotropic compounds and neuropsychiatric disorders.

• Title: A Novel Microfluidic-Platform Liver Model System for Testing Drug Toxicity  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: Drug-induced liver injury (DILI) is a common reason for stopping drug development, failure to acquire governmental drug approval and withdrawal of a drug from the market. There is no human liver model system that can be used to test DILI. Attempts to make a human liver system have been hampered because large quantities of human liver cells are unavailable. There is a need to create a human liver model that retains normal liver architecture and uses small numbers of cells. In this project, we will use rat liver cells and microfabrication of microchambers (1cm x 100um) to produce a functional mini-liver unit to test DILI. Our long-term goal is to use experimental conditions derived from studies of the rat mini-liver model to generate a human mini-liver system. This system will be used to study human liver biology and DILI.

• Title: Vascular Complications in Diabetes: Effect of High Glucose Extracellular Matrix Alterations on Angiogenesis  
Type of Research: Biomedical  
Focus: Cardiovascular Sciences  
Purpose: The purpose of this project is to study how high blood sugar levels contribute to increased cardiovascular disease in people with diabetes. Angiogenesis, the growth of new blood vessels, is particularly disturbed in diabetes, which can lead to blindness, kidney failure, and poor wound healing. Angiogenesis is a tightly regulated process in which endothelial cells, which line all blood vessels, respond to chemical signals in the environment to either produce or regress blood vessels. High glucose concentrations, such as might be seen in diabetes, have been shown to alter the cell environment in ways that both enhance and reduce angiogenesis. In this project, we will determine how a combination of high glucose changes in the extracellular environment cause endothelial cells to produce or regress new blood vessels.

• Title: Implantable Microdevice for the Treatment of Hydrocephalus  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: This research project will develop an innovative implantable device for the treatment of hydrocephalus which is one of the most frequently encountered problems in Neurosurgery. An implantable microdevice that resembles the function of the native arachnoid granulations which acts as biological valves to eliminate cerebrospinal fluid will be developed using microfabrication technology. The proposed microfabricated arachnoid granulations (MAG) will make it possible to
replace the malfunctioning arachnoid granulations that lead to hydrocephalus. If successful, the proposed MAG may pioneer a new era in the treatment of hydrocephalus.

**Duquesne University ($84,549)**

**Research Projects:**

- **Title:** Expanded Health Belief Model and Adherence to Mammography Screening in Women  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** The purposes of this study are to describe and examine the variables associated with the Expanded Health Belief Model (EHBM) and adherence to mammography screening in women with rheumatoid arthritis (RA), and to explore the extent to which the EHBM variables can predict adherence to mammography screening in women with RA compared to women without RA.

- **Title:** Development of a Bone-Regenerative Scaffold  
  **Type of Research:** Biomedical  
  **Focus:** Bioengineering, Surgical Sciences and Technology  
  **Purpose:** The goal of this project is to develop a novel therapy to aid in the formation of bone by first developing a ceramic scaffold on which stem cells will attach, grow, and form bone; and by second attaching to the scaffold a hormone (melatonin) that has the ability to enhance the formation and function of these bone-forming stem cells.

**Fox Chase Cancer Center ($3,038,276)**

**Research Projects:**

- **Title:** Evaluation of Clinical, Epidemiologic, and Genetic Factors in Men at High Risk for Prostate Cancer  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** Established risk factors for prostate cancer include increasing age, a family history of prostate cancer, and African American ethnicity. Several studies have shown that the risk of prostate cancer increases dramatically with increased number of relatives with the disease. Furthermore, African American men are at twice the risk of developing and dying of prostate cancer. No causal genes or definite epidemiologic associations have been found for prostate cancer risk. The purpose of this project is threefold: (1) develop one or more models predictive of prostate cancer based on health history information collected from high-risk men; (2) identify epidemiologic factors and their magnitude of association to prostate cancer risk; and (3) evaluate genetic markers in Caucasian and African American men for association to prostate cancer.

- **Title:** The Role of the Tumor Suppressor VILIP-1 in Lung Cancer  
  **Type of Research:** Clinical Research  
  **Focus:** Oncological Sciences  
  **Purpose:** VILIP-1 is expressed in the basal cells of murine and human bronchial epithelium and it is lost in most human lung cancer cell lines; thus, in this application, we propose to investigate its putative function as a tumor or invasion suppressor gene in human lung tumor development and progression. In addition, we will focus on the mechanisms that regulate VILIP-1 gene function loss (silencing) in human non-small cell lung carcinomas (NSCLC). The central hypothesis to be tested is that VILIP-1 expression modulates tumor growth, motility and/or invasiveness of human lung cancer cells. We plan to further evaluate the epigenetic mechanisms
(promoter methylation and deacetylation) that seem to be at work during VILIP-1 gene silencing.

- **Title:** The p53 Tumor Suppressor and Cancer Risk and Therapy  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The p53 tumor suppressor protein is the body's single most important protector from cancer. We have discovered that 5% of African Americans possess a variant of the p53 gene (Serine 47) that has reduced ability to function. We have experience creating mouse models of p53 variants and have already discovered that a different variant of p53, also more common in African Americans, increases the risk of lymphoma in mouse. We propose to make a mouse model for the Serine 47 variant of p53 in order to determine the impact of this variant on cancer risk and therapy in this population. In other investigations, we have identified three critical cell cycle enzymes, called kinases, which are over expressed in human tumors. We propose to identify inhibitors of these enzymes and assess their potential as chemotherapeutic drugs.

- **Title:** Notch Signaling-mediated Mechanisms of Cell Fate Control  
  **Type of Research:** Biomedical  
  **Focus:** Biology of Development and Aging  
  **Purpose:** The purpose of this project is to reveal the evolutionarily conserved mechanisms that control Notch signaling to establish different cell fates during development. We use the peripheral nervous system of the fruit fly, Drosophila, as a model system to build on the genetic framework. Our lab and others have established that a subset of conserved membrane trafficking regulators act on a transmembrane protein Sanpodo to assign correct Notch-mediated cell fate assignments after asymmetric cell division. Understanding how fundamental cell biological mechanisms are mobilized to establish a specific context to regulate the Notch signaling pathway will provide insights into how dysregulation of these mechanisms in stem and progenitor cells contributes to human diseases, including cancer.

- **Title:** A Study of the Communication of GENetic Test Results by Telephone (COGENT Study)  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** The overall goal of this research is to develop and study a method for telephone disclosure of BRCA test results to patients undergoing genetic testing for breast cancer. We will conduct crucial preliminary work to develop a protocol for communication of genetic test results by telephone, and will then conduct a clinical trial to compare telephone disclosure to in-person disclosure of genetic test results. Ultimately, this research will require longitudinal participation at multiple centers to produce results that can support a change in the current standard of care. We expect this research and the larger future trial to significantly inform policies regarding genetic testing for breast cancer. Ultimately, this research has the potential to reduce barriers to receiving genetic testing and to promote the development of individualized breast cancer risk assessment and prevention.

**Geisinger Clinic - Weis Center for Research ($92,771)**  
**Research Project:**

- **Title:** Genetics of Morbid Obesity  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The high prevalence of obesity in the US is well known. Obesity can lead to a number of related medical conditions, including hypertension and diabetes. An important but often overlooked condition associated with obesity is non-alcoholic steatohepatitis (NASH). This disease is marked by accumulation of fat in the liver, liver inflammation, and fibrosis. NASH can lead to liver failure, and is thought to be a precursor to liver cancer. NASH is often under diagnosed because of the lack of reliable non-invasive tests. There is evidence for a genetic pre-disposition to the development of NASH. The purpose of this study is to identify specific genetic variants that are associated with NASH. This information will allow individuals at high risk for the disease to be identified and monitored, and should provide new information on the underlying causes of this disease.

Hepatitis B Foundation ($3,707)
Research Projects:

- **Title**: Effect of a Glucosidase Inhibitor on Expression of Cell Surface Glycoproteins  
  **Type of Research**: Biomedical  
  **Focus**: Immunology  
  **Purpose**: The purpose of this research project is to gain new insight into the process by which the immune system mediates a response to the hepatitis B virus and other viral or cancer-associated antigens. The long-term benefits of this project include identifying new treatment methods for chronic hepatitis B infection, and preventing hepatitis B infections from becoming chronic (leading to severe liver disease). The research project will be conducted at the Hepatitis B Foundation and its research affiliates at the PA Biotechnology Center of Bucks County, by select undergraduate students interested in biomedical research, during a summer internship. In addition to the promise of new therapies for hepatitis B infection, this project encourages PA students to seek careers in biomedical research, thereby increasing the future pool of promising researchers in Pennsylvania.

Lankenau Institute for Medical Research ($214,033)
Research Projects:

- **Title**: Targeting Radiation Resistant Hypoxic Cells in Lung Tumor  
  **Type of Research**: Biomedical  
  **Focus**: Oncological Sciences  
  **Purpose**: Radiation is one of the main treatments for lung cancers. Low oxygen (hypoxia) is prevalent in most solid tumors, including lung tumors. Hypoxic cells are three times less responsive to radiation therapy. Previously several approaches have been tested to increase the response of hypoxic tumors to radiation. These approaches used drugs that produced “repairable damages” in low oxygen tumors but they did not target the tumor’s repair capacity, which is a major contributing factor to the poor outcome of radiation and chemotherapy. We will use a novel approach by exploiting the low glucose microenvironment of the tumor, which is also associated with hypoxia, to increase lung tumor response to radiation by inhibiting the function of repair proteins in tumor cells. We have recently demonstrated that this strategy works in increasing the response of breast tumor to chemotherapy.

- **Title**: Role of TIMP-4 in Breast Cancer Progression  
  **Type of Research**: Biomedical  
  **Focus**: Oncological Sciences  
  **Purpose**: This project aims to create a test that clinicians can use to identify small but highly aggressive breast cancers at the time of diagnosis. We will also test why this marker can be found in breast cancer and what changes it causes that could
explain why a cancer becomes more aggressive in its presence. Combined, these results will help us find a treatment to prevent or reduce the effects of this marker.

**Lehigh University ($116,442)**

Research Project:

- **Title:** Interactions of Caveolin Transmembrane Domains in Bicelles: Implications for Biomedical Diseases  
  Type of Research: Biomedical  
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  Purpose: The primary purpose of this project is to study the caveolin family of proteins through the purchase and use of a matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometer. Caveolins reside in “flask-shaped” microdomains of the plasma membrane called caveolae, where they participate in a variety of essential cellular processes. Recent evidence has shown that misregulation of caveolins can result in a variety of disease states including cardiomyopathy, muscular dystrophy, Alzheimer’s, and cancer. Our focus lies in determining how the portion of the caveolin protein that resides in the plasma membrane governs caveolin structure and function in both normal and disease states.

**Magee Womens Research Institute ($894,069)**

Research Projects:

- **Title:** The Effect of Uric Acid on Placental Amino Acid Transport and Endothelial Trophoblast Interaction in Preeclampsia  
  Type of Research: Clinical  
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  Purpose: Preeclampsia is associated with increased concentrations of uric acid in blood. We propose that uric acid, considered only a marker of the severity of preeclampsia, may itself cause damage. Fetal growth restriction is more common in preeclampsia and the higher the uric acid in the mother’s blood the greater the risk of fetal growth restriction. Normal fetal growth requires the placental transfer of nutrients to the fetus and an increase in the delivery of nutrient-containing blood to the placenta facilitated by modification of the mother's blood vessels that supply the placenta. We will test if uric acid can reduce the transfer of the important nutrients, amino acids, across the placenta and interfere with the interaction of fetal trophoblast cells and maternal endothelium; a process required for the maternal vessels to increase the delivery of blood to the placenta.

- **Title:** Biomarker Discovery for the Minimally Invasive Diagnosis of Fetal Genetic Disease  
  Type of Research: Biomedical  
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  Purpose: Aneuploidy is a change in the number of chromosomes that can lead to a chromosomal disorder. Common chromosomal disorders resulting in live births include Down, Turner, Edwards and Klinefelter Syndromes. Human aneuploidy causes 25% of all miscarriages and has been estimated to be present in as many as 30% of all conceptions. Affected infants suffer a variety of neurological and physical abnormalities. Definitive prenatal diagnosis by amniocentesis and chorionic villus sampling (CVS) carries inherent risks and existing minimally-invasive screening methods based on the analysis of proteins in maternal blood do not achieve the desired level of accuracy. This pilot project will, therefore, focus on the discovery
and development of novel genetic biomarkers that will allow the accurate diagnosis of fetal aneuploidy using maternal blood samples.

- **Title:** Immune System-Tumor Cell Interactions in Primary and Metastatic Sites in Late Stage Ovarian Cancer  
  **Type of Research:** Biomedical  
  **Focus:** Immunology  
  **Purpose:** Ovarian cancer is the most lethal gynecologic cancer. The high mortality rate is due to the fact that most patients are diagnosed in late stages, when disease is no longer confined to the ovary and has spread to the peritoneal cavity. Standard treatment for this disease begins with surgery followed by chemotherapy. However, these approaches are often unable to eradicate the residual disease, thus raising the need for new and improved therapies. The patient’s immune system has the ability to recognize the residual tumor cells and to eliminate them, making immune therapy an attractive approach. However, little is currently known about how the immune system interacts with tumor cells in different anatomical environments (in the ovary versus metastatic sites). In this project, we will study immune cell-tumor cell interactions in late stage ovarian tumors.

- **Title:** Circulating Fatty Acids in the Pathogenesis of Preeclampsia  
  **Type of Research:** Biomedical  
  **Focus:** Cardiovascular Sciences  
  **Purpose:** The hypertensive pregnancy syndrome preeclampsia is a leading cause of maternal death and increases fetal death five-fold. Vascular endothelial cells form a lining called the endothelium -one cell thick- for all the blood vessels in the body. Although endothelial cell dysfunction is a cause of the vasoconstriction, hypertension, and multi-organ damage that occurs during preeclampsia, the mechanisms of endothelial dysfunction are poorly understood. Angiogenesis-related activities of endothelial cells, including proliferation and tubule formation, are important for vascular repair and maintenance of a healthy endothelium. Preliminary data suggest that abnormally high levels of lipids called free fatty acids may adversely affect the functions of endothelial cells. The overall hypothesis is that elevated free fatty acids inhibit endothelial angiogenic functions in preeclampsia.

**Monell Chemical Senses Center ($213,928)**

**Research Projects:**

- **Title:** Brain Mechanisms for Wanting Versus Liking  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** This research will lead to a better understanding of how cravings for foods and drugs are learned. We now know that people can learn to crave healthy foods. One purpose of this work is to find out how to make people crave healthy foods more frequently. A second purpose of this project is to find out how the brain responds to healthy foods as compared to junk foods. Such information can then be used to develop better treatments for obesity and for drug addiction.

- **Title:** Effect of Smoking on Fat Taste Reactivity, Sensitivity and Preferences in Women  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** The purpose of this ongoing research project is to expand upon recent findings that smoking is associated with a lower sensitivity to detect sweet tastes and increased food cravings, especially for carbohydrates and high fat foods, in women. We will initiate a new study to determine how smoking alters fat perception and preferences in women. The information gleaned from this research may enable
a better understanding on how changes in taste perception may explain changes in eating patterns when women smoke and during the initial stages of smoking withdrawal.

**MPC Corporation ($136,227)**

**Research Projects:**

- **Title:** Brain Pathways to Cardiovascular Health  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** The purpose of this project is to use noninvasive brain imaging methods to determine the human brain systems that mediate individual differences in blood pressure reactions to mental stress. Research suggests that individuals who show large-magnitude increases in blood pressure during mental stress are at increased risk for developing coronary heart disease (CHD). From a public health perspective, the importance of this project is that it will help to determine the brain pathways by which mental stress may influence CHD risk. It may also reveal markers of stress-related brain activity that could be objectively measured and possibly targeted for modification in people at risk for CHD.

- **Title:** Justifying Underlying Motivation in Adolescents  
  **Type of Research:** Biomedical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** This project focuses on investigating the relationship among regulatory processes—obesity, sleep, and emotion—in a sample of adolescents, with a long-term goal of better understanding the interrelationships and pivotal aspects to broad-based interventions to treat obesity. The project includes an innovative strategy for measuring regulatory processes in adolescents that integrates psychological (mood), behavioral (eating, physical activity, sleep), and biological (endocrine, inflammation) pathways to optimize long-term wellness. This goal will be achieved by using state-of-the-art ecological momentary assessment (EMA), namely answer-only cellular phones and BodyMedia SenseWear Weight Management Solution™, to capture data in “real time” within the adolescent’s environment.

- **Title:** Familial Pathways to Early-Onset Suicide Attempts  
  **Type of Research:** Biomedical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** There are very few empirically validated treatments for suicidal behavior, and none exist in adolescents, who are at highest risk for incident attempt. The major goal of this project is to evaluate potential clinical and biologic intermediate phenotypes that bridge the gap among genes, childhood adversity, and the clinical risk factors for suicidal behavior in order to move from a descriptive to an explanatory model. The results of this study should help to identify the temporal and likely causal sequence and interactions that result in the onset of suicidal behavior and, thus, help to establish a framework for treatment and prevention of suicidal behavior in high-risk individuals.

- **Title:** Genetic Vulnerabilities to Stress-Elicited Risk for Upper Respiratory Infectious Illness  
  **Type of Research:** Biomedical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** We are all exposed to common upper respiratory viruses most days of our lives. However, we don’t always get sick, and some people are more likely to get sick than others. In 25 years of studying common colds, we have found that people experiencing higher levels of psychological stress are more likely to develop a symptomatic illness when exposed to common cold viruses than those reporting less
stress. Even so, not everyone who is stressed develops a cold. The purpose of this project is to study the interaction of psychological stress and gene polymorphisms that regulate the production and/or action of inflammatory chemicals (cytokines) and of a stress hormone (cortisol) in regulating illness during infection with a common cold virus. We predict that such interactions may account for why some people are less affected by stress than others in terms of their susceptibility to upper respiratory illness.

- **Title:** Financial Incentives to Improve Health Among Elderly Populations  
  **Type of Research:** Biomedical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** The objective of this study is to determine the effectiveness of four varied monetary incentive systems to motivate healthy behaviors and improve health outcomes in elderly populations. Improving our understanding of the use of monetary incentive systems to promote healthy behaviors is becoming increasingly important as use of these types of incentives has increased rapidly in wellness programs intended to increase preventive health activity and decrease long run health costs.

**National Disease Research Interchange ($53,760)**  
**Research Project:**
- **Title:** T1D Microvascular Complications: Defining Phenotypes to Identify Susceptibility Loci in Candidate Genes  
  **Type of Research:** Health Services  
  **Focus:** Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  **Purpose:** The Human Biological Data Interchange (HBDI) database is a vast repository of family and medical information focused on the study of type 1 diabetes (T1D) and its complications. A previous PA state-funded project confirmed that genetic factors likely influence susceptibility to 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 newly genotyped HBDI samples. To enhance the statistical power and precision of our analyses and maintain the scientific value of our dataset, we will also continue our program of administering annual follow-up questionnaires and collection of patient medical history records, begun in 2007 with funds from the state of PA. The additional information that we will collect will better define the genetic contribution to complications.

**National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation ($1,306,064)**  
**Research Project:**
- **Title:** Mutation Profiling of Breast and Colon Cancer  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Cancers are caused by mutations of the genes that control important functional components within the cells. These gene mutations, therefore, govern the behavior of cancer cells. Studies have shown that within a certain cancer type such as breast, there are different sets of mutated genes. These differences (also called heterogeneity) of gene mutations result in different clinical behaviors of cancer cells, i.e., differential prognoses and responses to anti-cancer therapies. The goals of this project are to characterize gene mutations in breast and colon cancers and categorize them according to matched clinical behaviors so that the information can
be used to optimize treatment for breast and colon cancers as well as to identify new targets for anti-cancer therapies.

**Oncology Nursing Society ($23,037)**

Research Project:
- **Title:** Ambulatory Oncology Nurses’ Perception of Evidence-Based Practice Resources
- **Type of Research:** Health Services
- **Focus:** Health of Populations, Behavioral and Biobehavioral Processes
- **Purpose:** The project will increase understanding of the factors which influence the use of evidence-based practice resources for the care of people with cancer in the outpatient setting. Oncology nurses who work in outpatient settings will participate in discussion groups and/or complete a survey. The discussion groups and survey will address the nurse’s use of evidence-based practice resources, the characteristics of the practice environment, and the facilitation strategies that support the use of evidence-based practice resources.

**Pennsylvania College of Optometry ($63,639)**

Research Project:
- **Title:** Modulating the Properties of Retinal Cells Related to Normal Vision and Visual Disorders
- **Type of Research:** Biomedical
- **Focus:** Neurosciences
- **Purpose:** Congenital rod and cone degeneration, such as retinitis pigmentosa or Leber congenital amaurosis, cause blindness by destroying photoreceptors, the only light sensitive neurons in the retina. We previously demonstrated that light sensitivity of the retinas lacking photoreceptors can be partially restored by expressing an artificial light-sensitive microbial channel, called channelrhodopsin 2, in retinal ganglion cells. We have also attempted to express the channelrhodopsin in a different population of retinal neurons, bipolar cells, using one of known genetic elements, which target protein expression to the bipolar cells. This attempt demonstrated that the channelrhodopsin can be expressed in bipolar cells, but the density of expression was low. The purpose of this pilot study is to continue the attempts with converting secondary neurons of the mouse retina to light-sensitive cells in order to mitigate the loss of light perception caused by congenital retinal photoreceptor degeneration. We will explore the possibility of imparting the light-sensitivity directly to the second-order retinal neurons using a different genetic element that determines the specificity of protein expression in bipolar cells of the retina. The long-term goal of this line of research is to restore light perception in blind retinas lacking rods and cones.

**Pennsylvania State University ($7,538,293)**

Research Projects:
- **Title:** High Field MRI - Limitations and Solutions
- **Type of Research:** Biomedical, Clinical, and Health Services
- **Focus:** Bioengineering, Surgical Sciences and Technology
- **Purpose:** We are in the process of developing new techniques and technology that will make Magnetic Resonance Imaging (MRI) more accurate, more effective, more versatile, faster, and safer in the future. Because of the wide utility of MRI, this will have major benefits on many areas of medicine. We have recently ended a period of funding from the NIH regarding this work and have received very good scores with easily-addressable concerns in our first renewal application. We anticipate further NIH funding upon review of our revised renewal application. Pennsylvania
Department of Health (PA DOH) funding will allow us to continue progress without major interruption during a gap in federal funding and allow for continued demonstrable progress should a second revised application for federal funds be necessary.

- **Title:** Interactions of the CA Protein in the Retrovirus Core  
  **Type of Research:** Biomedical  
  **Focus:** AIDS and Related Research  
  **Purpose:** In retroviruses such as HIV, the human T-cell lymphotrophic virus and the Rous sarcoma virus, a stage of the virus life cycle known as maturation involves very dramatic structural changes in the interior of the virus particle, leading to the activation of its infectious potential. The studies conducted as part of this project will use a combination of genetic and protein structural approaches to examine the molecular mechanisms that control this process in the formation of the functional core in the interior of the infectious particle. A detailed understanding of this essential step of virus infection will allow development of better inhibitors of capsid assembly for use as anti-retroviral drugs.

- **Title:** Evaluation of Patient-Driven Playbook (A Patient Education Tool)  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** Diabetes has devastating consequences in terms of morbidity, mortality and health care costs. Between 2003 and 2004, two out of three Americans did not meet clearly identified evidence-based treatment goals. Yet the vast majority (84%) of patients believed that they were doing a good job managing their disease. A clear knowledge gap and educational opportunity thus emerged. By using a patient advocacy group, patient authors, and patient focus groups, a new tool, called the Penn State Diabetes Playbook, was developed to teach patients diabetes disease awareness and self-management skills. This project is designed to evaluate the Playbook alone or with nurse dialogue using motivational interviewing when it comes to educating, motivating, and altering the behavior of patients with diabetes in a primary care setting.

- **Title:** DeltaFosB and Reward Comparison in Mice  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** Drug addiction often leads to decreased motivation for things that were once pleasurable before drug use such as friends, family, work, hobbies, and even personal hygiene. This devaluation of naturally rewarding stimuli in the environment, in favor of the drug of abuse, leads to personal and public costs as the addict is no longer able to beneficially function in society. The present project seeks to further elucidate a possible molecular mediator of the neural plasticity that leads to this behavior using a mouse model.

- **Title:** Iron-Induced Changes that Predispose to Malignancy  
  **Type of Research:** Biomedical  
  **Focus:** Digestive Sciences  
  **Purpose:** Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and also one of the most deadly. It is clear that chronic excess iron deposition is implicated in the development of HCC. Understanding the cellular and molecular changes occurring in the liver exposed to chronic excess iron deposition may lead to the future identification of biomarkers for early detection of progression and may also provide improved strategies for early chemopreventive intervention.

- **Title:** Nutrient Overload as a Causative Factor in Diabetic Retinopathy  
  **Type of Research:** Biomedical  
  **Focus:** Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: The research project focuses on the novel view of nutrients as signaling molecules that act through signal transduction cascades to regulate various cellular functions. The nutrient sensing signaling pathways are not only interconnected at multiple levels but they are also coupled to the insulin receptor signaling pathway. Diabetes is a disease characterized not only by an impaired insulin receptor signaling pathway (due to lack of insulin and/or insulin resistance), but also by elevated blood concentrations of nutrients such as glucose, fatty acids and branched-chain amino acids. Therefore, the overall purpose of the project is to gain a better understanding of the relative contributions of the impaired insulin receptor and the nutrient-activated signaling cascades to the development of diabetic retinopathy.

- **Title:** Co-Crystals of Novel Integrase Mutants and Retroviral DNA  
  **Type of Research:** Biomedical  
  **Focus:** AIDS and Related Research  
  **Purpose:** The permanent integration of retroviral DNA into cellular DNA leads to immunodeficiency, neurological, and neoplastic diseases. The long-term goal of this project is to benefit human health by developing ways to interfere with retrovirus integration. The viral integrase enzyme causes integration by specifically nicking the ends of viral DNA at a precise location, and then inserting that viral DNA into any site in cellular DNA. However, our understanding of how this one enzyme interacts with, and acts on, two different kinds of DNA is limited. Analyzing the molecular structures of crystals that contain integrase bound to viral DNA could finally reveal how integrase distinguishes between viral and cellular DNA. Thus, this project is directed at making it possible to obtain these long-sought crystals.

- **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 infections diseases requiring high level biocontainment.

- **Title:** Translational Research in Polycystic Ovary Syndrome  
  **Type of Research:** Biomedical  
  **Focus:** Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  **Purpose:** The purpose of this project is to continue studies that will identify genetic contributions to Polycystic Ovary Syndrome (PCOS). PCOS is the most common cause of infrequent menses and excess male hormone in women and affects 5-10% of the female population. We intend to closely study families, where this disorder clusters, to better understand the heritability of its traits, as well as by studying the children of PCOS mothers to better understand how it develops. We will collect and study DNA and human thecal cells from ovarian follicles to better understand how a genetic variant in the Fibrillin 3 gene on chromosome 19 contributes to the etiology of the syndrome.

- **Title:** Neural Systems of Ingestive Behavior  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** The purpose of this project is to investigate the pathways from the central gustatory system to brain structures that mediate reward, such as the nucleus accumbens. These experiments will elucidate where and how the hedonic effects of a taste, its pleasure or aversion, are elaborated from the afferent sensory message.

- **Title:** Nuclear Trafficking of the Retroviral Gag Protein  
  **Type of Research:** Biomedical  
  **Focus:** Infectious Diseases and Microbiology
Purpose: This project will support a graduate research assistant who is studying how retroviruses interact with the cells they infect. The project is designed to elucidate the mechanisms by which retroviral Gag proteins, the major viral structural proteins, utilize cellular transport machinery to travel throughout different subcellular compartments. The long-term goal of this work is to identify novel targets for anti-retroviral therapy.

- **Title:** Chronic Oxidative Stress and the Redox Proteome in Normal Breast Parenchyma  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Breast cancer is a disease that is a long time in the making during decades of exposure of breast tissue to pro-carcinogenic conditions. In this project we will test the hypothesis that increased levels of reactive oxidants (molecules that disrupt protein function and may be related to carcinogenesis) in human breast tissue are associated with altered levels of specific regulatory molecules in these cells, thereby disrupting normal function. We will use newly developed proteomic techniques to obtain a global picture of the oxidized proteins present in human breast tissue. Demonstrating that these alterations occur would implicate the chronic and progressive exposure to oxidants as a pro-carcinogenic event and potentially provide endpoints that could be assessed during dietary and other therapeutic interventions designed to minimize or reverse these changes.

- **Title:** Research Infrastructure for New Pesticide Technologies for Control of Insect-Borne Diseases like Malaria  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** This project is to provide the eight environmental chambers which will form the core of a state of the art Laboratory for the Experimental Analysis of Human Infectious Insects at Penn State. Insects vector some of the globally most important human diseases, including malaria, and the control of mosquitoes continues to be one of the most potent weapons against these diseases. But existing chemical insecticides are failing. The new laboratory will develop novel strategies and technologies for sustainable control of vector-borne diseases. Fungal biopesticides offer considerable promise as a new, sustainable and environmentally friendly approach to protecting human health. In addition to globally significant research and extension outputs, this project has many potential Pennsylvania population based applications for other vector borne diseases, such as, West Nile, Lyme, erratically present diseases such as Eastern Equine Encephalitis and St Louis Encephalitis. All of these diseases have wildlife reservoirs and are carried to humans via insects. History shows that we can expect a variety of other vector-borne diseases which will emerge in future years.

- **Title:** Coupling Mechanisms of NOP Receptors and Calcium Channels  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** There are four opioid receptors that have been described and that are involved in transmitting pain signals within the nervous system. One of these receptors is known as the ‘opioid receptor-like 1 receptor’ or NOP receptor. When this receptor was discovered, it was found that activating the receptor would either cause pain or inhibit pain. Our laboratory has found that this receptor is expressed in stellate ganglion neurons and that it has the ability to be either silent or active in the absence of any agonist. The purpose of this research project is to study the pharmacology of constitutively active NOP receptors and study the mechanism by which these receptors obtain an ‘active’ state in the absence of agonists.
• Title: Dilatory and Constrictor Control of Coronary Blood Flow Velocity  
Type of Research: Biomedical  
Focus: Cardiovascular Sciences  
Purpose: The purpose of this study is to better understand mechanisms that control blood flow in the coronary arteries. This is important because the coronary arteries provide all of the oxygen to the heart muscle. The coronary circulation is highly unusual because the heart muscle cannot change the percentage of oxygen removed from blood as the amount of activity increases. Thus blood flow regulation becomes crucial and understanding how the heart works. In this project we will examine what substances make blood vessels enlarge and how and why the nervous system may make them become smaller.

• Title: Environmental Heavy Metals, Biomarkers of Susceptibility and Renal Cancer  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: This research will assist important efforts in cancer prevention by investigating cancer risk in a large population-based study among individuals at higher risk of renal cell cancer (RCC) (i.e., male smokers), by the use of established biomarkers of heavy metal exposure. The overall goal of the proposed study is to identify the risk of heavy metal exposure in the development of RCC at levels of exposure experienced by the general population and to determine whether there are other susceptibility factors (both genotypic and phenotypic) that can help predict cancer risk.

• Title: Molecular Basis of Mechanotransduction in Bone Cells  
Type of Research: Biomedical  
Focus: Musculoskeletal, Oral and Skin Sciences  
Purpose: The purpose of this project is to establish an animal model for studying mechanical loading-induced bone formation, and identify important proteins involved in the loading-induced bone formation. Understanding of the loading-induced bone formation will lead to novel treatments for osteoporosis.

• Title: Disseminating Effective Habits for Long-term Weight Loss  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: Most weight-loss interventions are not effective in producing long-term weight loss. The National Weight Control Registry (NWCR) has followed over 4000 individuals who achieved long-term weight loss to try to identify the characteristics of individuals who successfully maintained meaningful weight loss, including their dietary and exercise habits. We proposed to extend this study by developing a website http://www.achievetogether.com that will use information gathered from individuals who have successfully lost weight and kept it off to help guide those looking to lose weight. This data will include identification of successful strategies, details of how these strategies were implemented, and how barriers were overcome. We will then determine whether use of the website is effective in producing weight loss, and how patterns of use predict successful weight loss.

• Title: Selective Autophagy in Yeast and in Mammalian Cells  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The objective of this project is to examine whether a selective autophagy pathway that we originally identified in Saccharomyces cerevisiae is also present in mammalian systems. Vacuole Import and Degradation (VID) genes were isolated in regards to their role in the vacuole dependent degradation of gluconeogenic enzymes in yeast. Our preliminary results indicate an even broader role for VID genes in the
survival of cells during chronological aging and during oxidative-stress in yeast. Cells lacking several of the VID genes are sensitive to oxidative stress and they have shorter life spans. Thus, VID genes protect cells from these stresses. Homologues of VID genes are found in mice and humans. It is the goal of this study to examine whether a similar Vid pathway exists in mammalian cells.

• Title: Netrin-1 in Ischemia Reperfusion Injury of the Kidney
  Type of Research: Biomedical
  Focus: Renal and Urological Sciences
  Purpose: The purpose of this project is to gain a better understanding of how netrin-1 prevents ischemic renal injury. We will determine the receptors subtype which mediates netrin-1 protective effect against ischemic kidney injury and pathways through which netrin-1 mediates the protective effects.

• Title: Structures in the Unfolded State Initiate Protein Folding
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The central dogma of molecular biology states that DNA is transcribed into a messenger RNA which is translated into the amino acid sequence of a protein. However, we do not understand the means by which that linear sequence of amino acids is transformed into a unique three dimensional structure that is capable of function. This project examines the mechanism by which protein folding is initiated, identifying individual residues and structures that direct the folding of the protein to the correct final structure.

• Title: Mechanisms of Gene Regulation by EBV EBNA-1 Protein
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The potential of Epstein-Barr virus (EBV) to cause cancer is dependent on establishment of a life-long latent infection within its human host’s B lymphocytes. We have discovered a novel autoregulatory mechanism through which EBV can control expression of its EBNA-1 protein, whose function is critical to EBV persistence in B cells. We hypothesize that this enables the virus to maintain EBNA-1 levels below a threshold to prevent detection and removal of infected cells by the host’s immune surveillance. The purpose of this research is to evaluate autoregulation of EBNA-1 expression in the context of infected B cells to permit us to test whether it is capable of allowing infected cells to evade the immune response. Ultimately, this may lead to therapeutic approaches to disrupt autoregulation of EBNA-1 to enhance the anti-EBV immune response.

• Title: Regulation of Mitochondrial Dysfunction and Diet-induced Obesity by ALCAT1
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Cardiolipin is an important lipid required for health and diseases. Like cholesterol, there are “good” and “bad” cardiolipins which are determined by the structure of the lipid. Increased levels of bad cardiolipin play a causative role in diabetes, obesity, hyperthyroidism, and aging. ALCAT1 is a cardiolipin synthetic enzyme recently identified in our lab. We have shown that this enzyme catalyzes the synthesis of bad cardiolipin, and its enzyme activity is elevated in diabetes and obesity. The project will validate ALCAT1 as a drug target for the treatment of diabetes and obesity using sophisticated molecular, cellular, enzymatic, and transgenic approaches.

• Title: Novel Pathway Mediating Peripheral Sensitization of Esophageal Vagal Sensory Afferent Nerves
  Type of Research: Biomedical
  Focus: Digestive Sciences
Abnormal esophageal sensations, such as esophageal-related noncardiac chest pain and heartburn, are common complaints. They are generated from noxious stimuli on esophageal sensory afferent nerves and transmitted to the central nervous system via both spinal and vagal pathways. Esophageal inflammation sensitizes sensory afferents and enhances these abnormal sensations to induce visceral hypersensitivity. This involves both peripheral and central sensitization. The mechanism of peripheral sensitization of esophageal sensory afferents is still unclear. The long-term goal of our research is to study the mechanism of peripheral sensitization in a validated esophageal hypersensitivity model. This project focuses on peripheral sensitization of vagal sensory afferents in our guinea-pig ex vivo esophageal-vagal preparation.

Title: The Role of Microglial Priming in Diabetic Retinopathy
Type of Research: Biomedical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: The purpose of this project is to conduct preliminary experiments to test the hypothesis that a systemic inflammatory event will couple with diabetes to cause a pronounced increase in retinal inflammation. We will use an animal model to determine if infection or inflammation in other parts of the body may cause excessive inflammation in the diabetic retina. If so, this response may explain why some diabetic patients suffer from extreme retinal damage, while others do not. We will also determine if microglial cells in the diabetic retina are the initiators of this hyper-response. If so, then treatments that control microglial behavior may be useful for preventing the progression of diabetic retinopathy.

Title: Gag and CA Protein Interactions in Retroviral Capsid Maturation
Type of Research: Biomedical
Focus: AIDS and Related Research
Purpose: This project examines the molecular mechanism by which the internal structure of infectious retrovirus particles, such as that of HIV, is formed during the process of virus release from the infected cells. Specifically, this work will test the novel hypothesis that a critical step in the virus assembly pathway is an interaction of the mature capsid protein CA with one or more molecules of its precursor protein Gag. This hypothesis will be tested with proteins derived from both the avian Rous sarcoma virus and HIV. By documenting the molecular mechanisms involved in detail, this project will provide critical insights that may be utilized for the development of new anti-retroviral drugs.

Title: The Effects of Air Quality on Human Reproduction
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: Air quality has been identified as a significant risk factor for respiratory and cardiovascular disease and for a variety of cancers. It is likely, based on preliminary data from this project that air quality also adversely affects human reproduction. We will use the model of assisted reproductive technology, i.e., in vitro fertilization (IVF) for our study. This paradigm allows us to determine exact dates of oocyte development, ovulation (i.e., the day of oocyte retrieval), fertilization, implantation, and duration of pregnancy, which allow for more accurate correlation of outcomes with ambient air quality. Our primary goal is to establish the relationship between air quality at the home zip code of the subject or in the IVF lab and fertility outcomes after IVF. Our long range objective of this study is to design a randomized trial to improve air quality both in the lab and in the IVF subject’s external environment to improve reproductive outcomes.

Title: New Methods for Studying Mitochondrial Mutations and Common Chromosome Fragile Sites in Cancer
Type of Research: Biomedical
• Title: Proteomic and Molecular Analysis of Formalin Fixed, Paraffin Embedded Tumors
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Every day, benign and malignant tumor tissues are biopsied or removed surgically and evaluated by a pathologist to establish a diagnosis and prognosis (i.e., Is it cancerous? What type of cancer?). However, much information that might aid in making a diagnosis remains unstudied within these collected tissue samples. One difficulty has been that the tissues are preserved in such a way (formalin fixation and paraffin embedding) that make standard methods of molecular biology difficult to use. Recently, emerging technologies have made it possible to obtain some of this untapped information. Our goal is to couple these techniques in a way that has not yet been done at Penn State University – College of Medicine (PSU_COM) to compare two different types of tumors. If successful, these methods will be important for basic science studies, and could be developed further as powerful clinical diagnostic tools.

• Title: Signaling Pathways in Epidermal Stem Cell Proliferation and Skin Carcinogenesis
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Our research will attempt to determine what role the polyamine pathway plays in early skin cancer development. There is strong experimental evidence indicating the location of epidermal stem cells that are modified by carcinogen exposure is in a specific area of the hair follicle. By directing expression of transgenes to this region of the epidermis in mice, we can modify gene expression in stem cells and ask what effect these genetic alterations have on tumor development. Understanding the pathways that control epidermal stem cell proliferation is important to the area of public health, because these cells are targets for gene therapy approaches in cancer prevention and treatment.

• Title: Genetic and Proteomic Analysis of the UL84 Gene of Human Cytomegalovirus
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: In immunocompromised individuals, opportunistic human cytomegalovirus (HCMV) infections can produce life-threatening syndromes involving almost every organ, but more commonly pneumonia, hepatitis, diseases of the central nervous system, and secondary immune suppression. In addition, HCMV can cross the placenta and is the most common viral cause of congenital defects. The purpose of this research project is to identify the mechanisms of action of an essential viral protein. Elucidation of these mechanisms could lead to the identification of therapeutic targets for management of HCMV illnesses.

• Title: Development of a Novel FdUMP Prodrug for Treatment of Breast Cancer
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: 5-Fluorouracil (5-FU) is one of the most active drugs in breast cancer chemotherapy. Studies have shown that the potency of 5-FU is mainly a result of the inhibitory effect by its metabolite FdUMP on the enzyme thymidylate synthase (TS). Conversion of 5-FU to FdUMP is very inefficient and requires multi-step enzymatic activation. This metabolic dependency often causes various resistance or toxicity to 5-FU and limits its clinical use. To offer more efficient and less toxic alternative of 5-FU, a novel agent FdTSP was designed to generate FdUMP in tumor cells through an enzyme-independent pathway and overcome the hydrophilicity of FdUMP that limits its entry into cells. The goal of this project is to establish the use of FdTSP as a superior alternative to 5-FU to treat breast cancer in an in vitro cell culture model.

- Title: Antihypertensive Effects of Tetanic Baroreceptor Stimulation  
Type of Research: Biomedical  
Focus: Cardiovascular Sciences  
Purpose: The purpose of this project is to investigate the effect of brief high frequency carotid sinus baroreceptor stimulation on chronic blood pressure reduction in dogs.

- Title: The Role of STAT1 Inactivation in the Development of Inflammatory Bowel Disease (IBD)  
Type of Research: Biomedical  
Focus: Immunology  
Purpose: The overall goal of this project is to elucidate the role of STAT1 and STAT3 signaling in inflammatory bowel disease (IBD) development. Our specific hypothesis for this project is that neutralization of interferon-gamma in a STAT3 deficient IBD model will reduce STAT1 activation and prevent IBD development. Our STAT3KO and STAT1/3KO double deficient model will provide a unique system to explore the downstream target genes for future exploration as novel therapeutics.

- Title: Effects of Early Diabetes on the Microvasculature: A Link between the Eye, Brain, and Heart?  
Type of Research: Biomedical and Clinical  
Focus: Cardiovascular Sciences  
Purpose: The purpose of this project is to examine the relationship between blood vessel responses from the eye, brain, and heart to stimuli, which cause the vessel to get bigger (i.e., dilate) or smaller (i.e., constrict) in individuals with pre-diabetes and diabetes. Dysfunction of the eye’s retinal blood vessels to dilate or constrict may prove to be a valid surrogate marker of stroke and heart disease. This project will use non-invasive Ultrasound Doppler to examine heart and brain blood flow and will use a novel tool known as the Dynamic Vessel Analyzer that allows direct visualization of the retinal blood vessels in healthy individuals and individuals with pre-diabetes and diabetes.

- Title: Adapting an RNA Sensor Platform to Protein Detection Using Aptamers  
Type of Research: Biomedical and Clinical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: We are developing a chip-based RNA sensor, with the initial application for detection of circulating tumor cells (CTCs) in the blood of patients. This device utilizes antisense oligonucleotides (ASOs) targeted to selected cancer-related RNA molecules. Nanowires (NWs) are functionalized with an ASO, and the selected marker RNAs are hybridized to the functionalized NWs. A second ASO, targeted to another site on the marker, is attached to Au particles, and in turn hybridized to the marker RNA bound to the NWs, forming a “hybridization sandwich”. This binding
causes a shift in the resonance frequency of the NWs, which can easily be detected. We have shown that derivatized NWs remain functional throughout conditions necessary for “bottom-up” assembly, allowing multiplexing for many different markers. While this platform is being developed, we have initiated a Clinical Trial with melanoma patients, where CTCs are harvested; melanoma marker RNAs are initially being detected using real-time PCR, and the balance of the samples are being banked for subsequent detection when the chip-based RNA sensor is ready.

- **Title:** Development of Novel Molecular Subtyping Methods for Identifying Pathways of Transmission of MRSA  
  **Type of Research:** Biomedical  
  **Focus:** Immunology  
  **Purpose:** This project will build on existing, unique research expertise at both University of Pennsylvania (UP) and Hershey Medical Center (HMC) to create a critical mass focused on preventing the transmission of methicillin-resistant Staphylococcus aureus (MRSA) in Pennsylvania communities and healthcare settings. It will translate basic scientific advancements in the fields of genomics, epidemiology, molecular epidemiology, infectious diseases, pathology and clinical medicine to prevent the transmission of MRSA to susceptible hosts. Combining these novel molecular subtyping methods with conventional epidemiologic analysis will allow us to determine the pathways by which specific endemic and epidemic clones are being transmitted in both Pennsylvania communities and at HMC. Once these pathways have been identified then targeted intervention strategies can be implemented to prevent MRSA transmission.

- **Title:** Sequencing of LGL Leukemia Retrovirus Genome  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The broad long-term objective of this project is to understand the etiology of large granular lymphocyte (LGL) leukemia and related autoimmune diseases, including rheumatoid arthritis (RA). Preliminary serologic and molecular data indicate a high likelihood that patients are infected with a novel retrovirus with similarities to both human T-cell leukemia viruses (HTLV) and human immunodeficiency viruses (HIV). In particular, we have demonstrated transmission of an infectious retrovirus from LGL leukemia cells to co-cultured HOS target cells. Evidence for retroviral infection in this LGL-HOS cell line includes morphologic signs of retroviral infection such as formation of syncytia and other cytopathic effects, demonstration of high levels of reverse transcriptase activity, and detection of 100nm retroviral-like particles of type C morphology using electron microscopy. So far, however, we have been unsuccessful in characterizing this virus at the genomic level. Recent advances in sequencing technology and bioinformatics capability pioneered by investigators at Huck Institute have led to characterization of ancient and environmental genomes. This project represents, then, a cross-campus collaboration aimed at characterizing the LGL virus. Specifically, we plan to determine the retroviral genome of the LGL virus utilizing pyrosequencing of LGL-HOS mRNA.

- **Title:** Mechanisms of Unexpected Drug Side Effects Related to Obesity and Diabetes  
  **Type of Research:** Biomedical  
  **Focus:** Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  **Purpose:** The long-term goals of the project are to elucidate the mechanisms underlying drug side effects related to obesity and diabetes. We believe that investigating the mechanisms underlying unexplained drug side effects is an innovative approach that may reveal new targets for the treatment of obesity and diabetes. Alternatively, it may yield new drugs with fewer side effects. Obesity and diabetes are epidemics facing our state and country. Understandably, our institution
has committed to this as one of the research focus areas, along with cardiovascular disease and cancer.

- **Title:** Dissecting the Interaction between Radiofrequency Ablation and Tumor Antigen-Specific Immune Response in Hepatocellular Cancer: A Murine Model and a Human Protocol  
  **Type of Research:** Biomedical and Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** Hepatocellular cancer can be a difficult disease to treat, with radiofrequency ablation (RFA) being a critical component of treatment for patients with inoperable cancer. The risk of recurrence associated with RFA makes it imperative that we understand the precise mechanism of RFA and methods to increase its efficacy. The proposed murine and human studies will help us understand the anti-tumor immune responses to RFA. We hope to build a foundation with our basic science findings and implement this foundation in clinical practice. The insights gained in our research and clinical practice will be used to raise new questions and guide further research. Our experimental endeavors strive to combine surgical modalities with potential immunotherapy that will enable us to harness one’s own immune system to fight the cancer.

- **Title:** Central Pennsylvania Women’s Health Study (CePAWHS): Extending the Strong Healthy Women Behavioral Change Intervention to Urban Areas  
  **Type of Research:** Biomedical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** This project builds on the highly effective Strong Healthy Women intervention, developed as part of the Central PA Women’s Health Study (CePAWHS). This intervention was designed to modify risk factors for chronic conditions associated with adverse pregnancy outcomes such as hypertension, diabetes, and obesity by changing behaviors related to physical activity level, nutritional intake, stress reduction, and tobacco and alcohol use; it is currently being tested in low-income rural communities in Central PA. The focus of the proposed research is to modify the Strong Healthy Women intervention to include racially and ethnically diverse urban women in Harrisburg, Lancaster, and York. We hope that this will lead to a reduction in risks of adverse pregnancy outcomes, and to the elimination of disparities in these outcomes across geographic and race/ethnic groups.

- **Title:** Biomarkers and Hedonic Correlates of Systemic Dysregulation in Recently Detoxified Opiate Addicts  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** Opiate addiction results in a state of physiological disturbance following detoxification that is thought to contribute to early relapse. This dysregulated state (or allostasis), includes sleep abnormalities, increased responsivity to stress, a decreased capacity of the nervous system to experience natural rewards as pleasurable, and, coupled with heightened responses to drug cues, is thought to be associated with increased risk of relapse. In this project, several biomarkers of allostasis, including brain responses to drug cues and emotionally relevant stimuli, sleep quality, cortisol levels, and daily mood states will be compared in recently detoxified opiate addicts, control subjects, and recovering addicts who have been abstinent for 3 months. The pilot data will support a grant application to NIDA to assess these biomarkers as mediators in a larger study.

**Philadelphia College of Osteopathic Medicine ($19,760)**

**Research Project:**

- **Title:** Entry Mechanisms of Mouse Hepatitis Virus, a Model for Multiple Sclerosis  
  **Type of Research:** Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: In order for viruses to infect cells, they must first bind to and enter potential host cells. There are several distinct pathways that viruses can use to enter cells, and understanding viral entry mechanisms provides important information on how viruses cause infections. This project investigates entry mechanisms of mouse hepatitis virus (MHV); the MHV strain used, MHV-A59, is studied as a model for multiple sclerosis (MS). Understanding more about MHV entry will provide information on how viruses infect the central nervous system, and may provide insight into how viral agents can contribute to changes observed in human demyelinating diseases such as MS.

Philadelphia Health Management Corporation ($14,218)
Research Project:
- Title: Physical and Emotional Health Needs of Transgender Individuals in Philadelphia
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Little information is known about the varied medical and emotional health needs of transgender populations in the city of Philadelphia. Previous research suggests there are a number of barriers to transgender persons accessing optimal health care, leading to significant health disparities. The purpose of this project is to conduct a needs assessment to gain a current understanding about barriers to healthcare access and identify health disparities and resiliencies of these communities. Based on the findings of this project, a report will be created with recommendations on how public officials, stakeholders, community based organizations and any other interested parties can help address the health disparities that exist among transgender Philadelphians.

Pittsburgh Tissue Engineering Initiative ($21,247)
Research Project:
- Title: Cell-based Therapy for Liver Diseases
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: The ultimate goal of this research program is to develop a cell-based therapy for liver diseases. We are proposing to isolate progenitor cells from the gall bladder of a human liver. This project will focus on the identification of these human progenitor cells. We believe that a human gall bladder stem/progenitor cell could be the basis for the development of cell-based therapeutics addressing many devastating human diseases, particularly human liver diseases.

Temple University ($1,957,901)
Research Projects:
- Title: Molecular Mechanisms of Calcium Entry in Cancer Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Numerous studies have identified altered Ca^{2+} signaling in cancer cells; recent work has led to the discovery and characterization of a previously unknown molecular regulator of Ca^{2+} signals named STIM1. Although cancer cells generally exhibit some changes in their Ca^{2+} responses, rhabdosarcoma cells exhibit loss of STIM1 expression; we propose to assess the impact of this on changes on Ca^{2+} signals, cancer cell growth and survival. This work will not only enhance our
understanding of this specific type of cancer but may also lead to generally applicable new treatment strategies.

- **Title:** Characterization of Transcriptional Elements Controlling Expression of DDH1 in Lung and Liver Cancer Cells  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Dihydrodiol dehydrogenases (DDH) are a family of aldo-keto reductases involved in the de novo detoxification of xenobiotics. Expression profiles have indicated increased expression of DDH1 in human lung, liver and esophageal tumors as well as in carboplatin- and cisplatin-resistant human ovarian and lung cancer cells. This increase in DDH protein expression was associated with the alterations in the transcription of the DDH gene suggesting that the promoter region of the DDH gene plays an important role in controlling its expression. This study aims to decipher the precise genetic elements and its associated transcription factor(s) that control the induction of DDH1 gene in human lung and liver cancer cells. Identification of the transcriptional controls of DDH expression will allow designing strategies to control its expression and thus interfere with the process of carcinogenesis as well as development of tumor cell resistance to anticancer drugs.

- **Title:** Mercury-Induced Cell Death: a Source of Autoantigen?  
  **Type of Research:** Biomedical  
  **Focus:** Immunology  
  **Purpose:** Recent work in the field of autoimmunity has focused on apoptotic cells as a possible source of autoantigen. In the setting of murine mercury-induced autoimmunity, mercury-induced cell death, which differs from apoptosis, may be the source of autoantigen. This study will aim to characterize the Hg-induced cell death process and its effects on fibrillarin, the self antigen most specifically targeted in murine Hg-induced autoimmunity.

- **Title:** Mechanism of JCV Involvement in Brain Tumors  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The human polyomavirus, JCV, infects greater than 80% of the human population worldwide and remains in a latent state throughout life. Under certain physiological conditions such as immunosuppression, JCV becomes reactivated and induces the fatal demyelinating disease, progressive multifocal leukoencephalopathy (PML) in the brain. In addition, JCV has been shown to possess oncogenic activity in several experimental animals and has been detected in a significant number of human brain tumors including medulloblastomas and glioblastomas. The purpose of this study is to unravel the underlying molecular events associated with tumorigenesis of JCV and translate the knowledge from these studies toward the development of therapeutic strategies.

- **Title:** Immune Regulation and Reactivation of JC Virus in the Demyelinating Disease, PML  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease caused by JC virus which has recently occurred in patients with autoimmune disorders being treated with the powerful immunosuppressive therapy, rituximab. Our project will lay a foundation for determining the mechanisms involved in immune regulation of JC virus and investigate how rituximab may promote JC virus infection through soluble immunomodulators.

- **Title:** The Role of ICOS in Mercury-Induced Autoimmunity  
  **Type of Research:** Biomedical
Focus: Immunology
Purpose: An inducible co-stimulatory molecule (ICOS) is a molecule expressed on the surface of white blood cells. It plays an important role in the immune response and blocking antibodies to ICOS are promising new treatments for conditions such as autoimmune diseases. We want to understand the role of ICOS in a mouse model of heavy metal-induced autoimmune disease and fully assess its role as a potential therapeutic target.

- Title: Role of Excess Ca2+ Influx in Cardiac Dysfunction after Myocardial Infarction
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Congestive heart failure (CHF) is a devastating syndrome with 50% mortality within five years. It develops after the heart is challenged with hemodynamic stress imposed by hypertension, cardiac attack and genetic alterations. The current view on CHF is that the myocyte (heart cell), the basic component responsible for heart contraction, is weaker than normal. In contrast, there is an emerging concept that the loss of working heart cells plays a critical role in the progression of CHF. In this study, we will use a transgenic mouse model with heart specific overexpression of the L-type calcium channel (Cav1.2) to determine whether the increase of contractility by overexpressing Cav1.2 will rescue heart failure induced by myocardial infarction (heart attack) or worsen CHF development by inducing myocyte loss.

- Title: Loss of Wilms' Tumor Suppressor 1 Regulates STIM1-mediated Ca2+ Entry
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Wilms’ Tumor is one of the most common pediatric tumors, occurring 1/10,000 people in North America. It is thought to result from the loss of a transcriptional regulator known as Wilms’ Tumor Suppressor 1 (WT1). Preliminary studies in our laboratory have linked WT1 with a Ca2+ entry pathway known as store-operated Ca2+ entry. This is important, because changes in Ca2+ concentration are linked cell growth, differentiation and cell death. Hence, our goal is to gain a better understanding of Ca2+ signals, how the loss of WT1 causes Wilms’ Tumor and how to design new treatment strategies.

- Title: The Role of Osteoactivin in Osteoblast Development and Function
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Osteoactivin (OA) has recently emerged as an important factor in osteogenesis. The identification of novel anabolic agents in bone and, perhaps even more importantly, gaining insights into their mechanisms of action, are subjects of intense clinical interest. Systemic or localized forms of bone loss are caused by a variety of diseases or conditions, including aging, and the resulting osteopenia is accompanied by an increased incidence of fracture. Treatment of patients with osteoporosis is a major health care challenge and many pharmaceutical companies are focused on identifying novel therapeutic agents that can selectively stimulate new bone formation.

- Title: Hyperhomocysteinemia and Thrombosis Formation
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The purpose of this project is to identify the mechanistic links between HHcy and thrombosis in homocysteinemia animal model.

- Title: Identification of the Cis- and Trans- Elements Required for Stress-Mediated Induction of Gadd45B
  Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Gadd45B is a small nuclear protein which is implicated in modulating the cellular response to physiological stresses. Gadd45B mRNA levels are robustly induced in mammalian cells following treatment with a variety of different stress agents, which either directly or indirectly damage DNA. The mechanism of this induction is unknown. Therefore, we plan to determine the extent to which this induction is regulated transcriptionally and post-transcriptionally, and identify cis elements and corresponding transcription factors required for induction. Knowledge of this mechanism is important in understanding how Gadd45B can become deregulated, and thus lead to a greater propensity to tumor growth and cancer.

Title: A Novel Approach for Engineering Neovasculature for Stem Cell Therapy
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: Most current pharmacological and/or invasive therapies aim to treat heart disease. During the past few years, however, there has been much excitement and interest in developing regenerative approaches for curing heart disease, by restoring the contractile function of the heart through engineering replacement myocardium and its supporting microenvironment, using approaches such as cell-based therapy. Recent attempts at rebuilding the myocardium using stem cells have yielded disappointing results. The overall goal of this study is to develop the technology to enhance the morphology and function of post-infarct neovasculature, prior to scar formation, and to establish the optimal time post-myocardial infarction (MI) when proangiogenic interventional strategies could result in maximal in situ renewal of myocardial tissue which has been lost to MI.

Title: Omega-3 Fatty Acids as Therapeutic Anti-inflammatory Agents
Type of Research: Biomedical
Focus: Immunology
Purpose: In recent years inflammation has emerged as an essential underlying process in diseases of various etiologies such as Alzheimer's disease, cardiovascular diseases and cancer, which joined classical inflammatory/autoimmune disorders such as arthritis, periodontal disease, septic shock, inflammatory bowel diseases, multiple sclerosis, lupus erythematosus, etc. Although both steroidal and nonsteroidal anti-inflammatory therapies have been developed, there is a pressing need for new therapeutic anti-inflammatory agents with fewer side effects and better efficacy.

Title: Angiocidin Induces Stem Cell Activation and Differentiation
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Our laboratory has discovered a protein which we call angiocidin. When the protein is injected into mice that have cancer, it keeps the cancer from growing and spreading. The purpose of our project is to see if angiocidin inhibits cancer growth by inhibiting the growth and spread of cancer stem cells, a subset of cancer cells that are thought to cause cancer growth and spread.

Title: Diversificiation of Streptococcus pyogenes during Persistence
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: The bacteria Streptococcus pyogenes causes many human diseases including pharyngitis (strep throat), impetigo (skin infection), streptococcal toxic shock syndrome and necrotizing fasciitis. In addition, after these acute diseases have been cured, post-streptococcal sequelae can develop that affect the heart (rheumatic fever) and kidneys (glomerulonephritis). To cause this myriad of diseases, S. pyogenes produces many virulence factors. When S. pyogenes is isolated from a patient, the strains are often not the same. This diversity of strains
makes it difficult to determine which virulence factors are contributing to which diseases. The goal of this project is to determine, using laboratory models, how *S. pyogenes* diversify into unique strains during slow growth in stationary phase or inside human (eukaryotic) cells.

- **Title:** Extended Chemosensitization with a Novel Small-Interfering RNA (siRNA) Sustained Release Nanosystem  
  **Type of Research:** Biomedical  
  **Focus:** Bioengineering, Surgical Sciences and Technology  
  **Purpose:** The overall purpose of this project is to use the recent advances in nanotechnology to develop an effective and safe siRNA-based therapeutic strategy for drug-resistant ovarian cancers. Ovarian cancers are frequently resistant to standard chemotherapy. siRNA are a new class of therapeutic molecules that may provide a novel means to improve the effectiveness of chemotherapy; however, current use of siRNA for clinical purpose is largely limited by its short action, potential toxicity and inefficient delivery. This project will develop a novel platform that is capable of substantially prolonging the siRNA activity with reduced adverse effects. This may help translate this promising new treatment into a clinically useful form of treatment for a cancer that is normally refractory to the current standard drug therapy.

- **Title:** Using an IVR-Cellular Telephone System to Improve Outcomes in Chronic Obstructive Pulmonary Disease  
  **Type of Research:** Clinical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** We intend to extend our findings of reducing the incidence and severity of Chronic Obstructive Pulmonary Disease (COPD) exacerbations by using a PDA-computer based management system to one that uses an interactive bidirectional cell or land-based phone technology.

- **Title:** Immunotherapeutic Strategies for Alzheimer’s Disease  
  **Type of Research:** Biomedical  
  **Focus:** Biology of Development and Aging  
  **Purpose:** A promising and understudied animal model of Alzheimer’s disease (AD) is the cholesterol-fed rabbit. In the last three years, we replicated the demonstration that a rabbit model of AD carries a number of AD neuropathologies and is impaired in associative learning and extended the AD rabbit model to the domain of therapeutics by demonstrating efficacy of galantamine (Razadyne™) in ameliorating learning impairment in these rabbits. Whereas drugs such as Razadyne™ treat cognitive impairment in AD, their efficacy is modest. Immunotherapy may have the potential to prevent the development of AD in later life as well as to treat and reverse symptoms. Using AD model rabbits, we aim to test immunotherapeutic strategies that will maximize humoral (antibody) immune responses while minimizing proinflammatory responses.

- **Title:** Improving Biomedical Informatics Support at Temple Health Sciences Center  
  **Type of Research:** Clinical  
  **Focus:** Bioengineering, Surgical Sciences and Technology  
  **Purpose:** An increasing number of basic and clinical studies at Temple University require merging and analyzing a large volume of biomedical data collected from a variety of sources. Mastering appropriate informatics skills is one of recognized current challenges is the forefront of personalized medicine development. The purpose of the project is to provide informatics support within Temple Health Sciences Center (THSC) that will correct interoperability among existing clinical, molecular and other data resources and allow more efficient and potentially more accurate inference for the purpose of understanding disease states and
pharmacotherapies. In particular, we propose developing effective tools for biomedical data management, retrieval and data mining and providing informatics and analytical help as to efficiently support comprehensive translational research within THSC.

- **Title:** Neuroimaging of Dextroamphetamine Effects in Aphasia  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** Aphasia is a neurological disorder characterized by a loss of the ability to understand or produce speech that occurs when language areas of the brain are damaged. The main treatment for the disorder has traditionally been speech and language therapy. However, recent studies have suggested that the outcome of this therapy can be significantly enhanced with the use of a particular medication called dextroamphetamine. The purpose of this project is to use an advanced brain imaging technique (fMRI) to examine the influence of this medication on brain activity while individuals with aphasia are engaged in tasks requiring speech processing. This type of assessment will facilitate an understanding of the nature of the positive treatment effects that have been described and may eventually allow us to predict which patients are likely to benefit from this form of adjuvant treatment.

- **Title:** Geographic Information System (GIS) and Visualization for Health Disparities Research Core Facility Infrastructure  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** Temple University's Department of Geography and Urban Studies is undergoing a significant expansion to invigorate its research environment and to improve the education of the next generation of GIS scientists. To advance biomedical research, there is an urgent need for a new core facility that has the capacity to conduct state-of-the-art GIS and visualization research on health disparities, environmental health, and the study of the human impacts and health effects of natural disasters and technological hazards. These improvements will involve the reconstruction of an outdated 1200 square foot lab. Currently, this space does not have necessary information and communication technologies (ICT) infrastructure to support the use of new equipment or new telecommunications tools for transmitting data and analytical outputs across a growing network of collaborators on health, environment, and disaster/hazards research. The planned infrastructure project includes both the ICT and space renovations to accommodate new equipment that will be used for GIS, visualization and telecommunications efforts in health disparities research.

**Thomas Jefferson University ($3,591,514)**  
**Research Projects:**

- **Title:** Role of the RB Tumor Suppressor in Breast Cancer  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Breast cancer is a major health concern in the United States, wherein approximately 1 woman in 8 will be diagnosed with the disease. While significant strides have been made in improving therapy for breast cancer, an estimated 41,000 women in the United States will die from this disease in 2008. Therefore, there is clear need for providing better therapeutic options for women with breast cancer. The finding that a protein called RB plays a critical role in the response to therapeutic agents is of high clinical importance, as RB is known to be inactivated in a large
percentage of breast cancers. Thus, understanding more about RB function may lead to more appropriate and effective therapy for women with breast cancer.

- **Title:** How the Loss or Aberrant Cyclin D1 Regulation Impacts AR Activity and Prostate Cancer Progression  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** It is possible that cyclin D1 action can be altered in Prostate Cancer (PCa) by somatic mutation. Cyclin D1 mutations are generally thought to occur at low frequency in human disease, mostly based on observations in colorectal and breast cancer. However, recent studies showed that somatic alterations occur in some types of cancer. Dramatically, these mutations can significantly alter subcellular localization of cyclin D1. To date, no study has examined cyclin D1 mutation in Prostate Cancer (PCa). Of 30 primary tumors screened to date, one tumor-derived mutation occurring in a region that controls splicing of the exon that encodes the nuclear export signal has been detected. These data indicate that cyclin D1 gene alterations may be a mechanism to promote aberrant cyclin D1 expression and/or localization in PCa.

- **Title:** Novel Therapeutic and Prognostic Markers in Breast Cancer  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Breast cancer is a major cause of death in the United States and the western world. Advanced medical technologies and therapeutic strategies are necessary for the successful detection, diagnosis, and treatment of breast cancer. Novel technologies (tissue microarrays (TMA) and automated quantitative bioimaging (AQUA)) will be used to identify new therapeutic and prognostic markers for human breast cancer. This new molecular marker will allow researchers to improve diagnostic accuracy for individual patients, enhancing both the prognostic predictions as well as the prediction of drug responsiveness for a given patient.

- **Title:** Core Equipment and Renovations for Pathology Research–A Research Infrastructure Facilities Renovation Project  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this project is to establish a shared equipment facility containing state-of-the-art analytical equipment to facilitate the research objectives of the Department of Pathology, Anatomy and Cell Biology of Jefferson Medical College.

**Treatment Research Institute ($148,376)**  
**Research Project:**

- **Title:** Computer Assisted Learning in an Outpatient Setting  
  **Type of Research:** Clinical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** The purpose of this project is to assess the feasibility of using a computerized self-learning tool as a supplement to traditional outpatient care received by patients during the course of substance abuse treatment. Several treatment approaches that have met criteria to be classified as “evidence-based” involve teaching substance-dependent patients coping skills to assist them with avoiding future substance use. Currently, skill-teaching is provided primarily in group therapy sessions. This project will assess whether urban, substance-dependent patients will interact with a computerized learning system (called the
Therapeutic Education System) to help them learn these coping skills, and also provide an estimate of how strong the effect of a computerized system will be on patient skill learning and patient clinical outcomes.

University of Pennsylvania ($8,868,580)
Research Projects:

- **Title:** SVM Research Infrastructure—Behavioral Testing Laboratory  
  **Type of Research:** Clinical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this infrastructure project is to upgrade and renovate approximately 225 net square feet of laboratory space in the Hill Pavilion Vivarium Barrier Facility to provide necessary mouse behavior testing space for conducting extramurally funded research projects related to understanding the role stress plays in the development of obesity and depression. The renovated space will allow researchers to produce high quality, reproducible and consistent results. As rodent behavior is highly dependent on the testing environment, it is imperative for these studies that we have designated testing space that is soundproof and not utilized for any invasive procedures. The space will be temperature controlled and free from outside disruption and noise, and able to be controlled by testing investigators.

- **Title:** Financial Incentives for Smoking Cessation  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** Despite progress in recent decades in helping people to quit smoking, about 65 million Americans still smoke cigarettes. Tobacco addiction is the leading cause of preventable mortality in the United States, and even though 70% of smokers report wanting to quit, only about 3% of smokers succeed annually. The purpose of this proposal is to provide supplemental funding to complete a CDC-funded trial of financial incentives for smoking cessation. In this randomized controlled trial, we have completed follow-up of subjects at 12 months with highly significant differences in quit rates for subjects in the incentive (14.9%) and control groups (5.9%). Funding is requested to complete the 18 month follow-up visits for all patients so that we can learn what happens to relapse rates once incentive payments are discontinued and for analyses of cost effectiveness.

- **Title:** Center for Genetics and Complex Traits – Research Infrastructure  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this research infrastructure project is to renovate space on the second floor of Blockley Hall in support of the Center for Genetics and Complex Traits. This new center is a major initiative of the University of Pennsylvania School of Medicine's Research Strategic Plan and addresses three key needs that are shared by Penn, the NIH Roadmap, and the Commonwealth of Pennsylvania: Advancing new pathways of discovery (bioinformatics); Building research teams of the future (molecular epidemiology-statistical genetics-bioinformatics); and Re-engineering the clinical research enterprise (enhancing translational research). Renovation of space in Blockley Hall is essential to Penn’s efforts to create an interactive environment that both promotes the Center’s translational outreach initiatives and enables the recruitment of new faculty with expertise in statistical genetics and informatics. With these new collaborators and resources in a position to succeed, Penn’s Center will create new studies that lead genetics/genomics research into the future for the benefit of the citizens of the Commonwealth.

- **Title:** Integrated Approaches to Genome-based Therapeutics  
  **Type of Research:** Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: It is now widely appreciated that the genotype plays a significant role in outcomes of disease treatment. For example, the toxicity of a particular drug can be modulated by the patient's genome-wide genotype—leading to the recent idea of “Personalized Medicine.” Furthermore, about 2000 human diseases such as Parkinson’s, diabetes, and others are thought to arise from defects of genomic function, suggesting new therapeutic strategies that might use RNA/proteins/small molecules to affect system-level function. The purpose of this project is to identify strategies for genome-based therapeutics, develop an understanding of the interaction between individual genomes and intervention, RNA/protein based therapeutics, delivery systems for new therapeutics, and computational analyses to aid therapeutic design and system-level understanding of genomic dysfunction.

• Title: Isolation and Characterization of Lung Cancer Stem Cells
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Evidence from leukemia researchers has shown that the capacity of the tumor to grow, propagate, and resist therapy may be dependent on a small subset of cells, termed “cancer stem cells.” Although rare, they could regenerate a tumor identical in appearance to the parent cancer. The identification of cancer stem cells in solid tumors was first shown in 2003 in primary human breast cancer. If such cancer stem cells exist in other cancer types, like lung cancer, isolating them could have numerous implications in our understanding of tumor biology (i.e. interactions with the microenvironment) and in designing new therapies (biochemical, molecular, and immunologic). Our goal is to isolate lung cancer stem cells.

• Title: Phenotyping the PI3 Kinase-AKT Pathway in Human Breast Cancers by Immunohistology
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: We propose to develop an accurate and convenient method for determining the activity of a critical signaling pathway in breast cancer cells, the phosphatidylinositol-3-kinase (PI3K)-AKT pathway. The PI3K-AKT pathway is activated in many human breast cancers by mutations affecting a number of different genes. These mutations and activation of the PI3K-AKT pathway influence clinical behavior of breast cancers and response to drug treatment. Detection of these mutations currently requires performance of multiple genetic tests, most of which are available only on a research basis. Development of a test based on antibody staining of tumor tissue obtained at the time of initial diagnosis or surgery will allow PI3K-AKT pathway activity to be determined routinely and factored into the care of patients with breast cancer.

• Title: Neural Substrates of Varenicline (Chantix®) Efficacy for Smoking Cessation
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project aims to identify the neural mechanisms that underlie varenicline effects on early nicotine abstinence symptoms, specifically, smoking urges and deficits in emotional and cognitive (working memory) processing.

• Title: Combination Immunotherapy Targeting K-ras in Adenocarcinoma of the Pancreas
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Pancreatic cancer is the fourth leading cause of cancer mortality in both men and women. Despite a deeper understanding of cause of pancreatic cancer, extensive clinical research has yielded only modest improvements in the outcome of...
this devastating malignancy. Pancreatic cancer cells are naturally resistant to current chemotherapy and radiation therapy. Based on recent evidence that vaccines have promise in patients with surgically incurable pancreatic cancer, this research will test a new therapy involving a customized patient-specific vaccine in combination with chemotherapy, radiation therapy and when possible, surgery.

- **Title:** WISER Sister Pilot Study  
  **Type of Research:** Clinical  
  **Focus:** Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  **Purpose:** The WISER Sister pilot study will recruit 10 women aged 18-35 with elevated breast cancer risk to build to 60 minutes of daily exercise over 5 months and assess the effects of this intervention on factors that affect or reflect breast mitotic activity (including estrogens, MRI breast imaging, other sex steroid hormones, adipokines, and body composition). An ongoing parallel trial with 320 low risk women (the WISER study) will allow for novel comparisons of levels of commonly accepted risk factors for breast cancer.

- **Title:** Stem Cell Niche and Epithelial Tumorigenesis  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Stem cells rely on the surrounding microenviroment for their extensive proliferation and pluripotency. Recent evidence suggests that these distinct properties of stem cells are not autonomously achieved but are regulated by a level of external control. Transcription factor p63, a homolog of tumor suppressor p53, has been shown to serve as a master determinant of epithelial stemness in an epithelial-cell autonomous manner. However, the microenvironment controlling these stem cells has not been identified. In this project, factors provided by stem cell microenvironment will be explored. In addition, these factors will be analyzed in the context of epithelial tumorigenesis.

- **Title:** Targeting Aberrant BRCA-1 in Breast and Ovarian Carcinomas  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The purpose of this study is to determine whether a process called methylation contributes to the inactivation of the BRCA-1 gene in breast and ovarian cancers, even in those patients who do not have mutations of the gene. Our goal is to characterize patients and tumors in which methylation of the BRCA-1 gene occurs, in order to identify patients whose tumors might respond to a new class of drugs called PARP inhibitors. In addition, we will examine whether methylation is associated with an inflammatory response that might be used as a basis for immune-based therapies in this patient population. These strategies are aimed at developing personalized treatment approaches for patients with breast and ovarian cancer.

- **Title:** Understanding the Role of Autophagy Inhibition in Cancer Therapy  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** Many existing cancer therapies can induce cancer cell death in laboratory cell lines but have modest effects when used in cancer patients. Autophagy is a process of “self-eating” that has been observed in human cancer cell lines deficient in the ability to undergo cell death in response to a variety of cancer therapies. Recent evidence suggests therapy-induced autophagy promotes tumor cell survival and resistance to existing therapies by allowing cancer cells to clear the damage caused by these therapies. These results have established autophagy as a therapeutic target in cancer. The proposed clinical trials will determine if high doses of the autophagy inhibitor hydroxychloroquine (HCQ) can be safely combined with existing cancer
treatments and if autophagy inhibition can be detected in patients receiving this treatment. In each of these clinical trials, blood and tumor tissue will be collected from patients in order to characterize the relationship between HCQ concentration and changes in autophagy. The results of these studies will provide knowledge that will inform the design of future phase II and phase III trials that will test the hypothesis that autophagy inhibition combined with standard therapies can improve outcomes in a wide variety of cancers.

- **Title:** Research Recruitment, HPV, and Cervical Cancer Prevention in Asian American Women  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** Cervical cancer is an important public health concern, among minority populations, including Asian American women, who are disproportionately affected by this disease. At the same time, participation by Asian Americans in clinical trials and other biomedical research is low. In this three-step project, we propose to: (Step 1) assess barriers and promoters to research participation among Chinese- and Vietnamese-American women; (Step 2) test different communication and outreach strategies to maximize recruitment of these women into a study using two methods of data collection: a self-administered questionnaire and biosampling; and (Step 3) perform a preliminary study of the epidemiology of Human Papillomavirus (HPV) among these women.

- **Title:** Individualized Therapy for Advanced Non-small Cell Lung Cancer Based on Clinical and Molecular Typing  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The main purpose is to show that non-empiric therapy scientifically chosen on the basis of existing clinical and molecular markers can result in improved progression-free and overall survival (PFS and OS) in good performance status patients with advanced Non-small Cell Lung Cancer (NSCLC), compared to historic controls and contemporaneous subjects who are treated empirically. Subsidiary objectives include (1) the collection of tumor tissue and serum to further elucidate the molecular typing of patients with advanced NSCLC; (2) the development of a broad-based, interactive, collaborational database of advanced NSCLC patients treated at the University of Pennsylvania; and (3) parity or improvement with respect to expected toxicities and adverse events (AEs).

- **Title:** Research Infrastructure: Renovation of Space for the Center for Cognitive Neuroscience  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this project is to provide office and laboratory space for the Center for Cognitive Neuroscience, whose member faculty are currently scattered across the campus in different locations despite their need for close collaboration, and whose faculty are also currently working in poor-quality facilities. The new space will facilitate the research productivity of the group by enabling them to work more collaboratively and to carry out their research programs with adequate office and dry lab facilities.

- **Title:** Construction of a Nano/Bio Research Facility – Research Infrastructure  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** This research infrastructure project covers construction of the Nano/Bio Interface Center in the Krishna P. Singh Center for Nanotechnology. This expansion of research space will allow Penn to expand its effort in the design of molecular
Researchers will be able to probe individual molecules for their electrical and mechanical properties. This will facilitate the recruitment of faculty members with expertise in designing cell sensors and intelligent medical devices. As such, this facility will address key needs that are shared by Penn, the Commonwealth, and the major federal agencies supporting biomedical research. Completing this renovation will provide a stronger biomedical research base that will inevitably generate a new set of discoveries that will benefit citizens of the Commonwealth.

**University of Pittsburgh ($8,868,580)**

**Research Projects:**

- **Title:** Research Infrastructure: Biomedical Science Tower Chilled Water Plant Upgrade  
  Type of Research: Biomedical and Clinical  
  Focus: Research Infrastructure Project  
  Purpose: The chilled water plant in the Thomas Starzl Biomedical Science Tower (BST) is necessary for normal operations of the research laboratories and animal facilities within the building. The existing chillers, cooling tower, and condenser piping were installed when the building was constructed in 1988 and have degraded to the point at which they require refurbishment or replacement. Because failure of the BST chilled water plant would be catastrophic to building operations, this project will provide upgrades to increase the plant's capacity, efficiency, and reliability.

- **Title:** Organization of the Brain’s Primary Motor Cortex and Premotor Areas  
  Type of Research: Biomedical  
  Focus: Neurosciences  
  Purpose: Concepts about the cortical control of movement have changed dramatically in recent years. In the past, the primary motor cortex (M1) was viewed as the sole source of spinal cord signals that produce movement. Subcortical areas, like the basal ganglia and cerebellum, were thought to mainly influence movement control through direct M1 connections. It is now known that the frontal lobe contains six premotor areas. Each of these cortical areas projects not only to M1, but also directly to the spinal cord, bringing to question the origin of central commands for movement. This project will examine (1) how cortical neurons that influence individual muscles in the hand, arm, and shoulder are distributed in the cortical motor areas and (2) how the circuits that link the basal ganglia and cerebellum with the cortical motor areas are organized.

- **Title:** Racial Differences in Atherosclerosis and Plaque Vulnerability in Cardiovascular Disease  
  Type of Research: Clinical  
  Focus: Cardiovascular Sciences  
  Purpose: Cardiovascular disease (CVD) is the leading cause of death in the United States. Blacks are disproportionately affected by CVD, with a 29 percent higher age-adjusted coronary heart disease death rate and a nearly twofold higher prevalence of stroke than whites. In Pennsylvania, blacks have about a nine-year lower median age for CVD death than whites. These observations are only partially explained by racial differences in prevalences of traditional CVD risk factors. Despite having higher rates of CVD, blacks are less likely than whites to have severe obstructive arterial atherosclerosis. Accordingly, the investigators hypothesize that blacks are more likely to have vulnerable atherosclerotic plaques. This research project will investigate relationships among race, anatomic extent of atherosclerosis, measures of plaque vulnerability, and CVD events.

- **Title:** Synthesis and Testing of Peptide-Guided Dual Detection Dendrimers for Cancer Imaging
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: This project uses a small protein fragment (peptide) known to target the blood supply of cancers to specifically deliver imaging agents to cancers. The targeting peptide is attached to the core of the imaging agent, known as a dendrimer, which, built with multiple branching units, carries gadolinium molecules that provide the magnetic resonance imaging (MRI) signaling. The core is also a dye with spectral properties that allow its detection in the near-infrared range. Thus, the coupling of the targeting peptide to the core enables two different ways to locate tumors using a single agent. This project will establish the step-wise chemical synthesis of this targeted dual imaging agent and test it at each synthetic iteration. The project is a proof of concept of targeted imaging for dual detection of cancer, which will be performed in tumor-bearing mice with the final synthesized dendrimer.

• Title: Molecular Mechanisms of Neovascularization
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The long-term goals of this research are to elucidate molecular mechanisms of neovascularization, the development of blood vessels during physiological and pathological processes, and to explore therapeutic approaches to inhibit blood vessel growth in human breast and pancreatic cancers and malignant gliomas. In this project, the investigators will examine the signaling pathways by which vascular endothelial growth factor and inhibitor modulate neovascularization.

• Title: Stem Cells in Esophageal Cancer
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The tumor stem cell is currently hypothesized to be responsible for cancer initiation, development, metastasis, and relapse, thereby serving as a potential cellular target for cancer therapies. In this project, the investigators will study stem cells from esophageal cancer. This project will combine the powerful techniques of immunohistochemistry and flow cytometry to develop a detailed profile of normal and malignant esophageal stem cells and map them to their anatomical niches.

• Title: Stem Cells in Prostate Cancer
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The tumor stem cell is thought to be responsible for cancer initiation, development, metastasis, and relapse. Therefore, it could be a potential cellular target for cancer therapies. In this project, the investigators will identify and study the role of pericytes, which are stem cells that control angiogenesis, in prostate cancer.

• Title: Identification of MicroRNA Regulation Targets in Breast Cancer by Quantitative Proteomics
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: MicroRNAs (miRNAs) are short segments of non-coding RNA that represent an important class of biomolecules that have recently been shown to deregulate the expression level of tens to hundreds of target gene products. Enzyme-miRNA complexes recognize, bind, and degrade a target message, thereby preventing protein production. More than 400 miRNAs have been identified to date, leading to speculation that the expression of every human gene might be modulated by miRNA activity. Despite growing knowledge of the catalog of miRNAs in humans, very little is known about the complete ensemble of genes that are targeted by any given miRNA. This project will develop and apply state-of-the-art high-throughput
proteomics for identification of gene products whose expression is regulated by ten miRNAs that have been implicated in breast cancer.

- **Title: Human Leukocyte Antigen Defects in Cancer Stem Cells**  
  Type of Research: Clinical  
  Focus: Immunology  
  Purpose: Cancer stem cells (CSC) are a subpopulation of cells in tumors that are responsible for metastases and recurrence of disease. The resistance of CSC to chemotherapy and radiotherapy has prompted the investigators to explore the possibility of using immunotherapy for the destruction of CSC. The clinical efficacy of this strategy requires that CSC express a set of molecules required for their recognition by the host immune system. Therefore, this project will (1) analyze CSC for the expression and functional properties of this set of molecules and (2) test strategies to correct these defects, should they exist, in CSC. The resulting information will represent important preliminary data to support the design rationale for effective therapeutic strategies targeting CSC.

- **Title: Ataxia-Telangiectasia Mutated and Programmed Death Receptor 1 Genes in Melanoma**  
  Type of Research: Clinical  
  Focus: Oncological Sciences  
  Purpose: Melanoma incidence and mortality rates continue to rise at an alarming rate, and there is currently no effective treatment for patients with advanced-stage disease. Thus, it is of fundamental importance to identify and characterize the genes that govern melanoma’s development and progression. This project will assess the roles of two genes: (1) ataxia-telangiectasia mutated (ATM), a gene essential in the deoxyribonucleic acid (DNA) repair pathway, which is expressed at high levels in melanoma, and (2) the programmed death receptor 1 (PD-1) gene, for which expression can impair human tumor antigen-specific CD8+ T cells in melanoma patients, thus influencing the anti-melanoma immune response.

- **Title: Optimization of Adenoviral Vector-Based Cancer Genetic Immunization Strategies**  
  Type of Research: Biomedical and Clinical  
  Focus: Immunology  
  Purpose: Adenovirus vector-based vaccines are often used in cancer clinical trials. To date, no standardized, reproducible laboratory tests are available that measure cellular and humoral immune responses to adenovirus. The objective of this project is to develop, evaluate, and validate a comprehensive set of laboratory assays that will be useful for serial monitoring of patients vaccinated or infected with adenoviruses. The goal is to develop a set of immune tests that can be used to specifically follow immune responses to the virus component of genetic immunotherapy vaccines in experimental clinical trials as well as be used to test for natural infection from the environment.

- **Title: Clinical Trials in Chronic Lymphocytic Leukemia**  
  Type of Research: Clinical  
  Focus: Oncological Sciences  
  Purpose: This project will evaluate a novel combination therapy for chronic lymphocytic leukemia (CLL) that attempts to reduce toxicity associated with already proven therapies. The approach will reduce levels of chemotherapeutics while increasing levels of antibody therapeutics. Results will be evaluated with regard to patient response rates as compared to the traditional treatment regimen.

- **Title: Clinical Trials in Melanoma**  
  Type of Research: Clinical  
  Focus: Oncological Sciences
Purpose: This project will evaluate the clinical response of melanoma patients to novel therapeutic regimens.

- **Title:** Clinical Trials in Prostate Cancer  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** This project will establish the safety and efficacy of a new vaccine targeted against mucin-1 (MUC-1) in patients with prostate cancer.

**UPMC McKeesport ($47,237)**

**Research Projects:**

- **Title:** Analysis of Pilot Data of Community “Inreach” Related to Cancer Screening Practices in McKeesport  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** In spite of a long tradition of community outreach and cancer screening efforts conducted by UPMC McKeesport, cancer patients continue to present with late-stage disease. The outreach involved a community group working with hospital cancer care staff and entering three distinct non-traditional sites. Two of the sites were predominantly African American and individuals or families of low socio-economic status. A third site was added and considered neutral or centrally located. The team developed a simple survey tool in an attempt to determine demographics and cancer screening practices within these diverse areas. We propose to conduct detailed analysis of the results of 130 surveys gathered with the intent to possibly modify future outreach efforts. It is hypothesized that many respondents will not have had a history of routine cancer screening.

**Wistar Institute ($1,473,209)**

**Research Projects:**

- **Title:** Role of SECTM1 in Survival Signaling in Melanoma  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Melanoma is a skin cancer that is increasing in the population at a rate greater than other types of cancer; and, as for most cancers, metastasis is the leading cause of mortality and morbidity. Interferon-α (IFN-α) is the only effective and FDA-approved adjuvant treatment for late stage melanoma patients, but it has shown limited therapeutic efficacy. It is unclear why some patients respond to IFN-α while others do not, so it is critical to find a biomarker that monitors the efficacy of IFN-α therapy and explains the mechanism of insensitivity in some patients. Our data suggest that a protein called K12/SECTM1 may be used as a biomarker for responsiveness to IFN-α therapy and as a potential target for improving therapy efficacy.

- **Title:** Epigenetic Regulation of Epstein-Barr Virus  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** The purpose of this research is to develop small molecule inhibitors of Epstein-Barr Virus (EBV). The small molecules will be identified from compound libraries and assayed for their ability to inhibit two viral proteins essential for the survival and propagation of the virus. EBV is a human pathogen that increases the risk of several cancers and immune disorders. EBV infects the majority of adults world-wide, and the infection is never cleared. Presently, there are no known
treatments for latent infection of EBV or compounds that specifically inhibit EBV during latent infection.

- **Title:** Identification and Characterization of Metastasis Promoting MicroRNAs Using a Forward Genetic Screen
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

**Purpose:** Metastasis is the formation of tumors at distant sites following the spread of cancer from a primary site. While early stage cancer can often be treated successfully, treatments after metastasis has occurred are much less successful. Using a cell based assay, we propose to identify miRNAs that transform non-metastatic cells into metastatic cells and to isolate miRNAs that control metastatic cell homing to specific secondary organs. MicroRNAs are short single-stranded noncoding RNAs representing a novel unique class of gene regulators. The novel strategy outlined will allow identification of genetic factors controlling cancer metastasis, specifically critical metastasis-promoting miRNAs. Inhibition of metastasis promoting pathways should halt metastatic progression, and in combination with chemotherapy should result in improved clinical outcomes for cancer patients.