

Health Research Formula Grants - State Fiscal Year 2006-07

Thirty-eight organizations received health research formula grants for the state fiscal year 2006-07. Grants may support one or more research projects and research infrastructure projects. The grants started 1/1/2007 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 (\$147,561)

Research Projects:

- Title: Exercise, Metabolic and Inflammatory Processes in Postmenopausal Minority Women
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Metabolic syndrome (MSY) is a clustering of cardiovascular risk factors coupled with insulin resistance that increases the chances of developing cardiovascular disease. It is prevalent among Latinas and African American women who also report very low levels of physical activity. The purpose of this exploratory study is to collect data from older African American women, who have risk factors associated with MSY, before and after participating in group personal training. These data will serve as preliminary data for a larger, randomized, controlled study examining the impact of exercise on the metabolic and inflammatory processes associated with MSY in postmenopausal African American and Hispanic women.
- Title: Effects of a Single Dose of Zolpidem on Patients with Disorders of Consciousness
Type of Research: Clinical
Focus: Neurosciences
Purpose: Recently, several case reports have been published in which individuals in the vegetative and minimally conscious states (VS/MCS) have paradoxically experienced major improvements in consciousness when given zolpidem, a commonly used sleeping medication. Because these were case reports, there is no way to know how many attempts at treatment with this agent have taken place relative to the few cases of dramatic response reported to date. The primary goal of this pilot study is to determine the rough frequency with which a clinical response to zolpidem occurs, and, if it occurs sufficiently often in the pilot sample, to develop hypotheses about features of drug responders that can be studied a priori in subsequent research.
- Title: Object Grasping and Object Use in Patients with Left Hemisphere Stroke
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Ideomotor apraxia (IMA) is a disorder of higher-level motor control that is a common consequence of left-hemisphere stroke (LCVA). Patients with IMA are impaired in their knowledge of the appropriate hand postures to use for skilled object-related movements (e.g., using a scissors) but perform normally when reaching to and grasping objects. The purpose of this work is to follow up on previous work with healthy subjects to increase our understanding of the hand posture deficits exhibited by IMA patients in skilled object use, and to better understand the relationships between skilled use postures and grasping postures in this population.

Allegheny-Singer Research Institute (\$223,389)

Research Projects:

- Title: Consequences of Lactate Elevation due to Insulin Resistance in Obesity and Aging
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: There is ample evidence that supports that heart failure and diabetes are the major diseases that are the consequences of obesity which has become the largest epidemic today. It is known that obese and older individuals have higher blood lactate levels. Although lactate is a metabolic source for the heart, it may also cause acidification of cells which may harm tissue. The broad purpose of this research is to determine if elevated levels of lactate in the blood cause metabolic abnormalities and mitochondrial dysfunction in the myocardium.
- Title: GABAA Receptor Mediated Inhibition in the Dentate Gyrus in Posttraumatic Epilepsy
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Patients with head trauma often develop temporal lobe epilepsy. The risk of posttraumatic epilepsy is especially high among military personnel after battle-sustained head injury. The latent period between head trauma and the onset of epileptic seizures is often accompanied by a number of biochemical and structural changes in the hippocampus that result in a disturbance of excitatory-inhibitory balance. Loss of inhibitory GABAergic neurons and alterations in the properties of GABAA receptors on the principal cells of the dentate gyrus (dentate granule cells, DGCS) are believed to be critical for epileptogenesis. The project will study the ability of the neurosteroid allopregnanolone to prevent epileptogenesis after traumatic brain injury in rats.

American Aging Association (\$1,638)

Research Project:

- Title: Effects of Magnetic Fields on Human Fibroblasts
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The development of communications, as well as industrial and medical processes have increased exposures to radiofrequency and magnetic fields. Although the effects of exposure to these energies have been studied by several groups, there is no consensus on whether their effects are harmful. The purpose of this study is to determine whether exposure of human cells to magnetic fields exerts any biological effects.

American Association for Cancer Research (\$79,766)

Research Projects:

- Title: The Role of Lysine Demethylation in the Regulation of p53 Activity
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: P53 is a tumor suppressor gene whose mutation and deactivation is implicated in many human cancers. This study seeks to address the role of demethylation of p53 in the repression of its transcriptional activity. With this information, it will be possible to test whether the demethylase enzyme could serve as a potential target for therapeutic intervention in cancer patients.

- Title: The Role of PP2A-associated Protein in DNA Damage Response and Tumorigenesis
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The addition and removal of phosphate groups is a ubiquitous mechanism whereby cells regulate their metabolism and biological activity. The purpose of this study is to examine how the removal of phosphate from key regulatory proteins affects the control of cell survival and tumor development.

American College of Radiology (\$2,511,654)

Research Projects:

- Title: Factors Associated with Attrition in RTOG Clinical Trials
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: To date, many studies have examined barriers to clinical trial recruitment; however, we know substantially less about retention of subjects enrolled in randomized controlled trials (RCT). Indeed, only one out of four subjects remains in RCT until study completion. Therefore, there is a compelling need to study retention in order to design strategies to enhance retention in Radiation Therapy Oncology Trials (RTOG). The purpose of the proposed project is to assess individual (e.g., socio-demographics of age, gender, race/ethnicity), organizational (e.g., community versus academic setting), and protocol-related factors (e.g., phase of trial, group assignment, adverse events) associated with attrition in all RTOG treatment studies that were opened to accrual as of January 1, 1985 and have completed accrual and had the primary endpoint published by January 1, 2005.
- Title: Identifying Interventions for Cancer Patients at High Risk for Poor Outcomes.
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: In this two-phase project, the first goal is to document the combined influence of gender, marital/partner status, and race in identifying patients with cancer at risk for poor outcomes in a pooled analysis of patients with cancers treated with radiotherapy on large, national clinical trials. This analysis will facilitate understanding how the interaction of these factors influences intermediate indicators [e.g., treatment breaks, weight loss, etc.] of primary outcomes [e.g., survival, quality of life]. The second goal is to use these results in designing a second phase of focus group discussions aimed at developing targeted interventions to improve both the intermediate indicators and, ultimately, survival and quality of life.
- Title: Translational Studies on Eliciting Effective Immune Responses to Pancreatic Carcinoma
Type of Research: Biomedical
Focus: Immunology
Purpose: Faulty immune responses are thought to contribute to the development of multiple forms of cancer including pancreatic carcinoma. Two molecules which are produced by pancreatic tumor cell and induce ineffective anti-tumor immune responses have been identified; these are interleukin-10 (IL-10) and transforming growth factor- β (TGF- β). This project explores new strategies to block inappropriate production of IL-10 and TGF- β . These studies will focus on using drugs (EGFR/ErbB2 and STAT3 antagonists), which are already either in preclinical or clinical studies in various tumor forms including pancreatic carcinoma. If successful the project will provide new therapeutic perspectives in which such inhibitors can be used as part of immunotherapeutic approaches to pancreatic carcinoma.

- Title: Correlating Tumor Markers/Genes with Clinical Outcome
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The vast RTOG clinical trials database offers extensive opportunities to explore associations between correlative data, such as tumor marker analysis, and patient outcome data. The purpose of this project is to perform translational research analyses that are not specified in the clinical trial protocol. The project will correlate translational data with clinical outcome and interpret the results for RTOG-run protocols for patients with brain tumors, sarcoma, pancreatic cancer, cervical cancer and head & neck cancer.
- Title: Emerging Imaging Technology Clinical Trials in PA: Part III
Type of Research: Clinical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: This project represents the continued development of a clinical trials research network (developed under the 2004 C.U.R.E.formula funding) which will perform early stage imaging studies at selected Pennsylvania academic medical centers to advance the role of imaging in the detection and/or treatment of disease. Participants of the network will conduct a clinical trial to evaluate the role of Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT) in assessing the effectiveness of drug interventions for treatment of patients suffering from Alzheimer's disease. The conduct of this specific trial will extend the study design work previously funded through the 2005 C.U.R.E. formula grant.

Arcadia University (\$15,155)

Research Project:

- Title: Multimodal Exercise Training for Older Adults After Hip Fracture
Type of Research: Clinical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: To determine if a 16-week, multi-component intervention, initiated 2-3 months post-fracture, leads to greater improvements in the ability to walk a distance indicative of the ability to ambulate in the community as compared to a randomly selected control group. We will also examine the effects of exercise on leg strength, walking speed, balance and function.

Bryn Mawr College (\$10,431)

Research Project:

- Title: Bending the K-Turn RNA Motif
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The goal of the project is to understand the details of an RNA-protein interaction important for regulation of gene expression in yeast. Understanding the structural and sequence features required for specific recognition of proteins that bind to kink-turn RNAs is the overarching goal. We hypothesize that the L30e protein requires the formation of a tight K-turn in order to bind with a high affinity. Our working framework is that RNA mutations that destroy K-turns have very weak protein binding affinities because they no longer form a bend. The purpose of this research is to develop methods to visualize and measure the RNA bending using electrophoretic, sedimentation, and microscopic techniques. These methods may then be applied to RNA viruses such as the HIV virus that causes AIDS.

Carnegie Mellon University (\$649,424)

Research Projects:

- Title: Predicting 3D Protein Structures
Type of Research: Biomedical
Focus: Immunology
Purpose: Automated structural prediction for tertiary and quaternary protein folding, and finding corresponding coding motifs in the DNA sequence are crucially important in computational molecular biology. This research will develop algorithms and software to identify the multiple peptide sequences in multiplexed tandem mass spectroscopy spectra through database searching and will develop approaches for comparing collections spectra representing different states of complex proteomes, including disease states. Our intent is to make sufficient progress that would permit us to seek larger funding from NIH, NSF, and perhaps DOE or the pharmaceutical industry.
- Title: Computational and Neural Mechanisms of Object Vision
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The purpose of this project is to test the idea that the visual cortex of the primate brain adjusts in response to experience so as to represent with maximal efficiency the things that have been seen. We will test this idea by using two kinds of images: natural scenes and faces. In each case, we will carry out parallel computational and electrophysiological studies. The computational studies will assess what features of natural scenes and faces carry the most information. The electrophysiological studies will test the idea that neurons in the visual cortex selectively represent these informational features.
- Title: Research Infrastructure Support for the Center for the Neural Basis of Cognition
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: This research infrastructure project is for renovation of 1,000 sq. ft. of space in the Mellon Institute (Room 134B) adjacent to the current quarters of the Center for the Neural Basis of Cognition (CNBC). This space will be converted to offices and laboratories that are badly needed to meet the needs of currently cramped CNBC faculty, postdoctoral researchers and students.
- Title: Risk and Addiction in Smoking
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is (1) to assess how perceptions of addiction moderate adolescents' reported willingness to try tobacco, and (2) to explore the relationship between their perceptions of the risk of smoking and risk of addiction. This project will draw on work showing that people over-estimate the risks of smoking, as they do with most other risky health behaviors, as well as work showing that people see their own risk as lower than other people's risk. We plan to illuminate this apparent contradiction by showing the role of perceptions of addiction risk in determining smoking behavior, through their effect on the perceived relevance of smoking risks. We believe that making addiction risk real to adolescents can enhance the effect of anti-smoking education. However, doing so requires conveying the phenomenology of an inherently unfamiliar state.

Children's Hospital of Philadelphia (\$3,315,523)

Research Project:

- Title: Genome Copy Number Variation Analytics

Type of Research: Biomedical

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

Purpose: This project seeks to discover and determine novel underlying genetic causes of and contributors to a variety of childhood diseases, by leveraging our institutional strengths in human genome surveillance, the use of electronic medical records, and computational techniques for processing and analyzing large and complex data sets. We propose to: 1) establish a computationally-based analysis pipeline for identifying variations in the genomes of individuals with or at risk for diseases with a known genetic contribution; 2) create tools and data visualization interfaces to assist with determining whether an individual has a genome copy number alteration that is likely associated with that individual's diagnosed or predisposed disease; and 3) to refine the analytical process for suitability as a novel and superior platform for clinical diagnostics of genetic abnormalities.

Children's Hospital of Pittsburgh (\$732,956)

Research Projects:

- Title: Cell Biology of Cystic Fibrosis Transmembrane Regulator (CFTR)
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: CFTR is responsible for transporting chloride from the cells lining the airway, digestive tract, biliary tract, pancreatic duct and kidney tubules into the body fluids. Impairment of this function results in the lung disease, pancreatic insufficiency, liver disease, malabsorption and other clinical problems of cystic fibrosis. This project is designed to identify specific factors that determine how CFTR gets to, and stays, at the cell membrane where it needs to be for optimal functionality. The goal is to exploit knowledge of these factors for the design of novel pharmacotherapeutic agents that enhance the functionality of the mutant CFTR in patients with cystic fibrosis.
- Title: Inhibition of Chloride Secretion by Cigarette Smoke
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The project uses laboratory techniques to study the effect of cigarette smoke on chloride secretion in cultured human bronchial epithelial cells. Changes in chloride secretion by airway cells, changes in airway surface liquid height, and changes in mucociliary clearance will be measured with the hypothesis that decreases in chloride secretion will result in decreased periciliary fluid height and decreased mucociliary clearance.
- Title: IL-23: Actions and Regulation in *Pseudomonas aeruginosa* Pulmonary Infection
Type of Research: Biomedical
Focus: Immunology
Purpose: The purpose of this project is to understand how the immune system responds to *P. aeruginosa*, a bacterium that causes severe pneumonias and lower respiratory tract infections. Understanding the immune response is key to the development of new therapies and treatments that are more effective, have fewer side effects and do not contribute to antibiotic resistance. The development of these new therapies is critical because pneumonia is among the top 10 causes of death according to the CDC National Vital Statistics Report.

- Title: Novel IL-17 Producing Memory Cells are Key to Vaccine-based Immunity in the Lung
Type of Research: Biomedical
Focus: Immunology
Purpose: The project uses laboratory techniques to study the role of a novel T-cell population, Th17 cells and how they control vaccine responses to tuberculosis (TB). This work is critical to develop a more effective vaccine against TB which remains a global health problem.

Drexel University (\$1,048,705)

Research Projects:

- Title: An Improved Pre-clinical Mouse Model for Scleroderma: A New Therapeutic Approach
Type of Research: Biomedical
Focus: Immunology
Purpose: A better animal model for the serious and often fatal human disease scleroderma is needed. We will improve an existing mouse model to make it more like human scleroderma by breeding in an autoimmune accelerator locus (Yaa/ TLR7) to enhance scleroderma signs. Yaa/TLR7 has been shown to enhance B-cell mediated disease in another mouse autoimmune model, where it caused a switch to more pathogenic antibodies that see nucleolar autoantigens present on RNA and RNA-linked entities (RNPs, RNA-polymerase). This resembles a pattern in human scleroderma patients. This modification will also provide the basis for a novel therapeutic approach to this incurable disease, using oligonucleotide inhibitors of TLR7.
- Title: Development of an Ultrasound Contrast Agent for Detection of Ovarian Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: It is estimated that there will be about 15,310 deaths from ovarian cancer in the United States during 2006. Ovarian cancer is characterized by a lack of recognizable early-stage symptoms which results in only 19% of the cases being detected at a sufficiently early stage for effective treatment. The ultrasound images generated by transvaginal sonography (TVS), currently the best method for detecting ovarian cancers, can be enhanced by the use of contrast agents which are injected intravenously before performing a scan. Under this program a new type of contrast agent, which involves the use of very small bubbles (nano-bubbles), will be developed which will improve the sensitivity and specificity of TVS resulting in significant reduction in deaths from ovarian cancer.
- Title: Novel Approaches to the Treatment of Progesterone Receptor Negative Breast Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The proposed studies are designed to determine the molecular basis for the poor response of estrogen receptor positive/progesterone receptor negative (ER⁺/PR⁻) breast cancers, a tumor classification that increases with age and is refractory to the standard of treatment, selective estrogen receptor modulators (SERM), such as tamoxifen. Based on preliminary data, the transcription factor, Sp1 (a major research focus of the PI's lab for 20 years) may be a novel target for treatment of ER⁺/PR⁻ breast tumors. Sp1 DNA binding is significantly decreased specifically in this class of tumors. We propose to test whether reversal of the effects of the chronic oxidative stress on Sp1 associated with aging will activate expression of PR to increase efficacy of tamoxifen treatment in ER⁺/PR⁻ breast cancer.

- Title: Brain Machine Interface Control of Pelvic Robotic and Neuroprosthetic Systems
 Type of Research: Biomedical
 Focus: Neurosciences
 Purpose: Recently, as a result of various technical advances, direct neural control of external devices has been demonstrated. This, and advances in robotics, have enabled a series of direct neural control and neurorobotics experiments, and new types of potential therapies have been identified. Neurorobotics is the direct use of recorded neural signals to control a robot. Thus, a robot assistive orthosis or manipulator could be driven 'by thought'. These exciting approaches are expected to enable therapies that were previously unimaginable. The advances in this area have demonstrated cortical control of arm-like robots or pointing devices. This project extends testing of 'Brain Machine Interface' (BMI) devices to control of the trunk and lower limb in an animal model.
- Title: Drug Discovery for Treating Spinal Muscular Atrophy
 Type of Research: Biomedical
 Focus: Bioengineering, Surgical Sciences and Technology
 Purpose: The goal of this project is to develop compounds that may ultimately be used in treating the deadly disease, Spinal Muscle Atrophy (SMA). SMA is caused by mutations in a critical gene called SMN1, which results in a loss of the SMN protein. The loss of SMN protein in SMA patients results in cell death in the brain, spinal cord and muscles, leading to loss of motor function and death in early infancy (~ 2 yrs of age). The approach used in this project is to engineer novel compounds that will turn on SMN expression, and test efficacy in a transgenic mouse that mimics the human disease.
- Title: Roles of a Circadian Protein Timeless in Genomic Integrity and Cancer Development
 Type of Research: Biomedical
 Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
 Purpose: Environmental toxins or drugs that cause DNA damage lead to problems in copying DNA during cell proliferation. This causes accumulation of mutations in DNA, leading to the development of cancer. To thwart this problem, our cells monitor the accuracy of copying DNA by a mechanism referred to as a checkpoint. A protein called Timeless has been proposed to be involved in checkpoint systems. Interestingly, Timeless is also required for circadian rhythm, which controls day-night differences of our cells. However, how the Timeless protein prevents the development of cancer is unknown. Therefore, the purpose of this project is to understand the roles of Timeless in cancer development. Since a compromise in either checkpoints or circadian rhythm is known to cause cancer, results from this project should play a significant role in the treatment of cancer.
- Title: Targeting Protein O-GlcNAc Modifications in Breast Cancer
 Type of Research: Biomedical
 Focus: Oncological Sciences
 Purpose: In cancer a number of signaling pathways including phosphorylation/dephosphorylation cascades that add or remove phosphate residues are over-activated. Accumulating evidence suggests a less studied protein modification, known as O-GlcNAc, may globally regulate cell growth and death. The role of O-GlcNAc modifications in breast cancer phenotypes and signaling is not known. Moreover, we hypothesize that targeting enzymes which regulate O-GlcNAc modifications may be a novel therapeutic treatment for breast cancer. Using cell biological, chemical, and proteomic approaches, this project will test the novel

hypothesis that O-GlcNAc modifications regulate ERBB2 oncogenic signaling, and thus may serve as novel therapeutic targets in aggressive breast cancers.

- Title: Decision Making for Those with Intellectual Disabilities: A Parent's Perspective
Type of Research: Clinical
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Mental retardation is often the diagnosis assigned to those with significant limitations in intellectual functioning and adaptive behavior. The current more acceptable terminology is intellectual and developmental disabilities (I/DD). Deinstitutionalization moved individuals with I/DD into community-based residential systems. Others, besides parents routinely make health care decisions on behalf of I/DD clients. The purpose of this project is to get information that can help professionals better understand parents' concerns and fears related to their adult children with I/DD. To date there is a lack of information for health care professionals and policy makers to truly understand parents' experiences, and the impact of the complex decisions that need to be made for advanced care planning for these disabled individuals.
- Title: Rapid Assay of Prostate Cancer Biomarkers in Urine for Point-of-Care Applications
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: Current practice of prostate biopsy depends on digital rectal examination and prostate specific antigen levels. The statistic that only 17% (~200,000 malignant out of 1.3 million biopsies in US in 2003) of the biopsies are malignant suggests that the current practice is conservative, and improved cost-saving methods are needed. We propose to develop a method that uses the currently recognized biomarkers for prostate cancer using urine samples. Since the biomarker profile of the patient's urine can be determined in 15 minutes in the new method, the number of benign biopsies may decline and would result in cost savings. The proposed method is possible because of recently developed high sensitive sensors in the PI's laboratory.
- Title: New Preterm Infant Growth Curves
Type of Research: Clinical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: One of the primary goals for premature infants once medically stable is growth. The gold standard of growth for preterm infants is that of the fetus at the same gestational age, or intrauterine growth. The reference growth curves of intrauterine growth that are used in the clinical and research settings to compare an infant's size to the gold standard are either based on old data, heterogeneous, non-U.S. data, and/or lack a measure of body proportionality. The goal of this project is to develop a new set of growth curves for the assessment of growth status of premature infants in the clinical and research settings based on a large, U.S. population-based set of data.
- Title: Neural Mechanisms of the Contextual Interference Effect: An fNIRs and EEG Study
Type of Research: Clinical
Focus: Neurosciences
Purpose: The overall goal of this study is to gain insight into the neural mechanisms of learning multiple tasks. By examination of cognitive and behavioral output during the performance and learning of several computer maze tasks, and through a detailed examination of the neural activity obtained from functional near-infrared spectroscopy (fNIRs) and electroencephalography (EEG), it may be possible to gain insight into the impact of the amount of practice and the organization of practice on

learning fine motor skills. This insight may provide direction as to how to better develop instructional and rehabilitation protocols in addition to clinical interventions to facilitate the recovery of function, relearning and transfer of cognitive and fine motor skills based upon neural responses to physical practice.

- Title: Identifying Pyrazolourea Target in Malaria Parasites
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: In our investigations of a series of compounds that were identified through *in silico* screening based on myosin motor components of malaria parasites, we have found two compounds with low nanomolar inhibition activity against *Plasmodium falciparum* (*P. falciparum*). Interestingly, further biochemical, genetic and biophysical work suggests that the target of these lead compounds is likely to be other than the myosin light chain proteins. Our purpose is to identify the target of these compounds with the hope that this could lead to optimization of the lead compounds.

Duquesne University (\$71,320)

Research Projects:

- Title: Modulation of Antitumor Immunity with Anti-Foxp3 siRNA Nanoparticles
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of this project is to help develop alternative treatments for cancer patients. Conventional cancer drugs are highly toxic and often with poor efficacy. We propose to conduct research to attain a specific goal: to develop agents to remove a type of immune cells which are known to promote cancer.
- Title: Developing an Ophthalmic Estrogen Treatment for Cataract Prevention
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this study is to develop a topical estrogen therapy for application to the eye. Since estrogen has been shown to reduce the risk of cataract development, applying this estrogen therapy directly to the eye should provide the protection to the lens while limiting the amount of estrogen in other less desirable tissues, such as the breast. Using appropriate animal models, we will test whether this new ophthalmic estrogen therapy is safe to apply into the eye and supplies sufficient levels of estrogen to the lens. In addition, we will confirm that only minimal levels of estrogen enter the bloodstream to affect other tissues outside the eye.

Fox Chase Cancer Center (\$2,768,335)

Research Projects:

- Title: Clinical-Grade Anti-HER2 Diabody for Radioimmunodiagnosis of Breast Cancer
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: We are preparing to initiate a clinical trial to determine the ability of a diabody, a novel antibody-based molecule, to target breast cancer in patients. The C6.5 diabody specifically targets human HER2 expressing tumors and is capable of delivering radioactive particles for cancer detection and treatment in our animal model. Clinical grade (GMP) diabody will be produced by our collaborator, Dr. Richard Begent of the University College London. We will assess the quality of the GMP diabody and evaluate its ability to bind to recombinant HER2 and to cell-associated HER2 both in vitro and in vivo. Preclinical toxicology studies will be

performed by a contract organization as per FDA guidelines. These studies are required prior to the submission of an application to conduct clinical trials with the C6.5 diabody.

- Title: Effects of Estrogen on Tobacco Smoke-Mediated Female Lung Cancer
Type of Research: Health Services
Focus: Oncological Sciences
Purpose: The incidence of lung cancer has increased dramatically in women over the past decades. Lung cancer now exceeds breast cancer as the leading cause of cancer-related death among women. The reason why women develop more lung cancer than men remains unknown. Studies continue to suggest that the hormone estrogen contributes to the formation of lung tumors. This group is the first to detect estrogen within mouse lung tissue and has shown that smoke hastens estrogen conversion to cancer-causing substances. The purpose of this project is to investigate the response of mouse lung tissue to estrogen treatment. Findings from this project are anticipated to provide insight into the contribution of estrogen to female lung cancer. Results could aid in the development of a cancer preventive therapy for current and former smokers.
- Title: A Physical Activity Intervention to Prevent Weight Gain in Breast Cancer Patients
Type of Research: Clinical and Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Weight gain following breast cancer diagnosis is common and typically averages 2.5 kg to 6.2 kg, but greater gains are not unusual. Women who gain more weight following a diagnosis of early-stage breast cancer are more likely to relapse and/or have decreased survival. The underlying basis for weight gain by breast cancer patients is not clearly understood. Although dieting is more effective than exercise for weight control in the general populations, a major detrimental side effect of weight loss achieved by diet restriction is loss of lean body mass. Physical activity, including strength training and aerobic activity, may be most effective for weight control among breast cancer patients. This project proposes to study the feasibility of a structured physical activity program for breast cancer patients to prevent weight gain.
- Title: Identification of Biomarkers of Breast Cancer Risk
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: To develop and validate a panel of blood-based markers to assess BRCA1 and/or BRCA2 mutation status and detect breast cancer early in its development.
- Title: Novel Molecular Mechanisms of TSC Pathogenesis
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This project addresses the novel hypothesis that tuberous sclerosis complex (TSC) and other pathological conditions involving the kidney (including renal cell carcinoma (RCC) and polycystic kidney disease (PKD)) may all be connected by defective signaling at a cellular structure called the cilium. Strong preliminary data indicate that changes in two sets of proteins (TSC1/TSC2/Rheb and HEF1/AuroraA/Pak) may cause defective cell signaling in these diseases. We will study the role of these proteins in controlling signaling at renal cilia and begin to analyze their action in kidney pathology.
- Title: Loss of Oxidative Defense Mechanisms in Ovarian Oncogenesis
Type of Research: Clinical

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

Purpose: Ovarian cancer is the leading cause of death from gynecological cancer in Pennsylvania and in the United States. During 2006, approximately 20,180 new cases were diagnosed with 15,310 women in the US and 820 in Pennsylvania dying from the disease. Cellular defense mechanisms against environmental stresses are important in preventing cancer and other diseases. The purpose of this study is to determine the capacity of the ovary to defend against cellular stresses and how these defense mechanisms are weakened during the process of malignant transformation.

- Title: Immune Response Interactions Following Concurrent Pathogenic Challenges

Type of Research: Biomedical

Focus: Immunology

Purpose: The vast number and diversity of microbes in the environment pose continual challenges to the human immune system. Much of what we know about immunity following infection—including the activation of immune cells, recruitment of immune cells to the target organ, mechanisms of pathogen clearance, and maintenance of immunological memory—has been gleaned from mouse models. However, such models have typically evaluated immune response parameters after a challenge with a single pathogen, whereas expanding literature in human immunology indicates that humans are often bombarded with multiple pathogens simultaneously. The purpose of this project is to utilize a novel mouse model to determine how immune responses to two concurrent viral challenges interact, and how pathogen clearance is affected under these conditions.

- Title: Genome-wide siRNA Screens to Identify Targets for Chemotherapy

Type of Research: Biomedical

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

Purpose: One of the major challenges in cancer treatment is the ability of the cancer to develop resistance to the drug that is used to treat the patient. The reasons why cancer cells develop drug resistance are complex, but this is nevertheless an issue that must be tackled to improve treatment outcomes. We believe that drug therapy can be improved by identifying genes in the cancer cell that are responsible for this resistance. In the last several years, a new experimental tool, called siRNA, was discovered that allows scientists to inhibit virtually every single gene in any human cell type, including cancer cells. We propose to use robotics and high-throughput instruments to block the expression of all of the known human genes (~22,000), one at a time, to identify the genes that enhance cell killing by existing drugs that are used to treat pancreatic cancer.

Geisinger Clinic - Weis Center for Research (\$89,315)

Research Project:

- Title: Whole Genome Association Analysis of Complex Diseases

Type of Research: Biomedical

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

Purpose: While most common diseases have a measurable genetic risk, identifying the genetic factors that are responsible for increased risk for these diseases has been a challenge. New knowledge of the human genome and recent technical advances have led to improved experimental approaches to identify genetic risk factors for common diseases. The purpose of this research is to use an experimental approach

called whole genome association analysis to identify candidate genetic risk variants for chronic liver disease, asthma, and aneurysm disease.

Hepatitis B Foundation (\$5,368)

Research Project:

- Title: Characterizing the Molecular Mechanism of Action of a Novel Antiviral Drug
Type of Research: Biomedical
Focus: Immunology
Purpose: The purpose of this research project is to characterize the molecular/cellular mechanism of action of a novel antiviral drug identified through one of the ongoing small molecule drug screening programs being conducted at the Hepatitis B Foundation and its research affiliates at the Pennsylvania Biotechnology Center of Bucks County. The research will be conducted by selected undergraduate students interested in biomedical and public health research, during a summer research internship. The results of this project will lead to the next steps in the development of promising new antiviral treatments for chronic hepatitis B.

Juniata College (\$9,345)

Research Projects:

- Title: Use of Phage Display to Identify Bacterial Receptors for Abundant Plasma Proteins
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: To develop novel methods to deplete human serum samples of the most abundant normal proteins to aid identification of disease biomarkers.
- Title: Microarray Analysis of Gene Expression in Response to a Yeast Transposable Element
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Use microarray analysis to determine global changes in gene expression in response to induction of a virus-like DNA element in yeast cells.

Lankenau Institute for Medical Research (\$212,216)

Research Projects:

- Title: Validation of Breast Cancer Prognosis Marker
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to perform an unbiased study of a marker, tissue inhibitor of metalloproteinase-4 (TIMP-4), for disease-free survival for early stage breast cancer patients. Newly diagnosed breast cancer patients will be tested and their survival chances predicted based on the analysis of this marker. Predicted outcomes will be compared to actual outcome to determine the accuracy of this marker. We will also determine why some patients are lacking this marker which favors survival, and whether the marker can be tested by blood sampling.
- Title: Omeprazole-Induced Leak in Gastric Epithelial Tight Junctions
Type of Research: Biomedical
Focus: Digestive Sciences
Purpose: Our research group has observed an unexpected effect of the heartburn drug, omeprazole (Prilosec, Nexium, etc.), on the stomach. In a clinical trial we observed that on average, patients taking an 8 week course of omeprazole had a 3-fold leakier stomach lining than they did at the onset, before taking their medication.

In this project we would like to determine exactly how fast this effect of omeprazole occurs and how fast the omeprazole effect on leak reverses once a patient stops taking omeprazole. Omeprazole is a very widely sold drug in the US. This action of omeprazole may conceivably pose a cancer risk in certain patients on long-term omeprazole therapy.

Lehigh University (\$116,229)

Research Project:

- Title: Structural Bases of Cellular Communication
Type of Research: Biomedical
Focus: Biology of Development and Aging
Purpose: The primary purpose of this grant is to purchase an electron microscope to study cellular communication. How cells communicate with immediate neighbors is of fundamental interest to biologists curious about the manner in which inter-cellular signals control physiology. Many of these forms of communication involve the release and response of/to chemical messengers. However, physical contacts between and among cells are important to understanding biological phenomena. The equipment will be used to study physical contacts between cells at molecular, cellular and systems levels. We will study how specific proteins are trafficked within individual cells, how junctions between cells permit molecular passage across cell membranes, and how synaptic junctions permit the passage of information in complex tissues such as those in the brain.

Lincoln University (\$15,403)

Research Project:

- Title: Distribution and Numbers of *Cryptosporidium* Oocysts in a Rural Watershed
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: The purpose of the project is to identify the distribution and numbers of the oocysts of the protozoan, *Cryptosporidium parvum*, that occur in a rural watershed. This organism is responsible for a human disease called cryptosporidiosis, a condition characterized by watery diarrhea, dehydration, weight loss, stomach cramps, fever, nausea and vomiting. It can be life-threatening in individuals whose immune systems are already weakened by other conditions. The most common route of infection is drinking contaminated water, either from normal water supplies or from the accidental ingestion of water in recreational areas. Significant quantities of the oocysts in the watershed would indicate a potential for the occurrence of this disease.

Madlyn and Leonard Abramson Center for Jewish Life (\$19,011)

Research Project:

- Title: A Model for Introducing Culture Change Initiatives into Long Term Care Settings
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this qualitative project is to build on findings from previous research on the introduction of two different culture change initiatives in a Pennsylvania nursing home – one involving technology, the other palliative care. Based on qualitative data from the technology initiative, a Culture Change Model was developed. This project will further develop and refine this Model by applying new data from the palliative care study and mining further data from the technology study.

Magee Womens Research Institute (\$598,185)

Research Projects:

- Title: Elevated ADMA Mediates Vascular Dysfunction in Pregnancy and Obesity
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: The purpose of this project is to investigate the role of elevated asymmetric dimethylarginine (ADMA) in mediating vascular dysfunction in obesity and pregnancy. Thirty percent of the adult population is obese, making obesity the single most common public health issue in the Commonwealth of Pennsylvania. Obesity increases the risk of hypertension and diabetes, and is the single largest attributable risk factor for the pregnancy complication preeclampsia, accounting for 15 to 32% of the population attributable risk. However, the biological mechanism(s) by which obesity increases the risk of preeclampsia is unknown. ADMA is an independent risk factor for cardiovascular disease and is elevated in obesity. This project will test the hypothesis that elevated ADMA contributes to this obesity-mediated biological risk mechanism.
- Title: Natural Immunity to MUC1 Tumor Antigen in a Preclinical Model for Endometriosis
Type of Research: Biomedical
Focus: Immunology
Purpose: Women with endometriosis develop chronic inflammatory lesions and are at increased risk for developing certain types of ovarian cancer. The immune processes in endometriosis are not well understood and the best tool we have to explore them is an animal model. Following the progression of an organism from a normal to a pathogenic state is not possible in humans as we cannot predict when they may or may not get ill. Additionally, an adequate preclinical model will allow us to test novel therapies, such as vaccination for immune prevention and/or therapy. Our objective is to develop a mouse model for endometriosis using genetically engineered mice that progress to disease and express human MUC1 protein. Using these mice, we can learn about how to maximize success of vaccination with MUC1 in endometriosis and ovarian cancer.
- Title: Regulation of Insulin-like Growth Factor Binding Proteins by BRCA1
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The breast and ovarian tumor suppressor protein BRCA1 plays an important role in the regulation of gene transcription and cell cycle progression. Insulin-like growth factors (IGFs) and IGF binding proteins (IGFBPs) have been implicated in tumor cell growth. Previous cDNA microarray analysis revealed that some IGFBP genes were deregulated in ovarian cells derived from BRCA1 mutation carriers. The purpose of this study is to determine whether expression of IGFBPs is regulated by BRCA1 in ovarian cells. The long-term goal is to determine whether deregulation of IGFBPs is mechanistically involved in the development of BRCA1-associated ovarian cancer and whether they can be used as biomarkers for diagnosis and/or prognosis.
- Title: Transgenic Mouse Model for Paraganglioma
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this project is to generate a mouse model to study human paraganglioma tumors. Paragangliomas are rare tumors that often develop in the

head and neck and in the abdomen, where they are referred to as pheochromocytomas. Paragangliomas in the head and neck can damage important nerves and vessels, and pheochromocytomas can cause high blood pressure by secreting certain hormones. A significant fraction of paragangliomas are hereditary and caused by gene defects (mutations) in a protein complex called succinate dehydrogenase. To better understand mechanisms of paraganglioma tumor formation, an animal model is crucial. Here, we will generate a mouse model to study paraganglioma genes using a gene targeting vector that was previously generated.

Monell Chemical Senses Center (\$256,897)

Research Projects:

- Title: Learning Mechanisms in Food Craving
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. For example, this project will provide data on whether it is possible to learn to crave healthy foods in place of junk foods. Such information can then be used to develop better treatments for obesity and for drug addiction.
- Title: Effect of Smoking on 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 research project is to expand upon recent findings that smoking alters sweet taste perception in women. In this project, we will test the hypothesis that smoking diminished taste detection and recognition thresholds and alters the patterning of response to repeated presentation of pleasurable tastes in women. The information gleaned from this research may enable a better understanding on how changes in the perception of taste may explain changes in eating patterns following smoking cessation.
- Title: Improving Human Development Chemosensory Research Infrastructure at the Monell Center
Type of Research: Health Services
Focus: Research Infrastructure Project
Purpose: The project purpose is to provide an adequate, flexible and state-of-the art research lab for investigations on the ontogeny of chemosensation and flavor preferences in human infants, children and teenagers, and the effects of alcohol and tobacco consumption on women's health, chemosensory functioning and flavor and food preferences. The careful planning of a Human Development Chemosensory Research Laboratory to study development and women's health at the Monell Chemical Senses Center will insure seamless interfacing of scientists, architects, construction engineers and the construction company to realize a well-organized and appropriately equipped laboratory.

MPC Corporation (\$160,944)

Research Projects:

- Title: Interactive Search-Assisted Diagnosis of Pigmented Skin Lesions
Type of Research: Biomedical and Clinical
Focus: Oncological Sciences
Purpose: The ability to diagnose pigmented skin lesions, and in particular melanocytic neoplasms, with greater precision and accuracy, is a high health care priority. In addition to current methods of health care provider education, computer-aided diagnosis of the lesions has already been applied in radiology. The Jukic group

has developed and used this approach for the analysis of dermatopathologic and pathologic images in the past and now intends to apply the approach to both dermatopathologic and dermatoscopic images of pigmented skin lesions. This approach is unique in that it will assist both the clinician and the pathologist, and in that the resulting database will consist only of those lesions with clinicopathologic correlation.

- Title: Predicting Three-Dimensional Protein Structures
Type of Research: Biomedical
Focus: Immunology
Purpose: Automated structural prediction of tertiary and quaternary protein folding as well as finding corresponding coding motifs in the DNA sequence are crucially important in computational molecular biology. The research team has already made major inroads in precursor research, especially with respect to the computational mechanisms. The purpose of this project is to develop computational algorithms to predict the quaternary structure of multimeric protein strands.
- Title: Attentional Bias, Craving, and Smoking Related Cues: An fMRI Investigation
Type of Research: Biomedical, Clinical and Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this study is to further understand the mechanisms underlying self-regulation in people who smoke. The study will focus on the degree to which smoking-related items, or "cues," draw and capture attention. This effect, termed attentional bias, is thought to play a critical role in generating and maintaining drug craving and, importantly, is correlated with smoking relapse. This project will contribute to the understanding of (1) the cognitive and brain-based underpinnings of attentional bias for smoking-related cues, and (2) the relationship between attentional bias, craving, and subsequent smoking behavior. The research findings will be applicable to many other conditions in which attentional biases are a factor (e.g., general drug addiction, mood disorders, and eating disorders).
- Title: The Life Events Assessment Profile (LEAP): A Preliminary Psychometric Analysis
Type of Research: Biomedical, Clinical and Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: This pilot project will be conducted in partnership with the Pittsburgh Mind-Body Center, a National Institutes of Health funded center jointly operated by the University of Pittsburgh and Carnegie Mellon University. The project will systematically assess external environmental stressors (i.e., chronic burdens and resources) thought to result in adverse mental and physical health outcomes. Life stress has been posited as a key mechanism in the etiology and course of both psychological and physical health outcomes (e.g., depression and cardiovascular disease); however, research has been hampered by the limitations of available assessment methods. The purpose of this project is to test a newly developed instrument for assessing life stress, the Life Events Assessment Profile (LEAP).
- Title: The Effect of Sleep Deprivation on Acute Stress and Emotional Reactivity
Type of Research: Biomedical, Clinical and Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Sleep deprivation and stress are both associated with negative health outcomes and negative emotional responses. Few studies, however, have examined the incremental effect of stress under sleep-deprived conditions. The purpose of this project is to investigate the synergistic effect of stress and sleep deprivation by examining stress reactivity and emotional reactivity in healthy adults under both normal sleep and sleep-deprived conditions. The project also will examine the associations between stress reactivity and emotional reactivity. The ultimate goal of

this research is to develop therapeutic and preventive strategies to reduce the psychiatric and physical consequences of sleep loss.

National Disease Research Interchange (\$49,644)

Research Project:

- Title: Error Rates in Self-Reporting of T1D Complications: Improving Phenotype Definition
Type of Research: Health Services
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: The HBDI database is the world's largest repository of family and medical information crucial to the study of type1 diabetes and its complications. Previous PA state-funded projects used self-reported data to identify genetic factors that influence the development of complications. Discussions with the research community have suggested that medical verification of data will add considerable value to the findings. This will be accomplished by obtaining medical records from a subset of database families and comparing them with reported data. Also, using the ADA's updated guidelines for classifying complications, new questionnaires will be developed and used to improve the dataset. A refined database will enable us define specific phenotypes, providing for more precise analyses of the genes responsible for susceptibility to complications of T1D.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation (\$1,286,019)

Research Project:

- Title: Prediction of Response to Bevacizumab in Colon Cancer
Type of Research: Biomedical and Clinical
Focus: Oncological Sciences
Purpose: To get oxygen and nutrition, tumor cells need blood vessels in the tumor to grow together. This process is called angiogenesis. Understanding of the molecular steps involved in angiogenesis has led to the development of an antibody drug, bevacizumab, that blocks angiogenesis. The NSABP Cooperative Group has conducted a large clinical trial with bevacizumab in colon cancer. The results should be available in the next 2 to 3 years, and if they are positive, bevacizumab will be widely used. However, the drug is not expected to benefit every patient. It is also very expensive, costing about \$100,000 per patient, and has significant side effects. Therefore, it is critical to develop a diagnostic test that can be used to predict which patients will gain the most benefit from bevacizumab and to spare those who do not need it from unnecessary, costly, and toxic therapy.

Oncology Nursing Society (\$26,655)

Research Project:

- Title: Providers' Practices Related to Cancer Clinical Trials
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of the project is to describe the attitudes, knowledge, ethical concerns and practices of nurse practitioners in the Commonwealth of Pennsylvania toward clinical trails; identify the resources required for nurse practitioners to become aware of, keep up to date and be able to refer patients for appropriate clinical trials; and examine provider, practice, system, and ethical factors in relation to providers' willingness to recommend clinical trials to eligible patients.

Pennsylvania College of Optometry (\$52,788)

Research Project:

- Title: Rescue of Photoreceptors from Death Caused by Altered Cyclic GMP Synthesis
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Mutations in genes coding for retinal proteins often result in blindness by causing the death of light-sensitive neurons called photoreceptors. Conventional methods of treatment for such disorders are often unavailable, and the new sets of methods (called gene therapy) that are based on introducing the corrective genes to suppress the disease are widely sought as one of the most prospective approaches to the treatment of genetic diseases of the eye. The purpose of this project is to assess the feasibility of introducing the corrective synthetic genes into the diseased retinas in order to trigger the processes opposing to those that cause the diseases and thus rescue the photoreceptors from dying.

Pennsylvania State University (\$7,201,999)

Research Projects:

- Title: Regulation of Gene Expression during Inflammation
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: Inflammation must be tightly controlled to prevent damage to host tissues; however, there is little known about the signals and molecular events that prevent excessive inflammation and tissue destruction. Furthermore, how these signals lead to the suppression of genes that mediate inflammatory responses and the activation of genes that promote wound repair has not been investigated. We propose to look at signals and mechanisms that regulate the macrophage receptor tyrosine kinase RON, which has been shown to temper the response of macrophages in vitro and in vivo. We will employ animal models and molecular approaches to gain insights into how macrophages balance activities associated with inflammation versus wound repair during a normal immune response.
- Title: Meprins – Metalloproteinases of the Kidney and Intestine
Type of Research: Biomedical
Focus: Renal and Urological Sciences
Purpose: Urinary tract infections are one of the most common bacterial infections in humans, and around 50% of women are affected at some point in their lifetimes. There are multiple factors involved in recurrent infections; however, there is a need to understand the mechanisms involved to develop more effective therapies and prevent renal scarring associated with infection. We have reason to believe that meprin metalloproteinases are important factors that determine the susceptibility and severity of urinary tract infections. The purpose of our studies is to determine the role of meprins in the susceptibility to and progression of urinary tract infections.
- Title: Glucocorticoid/Stress Effects on Dendritic Cell Function
Type of Research: Biomedical
Focus: Immunology
Purpose: There is substantial evidence for psychological stress-induced, neuroendocrine-mediated modulation of the immune function. The long-range goal of this project is to define the mechanisms by which stress and its associated increase in corticosterone affect cytotoxic T lymphocyte (CTL) responses. An efficient and robust CTL lymphocyte response is necessary for the successful defense against many diseases that are immunologically resisted, in particular, virus infections and some tumors. The efficiency and robustness of this response is dependent upon the efficient functioning of dendritic cells. In this project, those

components of crucial dendritic cell functions that are affected by stress and glucocorticoids and the resulting impact on the generation of CTL responses will be identified.

- Title: Cellular Machinery in Cytomegalovirus-mediated MHC Class I HC Degradation
Type of Research: Biomedical
Focus: Immunology
Purpose: Human cytomegalovirus is a beta-herpesvirus that infects approximately 70% of our population. The genome of this virus encodes specific genes that, when expressed as proteins, interfere with the detection and destruction of infected cells by the human immune systems. In one mechanism of immune evasion, the virus expresses a protein known as US11 that causes the degradation of MHC class I heavy chain proteins, leading to the absence of these proteins in infected cells. MHC class I heavy chain proteins at the surface of infected cells normally signal to immune cells the presence of viral infection. Thus, the absence of this signaling protein enables infected cells to escape detection. The purpose of this research is to identify the human machinery co-opted by the virus US11 protein for this evasion, with the long-term goal of designing therapeutic interventions.
- Title: Cytosol-Vesicle-Vacuole Protein Degradation Pathway
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Protein degradation is critical for cell cycle division, cell growth control, transcriptional regulation and metabolic control. The gluconeogenic enzyme fructose-1,6-bisphosphatase (FBPase) is degraded when yeast cells are shifted from poor carbon sources to fresh glucose, and this degradation prevents energy futile cycles that are harmful to cells. FBPase can be degraded either in the proteasome or in the vacuole depending on the duration of starvation. Our long-term goal is to understand the mechanisms underlying the vacuolar dependent pathway of FBPase degradation. The objective of this application is to understand why FBPase switches its degradation from the proteasome to the vacuole. We will test the hypothesis that the switch is controlled by multiple protein complexes that can be activated or inactivated depending upon the duration of starvation.
- Title: Innate Immune Responses to the Malaria Parasite
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: Malaria is a major public health crisis around the world, affecting ~40% of the population and killing 2–3 million people annually. Currently, malaria is spreading rapidly due to drug resistance. A significant number of people from non-malaria regions (military and business personnel, diplomats and visitors) are also at increased risk and are particularly vulnerable to severe or even fatal forms of the disease because of their non-immune status. Therefore, novel drugs/therapeutics and/or vaccines are needed urgently. We propose to study cell signaling mechanisms in the innate immune responses produced by the host in response to malaria parasite infection and the regulation of innate immune responses. The knowledge gained by the proposed studies should prove to be valuable in developing novel immunotherapeutics and/or vaccines for combating malaria.
- Title: Chromatin Structure in Silent and Active URA3 Gene In Vivo
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: We have developed a novel technique: EM-assisted nucleosome interaction capture (EMANIC) for studying nucleosome interactions in condensed chromatin in

vitro. The purpose of this work is to extend this technique to study chromatin organization of a single gene (URA3) in vivo. URA3 is one of the most widely used genetic models. This gene has been placed in a yeast *S.cerevisiae* plasmid under control of silencing (HML) and activation (STAR) genetic regulators and functionally tested.

- Title: The Effects of Sleep Deprivation on Addiction and Relapse
Type of Research: Biomedical
Focus: Neurosciences
Purpose: The proposed studies will evaluate whether chronic sleep deprivation (SD), akin to levels commonly experienced by humans, facilitates addiction and relapse to cocaine in rats, and the underlying neural mechanisms by which those effects are mediated.
- Title: Research Infrastructure: Renovations to Chandlee and Wartik Laboratories
Type of Research: Biomedical and Health Services
Focus: Research Infrastructure Project
Purpose: The demand for campus-wide core facilities has increased significantly in the last five years, particularly the Nucleic Acid Sequencing facility, the DNA Microarray facility, and the Biotechnology teaching labs. These facilities are currently housed in the 2nd floor of the Wartik laboratory and will be moved to the 4th floor of Chandlee. The renovation of Chandlee will allow researchers easy access to the new facilities. The 2nd floor of Wartik will then be renovated and become a state-of-the-art facility to house new faculty in Genomics and Proteomics, and will cater to the structural biology research needs of more than fifty investigators from five different colleges.
- Title: Analyzing Hepatitis B Virus Pathogenesis
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: The goal of this project is to investigate and characterize the effect of a novel anti-Hepatitis B virus (HBV) agent (shRNA-458) on HBV replication, specifically focusing on its effect on nuclear HBV covalently closed circular DNA (cccDNA) pools, which are responsible for HBV transcription and persistent HBV infections and the recycling of HBV nucleocapsids back into the nucleus. The efficacy of shRNA-458 will be compared to those of nucleoside and nucleotide analogues currently used to treat chronic HBV infections and other shRNA sequences targeting a different region of the HBV genome (HBV 2/20) other than that targeted by shRNA-458. The efficacy of shRNA-458, when administered at multiple doses and in conjunction with nucleoside and nucleotide analogues or HBV 2/20, will also be investigated.
- Title: Dopamine Mediated Calcium Dynamics in Schizophrenia
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Schizophrenia is a devastating neuropsychiatric disorder, the etiology of which is unknown. Dysfunction in dopamine neurotransmitter signaling has been implicated as an important component of the disease. However, no defects in the cellular receptors, which transduce the dopamine signal, have been found. This project will identify components of the dopamine signaling system that may be altered in schizophrenia. We have recently identified a novel dopamine receptor interacting protein called TRPC (transient receptor potential channel) that connects dopamine and calcium signaling pathways in cells. This channel has been shown to be required for nicotine dependent behaviors in *C. elegans*, a model genetic system. In this project, we seek to validate the dopamine receptor-TRPC interaction and to understand the significance of this interaction for cellular function.

- Title: Research Infrastructure: Center for the Treatment, Prevention, and Cure of Cancer
 Type of Research: Biomedical, Clinical and Health Services
 Focus: Research Infrastructure Project
 Purpose: To design and construct a new building for the Penn State Cancer Institute that will bring together patient care, and basic and translational research under one roof to enhance our ability to provide comprehensive, coordinated cancer care. The new facility will allow top researchers to work together to create new therapies and to bring them quickly into state-of-the-art clinical care for the patients of central Pennsylvania. The funds requested are in addition to tobacco settlement Year 2005 funds allocated, since the entire project cost is estimated to be ~\$100 million.
- Title: Role of Leucine Metabolism in Leucine Signaling
 Type of Research: Biomedical
 Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
 Purpose: Recent evidence has suggested that increasing protein in the diet or some high protein diets promote weight loss through unexplained mechanisms. A component of protein called Leucine appears to be responsible. To examine the effect of elevating leucine, we knocked out an enzyme (BCATm) that begins leucine metabolism. The resulting mice had high plasma leucine concentrations in most tissues except their brain. More importantly, they were lean (about 60% less adipose tissue) and robustly resistant to obesity with improved glucose tolerance and insulin sensitivity. They actually eat more food. Our research is now focused on the molecular mechanisms explaining how knockout of this gene and increasing leucine brings about this phenotype. It should be possible to make blockers for this enzyme to bring about the same effects in humans.
- Title: Mechanisms of TGF-beta Production in Human Cancer Cells
 Type of Research: Biomedical
 Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
 Purpose: Tumor cells that are resistant to the growth inhibitory effects of TGF β can still secrete TGF β , which enhances tumorigenesis. It is advantageous to block this secreted TGF β in late-stage tumors. These studies will investigate the role of a novel component (km23) in controlling TGF β 1 production using a novel, multidimensional approach. The results of the studies should reveal significant differences between human colon carcinoma cells (HCCCs) and untransformed epithelial cells (UECs) in the altered compartmentalization of signaling complexes, as well as in the differential utilization of signaling components. The goal of this project is to reduce production of a growth factor that enhances the spread of colon cancer. The results should lead to the development of novel approaches to treat colon cancer. The tobacco funds for this project will be used as bridge funding to enable a Senior Research Associate and a Postdoctoral scholar gather additional data in response to reviewer's comments for the renewal of our NIH grant # NIH 2 RO1 CA 090765.
- Title: Mechanisms of Cross Priming In Vivo
 Type of Research: Biomedical
 Focus: Immunology
 Purpose: CD8+ T cells can protect against many pathologies, including viral, bacterial and fungal infections, as well as against many different kinds of tumors. These cells are only triggered after recognition of pathogen- or tumor-derived peptides in complex with MHC Class I molecules. The processes by which these peptide-MHC complexes are generated have been investigated in vitro, but the contribution of different pathways has not been investigated in vivo. Information about the mechanisms involved in peptide-MHC complex generation is essential for

inclusion of the most efficient and effective formulation of antigen in vaccine preparations. In this project, those critical components of one antigen processing pathway, the cross priming pathway, will be identified.

- Title: Proteomics of Substance Abuse
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Ethanol abuse and alcoholism remain very serious societal problems producing a tremendous toll in terms of loss-of-life, adverse health effects, and lost productivity. A significant problem is the lack of a sensitive and specific clinical test to diagnose alcohol abuse either in the general population or within selected groups of individuals such as recovering/relapsing alcoholics. The goal of this project is to screen for signature biomarkers in a well-controlled and extensively documented non-human primate model of self-administration in order to develop diagnostic markers of excessive alcohol consumption.
- Title: Positive Selection-dependent Skin-homing of Fetal Thymic $\gamma\delta$ T Cells
Type of Research: Biomedical
Focus: Immunology
Purpose: To fight efficiently against cancers, infection and other diseases, immune cells reside in specific tissues where they function uniquely to protect the local tissues. Disruptive localization of the immune cells in proper tissues renders a body susceptible to diseases. Therefore, understanding molecular mechanisms of development and localization of these immune cells in specific tissues is important for our effort to improve our health. The purpose of this project is to determine molecular and cellular events regulating the developmental process of skin-specific $\gamma\delta$ T cells, an important class of immune cells.
- Title: In Vivo Brain Tissue Iron Measurement with R2* Mapping in Alzheimer's Disease
Type of Research: Biomedical
Focus: Neurosciences
Purpose: To develop quantitative *in vivo* MRI methods to evaluate brain iron associated with early Alzheimer's disease (AD) pathology.
- Title: Combined Effects of a Hypoxia Selective Prodrug and Herceptin to breast cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Clinical studies suggest that the addition of Herceptin to anthracycline-based chemotherapy, such as doxorubicin, increases its clinical benefit and reduces the recurrence rate by approximately 50%. Although doxorubicin is very effective against breast cancer, the development of heart toxicity and drug resistance by doxorubicin leads to a need in finding safe alternatives. A recently developed novel anticancer agent, acridiol-sulfoxide, may selectively kill solid tumor cells by being converted into its active form in the oxygen deficient environment of a tumor. Therefore, the goal of current study is to establish the use of acridiol-sulfoxide as an alternative to doxorubicin, in combination with Herceptin to treat breast cancer in *in vitro* cell culture models.
- Title: Nitroaromatics and Breast Cancer
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The cause of most breast cancers remains unknown. In addition to genetic predisposition, exposure to chemical carcinogens in the diet, tobacco, and polluted

air has been implicated as a factor in the development of breast cancer. A representative example is the environmental pollutant 6-nitrochrysene (6-NC) which is normally produced from incomplete combustion of organic compounds such as diesel, gas, kerosene and liquid petroleum; 6-NC is a powerful carcinogen in breast tissues of rodents. Studies have shown that 6-NC can be detected in human blood and can damage DNA in breast tissue of animals. The goal of this study is to use state of the art technology, liquid chromatography-tandem mass spectrometry (LC-MS-MS), to identify and quantify the levels of DNA damage induced by this environmental pollutant initially in animals, and eventually in humans.

- Title: Modeling Rapid Osteoblastic Bone Metastases
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The effects of intermittent parathyroid hormone (PTH) on the establishment of *osteoblastic* bone metastases are unknown. The work to be completed with the requested funds is to establish that increased bone formation as a consequence of intermittent PTH treatment, will facilitate colonization of human prostate cancer (PCa) cells in bone. Specifically, we plan to test two hypotheses: 1) that intermittent PTH treatment will facilitate the establishment and colonization of human osteoblastic PCa cells in bones of mice; and 2) that human osteoblastic PCa colonization of murine bone requires a bone environment that favors bone-formation.
- Title: Molecular Functional Studies of Neurog3 Gene Variants
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The goals of the present study are 1) to establish in vitro the impact of NEUROG3 rare and common variants on NEUROG3 transcription regulation and downstream target gene modulation; and 2) to establish the potential role in the pathogenesis of T2D of NEUROG3 promoter and regulatory variants, NEUROG3 haplotypes and diplotypes.
- Title: Role of Excess Nutrients in Diabetic Retinopathy
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: Interactions between dysregulated glucose and amino acid metabolism caused by Type 1 diabetes lead to inflammation followed by retinal cell death. Our goal is to evaluate these toxic processes and find out why they occur. Therefore, the study will facilitate development of drugs needed for reversal of toxicity. For example, interfering with the inflammatory response using the anti-inflammatory agent, minocycline, lowers neuronal cell death in diabetic rat retinas. Lowering formation of reactive oxygen species may also be therapeutic. These interventions will be studied for their potential in treating patients.
- Title: HFE Polymorphisms on the Chemotherapy and Patient's Outcome of the Brain Tumors
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: This project will demonstrate that individuals with brain tumors that carry an HFE polymorphism have a worse outcome than those with wild type HFE, and provide a cell culture model in which to identify the mechanisms by which HFE polymorphisms affect cell behavior and provide a first line in which to test intervention strategies.
- Title: Mu Opioid Receptor in Addiction
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: The mu-opioid receptor (MOR) mediates most of the actions of morphine and other clinically relevant analgesics as well as drugs of abuse such as heroin. Recent studies have identified a number of MOR interacting proteins (MORIPs) including filamin A, protein kinase C interacting protein, and periplakin, suggesting that the MOR is organized within a supramolecular signaling complex. Through the combined proteomic and functional studies outlined in this project, we will identify and characterize a set of novel MORIPs. Identification of these MORIPs will allow us to test our hypothesis that MORIPs play important roles in regulating MOR biogenesis and MOR-mediated signal transduction, as well as providing new insight into the etiology of opioid dependence (OD).

- Title: Role of TGF β in Microtubule Dynamics

Type of Research: Biomedical

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

Purpose: A major significance of the project relates to our finding that 42% of ovarian cancer patients have alterations in the motor protein subunit we discovered, termed km23, with no such alterations in normal tissues. Such a high alteration rate in ovarian cancer suggests that km23 plays an important role in this disease. The novelty of the proposed studies relates to the plan to investigate trafficking of specific TGF β signaling components in relation to the km23 motor subunits, and to determine how these events are altered by ovarian cancer mutations. The overall goal of this project is to better understand how a critical growth regulator sends its signals to stop growth, and how these events are altered in human cancer. The results will assist with the development of novel anti-cancer agents to treat ovarian and other cancer types.

- Title: Novel Therapeutic Strategies to Treat Malaria

Type of Research: Biomedical

Focus: Infectious Diseases and Microbiology

Purpose: Malaria causes 300-500 million new infections, 1-3 million deaths, and 1-4% loss of gross domestic product annually in Africa. The majority of its victims are young children and pregnant women. One child under five dies every 20 seconds of malaria and survivors frequently suffer brain damage and learning disabilities. There are few available anti-malarial drugs, no vaccines and embarrassingly few drugs in the anti-malarial drug pipeline. Thus, there is an unprecedented need to develop new drugs to treat malaria. Malaria parasites express two proteins, called 'ion channels', which are members of a large family of proteins that are essential for the survival of all living organisms. Preliminary findings indicate that targeting the malarial ion channels with drugs kills parasites *in vitro*. The purpose of this research is to develop a deeper understanding of the role ion channels play in the normal physiology of the malaria parasite and their potential as anti-malarial drug targets.

- Title: Center for Functional Genomics

Type of Research: Biomedical

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

Purpose: Our understanding of biological systems is becoming increasingly sophisticated, to the point where additional learning is being hampered by our inability to grasp the vast warehouse of knowledge. This bottleneck is being magnified exponentially as we develop increasingly more powerful means of high-throughput data collection. Moreover, teaching this complexity to students at all levels (K-12, college, and beyond) becomes increasingly more of a challenge as tech-savvy students expect more "user-friendly" learning environments. The purpose of this project is to develop a bioinformatic browser that helps students, scientist, and

lay people understand the complexity of the cellular nucleus. This project will also contribute to and draw from knowledge retained in the browser.

- Title: Regulation of Human Sebaceous Glands by 13-*cis* Retinoic Acid
Type of Research: Biomedical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: Severe acne can have profound psychological and physical morbidity for millions of affected patients. The overall goal of the research is to determine how isotretinoin, a potent drug for acne exerts its positive effects in the sebaceous gland by reducing sebum production and improving acne. Isotretinoin (13-*cis* retinoic acid) is the only drug effective against severe acne that targets each of the causative factors of this disease. 13-*cis* RA is also used in cancer chemotherapy. This drug however can cause birth defects. The specific goal of this project is to identify the active isomer or metabolite of 13-*cis* RA that induces apoptosis in human sebocytes. The experiments to be done with these tobacco settlement funds are critical to the overall success of a larger grant application to the NIH. This information can lead to the identification of potential therapeutic target sites that could be activated by drugs apart from 13-*cis* RA that would have an improved safety profile.
- Title: Center for Computational Proteomics
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this grant is to establish a Center for Computational Proteomics. The initial goals of this center are (i) to establish the infrastructure for the cutting edge computational tools we are developing which are capable of simultaneous measures of protein structure, function, and evolutionary information and (ii) to unify a core of researchers committed to utilizing this infrastructure towards answering important scientific questions related to human health and disease. Through the further development of these technologies, we hope to make large steps towards problems facing the health communities including rational drug design, drug delivery, and bioengineering. These tools will be available to the Penn State community at large and hopefully, in the future, to the entire scientific community.
- Title: Structures of Protein in a DNA Replisome
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The crystal structures of key proteins, the primase and the clamp loader protein will be sought. Although the structures of several individual protein components are known, structures for several key proteins are not available. Since it is highly improbable that the crystal structure of an intact replisome will be solved, the structure of individual proteins are required to construct and infer the structure of the replisome. Our understanding of the function of the replisome is incomplete without its structure.
- Title: Galaxy Workbench for Analysis of Biomedical Data: Application to Overlapping Coding Regions -
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: Biomedical research is rapidly becoming extremely data intensive. High throughput experimental techniques are putting biology on par with the physical sciences in terms of raw data generating capacity. In this project we aim to capitalize on these developments. First, we propose to build on our success to date and develop novel algorithms for the two most rapidly evolving areas of biomedical research: (a) human variation analysis and (b) processing of data generated by next

generation sequencing technology. Next, we will use the developed methodology for empirical and theoretical investigation of human genes with overlapping coding regions. This study will include Ink4a gene – a tumor suppressor locus implicated in ~50% of human cancers. Understanding the molecular dynamics of these genes will widen our understanding of human genome organization.

- Title: Using a Highmark-Medicare-Registry Merged File to Study Care, Outcomes, and Costs for Cancer
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The overall purpose of this project is to demonstrate how we can use existing linked cancer insurance claims and cancer registry databases to develop much more powerful and specific research regarding cancer care. This will allow us to link patient information (stage at diagnosis, age, co-morbidities, gender, etc.) with treatment information (surgery, radiation, chemotherapy, hormones, etc.) for a large population that will include both insured people under 65 years old and cancer patients who are Medicare recipients 65 years old and over. Such a strategy will allow us to investigate the factors that contribute to better quality cancer care.
- Title: Structural Determinants of Closed State Inactivation of N-type Calcium Channels
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The enhancement of inactivation is an excellent mechanism to reduce calcium channel activity that is utilized by a class of antihypertensives called dihydropyridines (e.g. Norvasc®). The recent FDA approval of Prialt® for the treatment neuropathic pain demonstrated the utility of blocking N-type calcium channels as a treatment for this debilitating human disease. However, the poor side effect profile of Prialt has limited its usefulness. Drawing from lessons learned from dihydropyridines, we are investigating drugs that enhance inactivation of these pain-mediating calcium channels. To facilitate this effort, we will use ion channel mutagenesis to determine structures within the N-type calcium channel that regulate inactivation. These structures would then be targeted for drug development to obtain lead compounds for further testing as pain treatments.
- Title: The Exaggerated Exercise Pressor Reflex in Rats with Heart Failure
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: The project will attempt to determine the role played by mechanoreceptors and metaboreceptors in evoking the exaggerated sympathoexcitation seen both at rest and during exercise in patients with heart failure. These sympathoexcitatory responses are important because they affect blood flow in peripheral circulation resulting in altered (poor) muscle perfusion. In addition, these responses may be in part responsible for the exercise intolerance associated with heart failure. Resolving the exact mechanisms of exaggerated sympathoexcitation is imperative in developing adequate treatments to improve physiological changes and the general quality of life for heart failure patients.
- Title: Epigenetic Chromatin Factors Involved in Cardiomyocyte Hypertrophy
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: The purpose of this project is to understand the role of epigenetic heterochromatin factors in cardiac hypertrophy, a heart muscle disorder leading to heart failure and increased mortality. Several epigenetic heterochromatin factors: histone methyltransferase Suv39H1, histone H3(K9) methylation, and histone H2A.Z have been previously shown to control muscle cell differentiation and/or cardiac

hypertrophy. Here we propose to examine chromatin organization in primary control and hypertrophic rat cardiomyocytes in parallel with cardiac myoblast cell culture and thus test the validity of primary cardiomyocytes and cultured cardiac H9C2 myoblast cell line as models for heterochromatin transitions. We also plan to conduct proteomic experiments with chromatin isolated from hypertrophic cardiomyocytes to reveal hypertrophy-associated changes of yet unknown epigenetic chromatin factors.

- Title: Blood-Brain Barrier Nutrient Transport

Type of Research: Biomedical

Focus: Neurosciences

Purpose: The primary focus of this project is to determine the mechanism by which glucose in the circulation traverses the endothelial cells that make up the blood-brain barrier and thus gains access to the brain. Specifically we will investigate the regulation of the glucose transporter(s) in the luminal (blood facing) and abluminal (brain facing) membranes of the endothelial cells that facilitate the transport of glucose across the respective membranes.

- Title: Interaction between Survivin and Aurora B in Primary T Lymphocytes

Type of Research: Biomedical

Focus: Immunology

Purpose: The major goal of this study is to determine the relationship of survivin and aurora B in primary T cells from survivin transgenic mice. We will define proliferation, expansion, cell cycle progression, cytokine production, survival, and memory development of T cells from survivin transgenic mice. Since survivin and aurora B have been suggested to promote T-cell proliferation and expansion, and sustain survival, we hypothesize that T cells from survivin transgenic mice will proliferate/expand strongly, and survive longer than T cells from normal background C57BL/6 mice.

Philadelphia College of Osteopathic Medicine (\$15,859)

Research Project:

- Title: Nutritional Factors in Prostate Cancer

Type of Research: Biomedical

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

Purpose: The purpose of this research project is to use the effects of resveratrol (RSV, a molecule particularly abundant in grapes and red wine) on prostate cancer as a model system to decipher the chemo-preventive mechanisms of nutritional factors in prostate cancer development (initiation, progression, and metastasis). Results from this research will be helpful in determining whether RSV should be clinically tested as a dietary supplement. In addition, the knowledge obtained from this research could also be applied in the exploration of newer and more efficient nutritional factors against prostate as well as other cancers.

Philadelphia Health Management Corporation (\$7,898)

Research Project:

- Title: HIV Testing and Unrecognized HIV Infection Among Black Men Who Have Sex With Men

Type of Research: Health Services

Focus: AIDS and Related Research

Purpose: Black men who have sex with men (MSM) are among the groups at highest risk for HIV. HIV testing provides an opportunity to link infected persons to treatment and reduce the likelihood that they will transmit the virus to others. It is important to understand more about men who are not adequately testing for HIV

and/or may be infected and unaware. This project will look at the characteristics and risk behaviors of Black MSM in Philadelphia who have never been tested for HIV or who have not taken a test in the past 12 months, as well as HIV-infected men who are unaware of their infection. The results of this project will help develop strategies to increase HIV testing among segments of the Black MSM population who are most at risk for contracting or transmitting HIV but are not receiving adequate HIV testing services.

Pittsburgh Tissue Engineering Initiative (\$25,651)

Research Project:

- Title: Expansion of Cancer Stem Cells in Bioartificial Liver Bioreactors
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The purpose of this project is to develop bioartificial liver bioreactors for the expansion of cancer stem cells. A problem facing cancer cell biology is the access of *in vitro* culture models to study cancer development. Here we propose to recapitulate *in vitro* in a bioreactor what happened *in vivo* in cancer patients when metastatic tumors invade an organ like the liver. This approach will allow us to better understand metastatic cancer and develop novel therapies for the future.

Temple University (\$1,839,493)

Research Projects:

- Title: Fracture Healing in Traumatic Head and Spinal Cord Injury: Role of Cannabinoids and Opioids
Type of Research: Biomedical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: Nearly 10% of skeletal fractures do not heal and become nonunions. Nonunion fractures often require surgical or nonsurgical intervention to be repaired. Many clinical studies have shown enhanced osteogenesis in patients sustaining traumatic brain injury (TBI) or spinal cord injury (SCI), with accelerated fracture healing and heterotopic ossifications being common phenomena in these patients. Recent studies have shown that the neuroendocrine systems particularly, the cannabinoid and opioid systems, have agonistic and antagonistic effects on bone remodeling and in the regulation of bone formation/resorption. The project hypothesis is that endogenous cannabinoids and opioids play a crucial role in regulating fracture healing and osteogenesis following TBI and SCI.
- Title: Targeted Nanoconjugates for Intracellular Cancer Therapy
Type of Research: Biomedical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: Killing cancer cells while sparing normal healthy cells has been a long-sought goal in cancer treatment. The goal of this project is to devise a cancer therapeutic drug which can be administered to patients by infusion into the bloodstream. The new drug would have several features: it would home in on cancer cells and bind to them; after binding it would enter the cancer cells; and once inside the cells a therapeutic agent would kill the cell. The therapeutic agent is designed to have no effect on normal cells, because it is specific for the cancer cell. The core of the new drug will consist of tiny particles (about 1/100 the size of a red blood cell) to which the targeting and therapeutic components are bound, and which can be detected by imaging to track them in the body. The purpose of this project is to construct and test this targeted drug approach.
- Title: Chemokine Interactions with Dopamine Systems in the Brain
Type of Research: Biomedical

Focus: Neurosciences

Purpose: Chemokines are a class of chemicals known to participate in the immune system. Recently, chemokines have been identified in brain cells, but their function in the brain is not understood. The overall goal of this project is to characterize the function of central nervous system chemokines and determine how they interact with other neurotransmitter systems, such as dopamine. A second goal is to study this interaction in a setting of drug abuse as our preliminary data demonstrate a significant interaction between chemokines and cocaine. Understanding the role of chemokines and their receptors in the behavioral effects of psychostimulants may ultimately lead to a novel therapeutic approach to treating cocaine and/or methamphetamine addiction, in addition to movement disorders involving central dopamine systems such as Parkinson's disease.

- Title: Leptin Agonist and Antagonist Peptides

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: Obesity has been identified as a risk factor for the development of approximately 30 different diseases and disorders, including cancer. There are currently no cancer therapeutics tailored for the obese population. In this project two accomplished investigators combine their experience in obesity-related cancer and drug design to develop peptide-based pharmaceuticals targeting leptin, a carcinogenic hormone produced by fat tissue.

- Title: Evaluating Sex Differences in Biomarkers of Inflammation of Cardiovascular Risk

Type of Research: Biomedical

Focus: Cardiovascular Sciences

Purpose: The purpose of this research is to understand how gender differences are manifested in cardiac vascular risk. More specifically, are the current clinical risk assessment tools sufficient for therapeutic recommendations? Our hypothesis is that the state of inflammation in cardiac tissues from a variety of metabolic factors and disease provides a more reliable risk assessment tool. Therefore, analytical tools to quantitatively assess the levels of inflammation will be developed; and these methods will be applied to understanding the development of cardiovascular disease and related gender differences using a rat model.

- Title: Inhibition of HIV Biogenesis by TULA, A UBA-Containing, Ubiquitin-Binding Protein

Type of Research: Biomedical

Focus: AIDS and Related Research

Purpose: In spite of considerable progress, HIV infection and AIDS are still a great threat to human health. Further progress in creating anti-HIV drugs is hindered by several peculiarities of HIV. One such peculiarity is the very high mutation rate of HIV proteins; they constantly change their "molecular signatures" - slightly enough to remain fully functional, but sufficiently to evade drugs and natural immune responses of the infected organism. However, HIV uses multiple proteins of the infected cells for its replication. Therefore, anti-HIV drug development focuses now on the cellular proteins involved in HIV replication. We have recently discovered TULA (T-cell ubiquitin ligand), a novel protein inhibiting HIV production. This project will be focused on understanding how TULA suppresses HIV and on establishing practical approaches for making TULA-based anti-HIV drugs.

- Title: Effects of Estrogen on GEC1 and K Opioid Receptor Levels In Vivo

Type of Research: Biomedical

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

Purpose: Studies in humans and animals have shown that females have enhanced analgesic or anti-nociceptive responses to kappa opioid receptor (KOR) agonists than males. The purpose of the project is to examine whether estrogen up-regulates GEC1 and the kappa opioid receptor. GEC1 is a 117-amino acid microtubules-interacting protein. Recently we have found that GEC1 is associated directly with the KOR and expression of GEC1 enhances cell-surface and total KOR in vitro. It has been reported that estrogen up-regulates GEC1 mRNA in vitro and in vivo. We propose to examine whether estrogen enhances protein levels of GEC1 and KOR in vivo.

- Title: Role of Metabolizing Enzymes in Efficacy of Prokinetic Agents in Gastroparesis
Type of Research: Biomedical
Focus: Digestive Sciences
Purpose: Gastroparesis is a gastrointestinal motility disorder with poorly understood etiology. Drugs used to treat gastroparesis are metabolized by liver enzymes. The purpose of this project is to identify the specific enzymes that metabolize and inactivate these drugs. Patients refractory to single drug therapy are given multiple drugs in combination. This project will study potential drug-drug interactions based on common enzyme pathways. Finally, the genetic make-up of gastroparesis patients may play a role in drug efficacy. This project will identify and evaluate genetic differences in drug-metabolizing enzymes relevant to gastroparesis. Thus, the project will aim at understanding the metabolism of gastroparesis drugs, drug interactions, and role of variable genetics in therapy among gastroparesis patient populations.
- Title: Development of a Bone Lengthening Device for Children
Type of Research: Health Services
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of the project is to develop a prototype of a bone lengthening device for children who have limb length discrepancy (LLD). Two internal fixator concepts are investigated. In the first concept, the lengthening is achieved using a remotely activated, motorized lead-screw actuation system. The device will be completely buried inside the body but mounted outside of the bone. In the second concept, the motorized lead-screw actuation system will be replaced by a magnetic smart memory alloy actuation system. The feasibility of the two concepts is currently studied in the Temple University's Composites Laboratory and the Philadelphia Shriners Hospital for Children.
- Title: The Role of TIM Molecules in Murine Mercury-Induced Autoimmunity
Type of Research: Biomedical
Focus: Immunology
Purpose: It is a newly learned concept that T-cell Ig-mucin (TIM) molecules play a role in modulating the immune system. This includes situations in which the immune system turns against its own body (autoimmunity), such as during Lupus, Rheumatoid Arthritis and Multiple Sclerosis. This project will aim to further classify the role of TIM molecules in autoimmunity, in order to define targets which may be acted upon to alleviate disease processes.
- Title: Effect of c-Cbl on Glioblastoma Motility
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Many brain tumors are highly invasive and therefore extremely difficult to treat. Cells from the primary tumor often infiltrate into surrounding brain tissues, so that removal of the main tumor mass is not sufficient to prevent recurrence. Therefore, it is very important to understand the properties of brain tumor cells that cause them to migrate. This understanding should help us to develop the tools that

reduce the migration rate of brain tumor cells. Glioma is the most common type of brain tumor. We have recently shown that c-Cbl protein has a strong inhibitory effect on the migration of glioma cells. This project will be focused on determining the mechanism(s) by which c-Cbl regulates migration of glioma cells with the ultimate purpose of using this knowledge to develop new drugs/therapeutic methods to treat brain tumors.

- Title: Structural and Functional Importance of Sterol Superlattices in Membranes
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The ultimate goal of this research is to understand the etiology of cholesterol-related biomedical problems. Cholesterol has been linked to many diseases, including atherosclerosis, hypertension, and diabetes. Previous studies on cholesterol-related diseases were mainly focused on blood cholesterol. This research attempts to demonstrate, eventually, that cholesterol in cell membranes is also biomedically important. The short-term goal is to reveal a novel biophysical principle, that is, that cholesterol content in membranes serves as a bio-switch turning on or off membrane activities, including the activities of membrane enzymes and channels.
- Title: A Role of Non Genomic Estrogen Receptor GPR30 in Cardiac Function
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Cardiovascular disease is more prevalent in men and postmenopausal women compared with premenopausal women, suggesting gender differences in cardiovascular regulation. Estrogen is considered to be one of the protective factors. In addition to its beneficial effects on lipid metabolism and blood vessels, estrogen has been shown to have cardio-protective actions by increasing parasympathetic nervous tone to the heart. It is hypothesized that the newly discovered non genomic estrogen receptor GPR30 plays a key role in regulating the heart rate. This hypothesis will be tested by complementary immunohistochemical, pharmacological, and in vivo approaches. By fully understanding the cellular and molecular mechanism underlying the cardio-protective action of estrogen, new therapies can be developed that will decrease the risks associated with gender-related health problems.
- Title: Identification of MTBP Binding Proteins
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The MTBP gene has recently been shown to play important roles in various proliferation control pathways and the protein is required for cancer formation. The mechanisms by which MTBP functions in these pathways are unknown. We plan to immunopurify MTBP interacting proteins, determine their identity and verify their interaction using alternative approaches. Successful identification of physiologically relevant MTBP binding proteins will provide essential clues of its molecular function.
- Title: Anti-Inflammatory and Anti-Restenotic Effects of Interleukin-19
Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: Cardiovascular disease is the number one killer of Americans. In vascular diseases, vascular smooth muscle cells (VSMC) migrate from the wall of the artery into the lumen of the vessel where they grow and synthesize inflammatory cytokines which occludes the artery. A great deal of attention has been given to the negative effects of pro-inflammatory cytokines in this process, but, little has been reported on the potential protective effects of anti-inflammatory cytokines on VSMC. We have novel preliminary data which shows that Interleukin-19 (IL-19) can prevent growth, migration, and expression of inflammatory genes in VSMC. The purpose of this

project is to identify the molecular mechanisms whereby IL-19 inhibits expression of inflammatory genes in VSMC, which leads to reduced growth of those cells.

- Title: Isolation and Characterization of Neural Progenitor Cells
Type of Research: Biomedical
Focus: Neurosciences
Purpose: Groups of morphologically distinct, small diameter cells, termed small intense fluorescent cells (SIF cells), exist in all known vertebral autonomic ganglia including human. There is evidence that SIF cells may represent neural progenitor cells. The goal of this project is to isolate, identify and characterize neural progenitor cells removed from sympathetic ganglia of the rat. Neural progenitor cells may be induced to differentiate into a specific phenotype by culturing in a defined medium or by mobilizing a specific intracellular calcium store. Differentiated neurons with defined phenotype may be grafted to a specific area of the brain or spinal cord to replace damaged neurons.
- Title: The Molecular Requirements for TGF- β 1 Induction of CTGF Expression in Osteoblasts
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: CTGF has recently emerged as an important growth factor in bone formation. We recently demonstrated that TGF- β 1 is a potent inducer of CTGF expression and that CTGF is a downstream mediator of TGF- β 1-induced extracellular matrix (ECM) production in osteoblasts. However, the mechanisms that control these TGF- β 1-induced CTGF mediated functions in osteoblasts are unknown. This project proposes to investigate the mechanisms whereby TGF- β 1 induces CTGF expression and to identify the signaling pathways that regulate CTGF mediated ECM synthesis.
- Title: Analysis of the Human DDH1 Promoter in Cisplatin Resistant Ovarian Carcinoma Cells
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Increased expression of Dihydrodiol dehydrogenase 1 (DDH1) protein has been demonstrated to induce cisplatin/carboplatin resistance in human ovarian carcinoma cells. The observed increase in protein expression was associated with the changes in the transcription of the DDH gene. This observation suggested that the promoter region of the DDH gene was essential in controlling its expression in the cisplatin-resistant cells. An approximately 3 kb region 5' to the ATG start site of the DDH gene has been identified to contain the elements that may be responsible for the increased expression of DDH1 in the cisplatin-resistant cells. This study aims to decipher the precise genetic elements and their associated transcription factor(s) that control the overexpression of DDH1 gene in the cisplatin resistant human ovarian cancer cells.
- Title: Identification and Functional Importance of Src Family Kinases(SFKs) in Platelets
Type of Research: Biomedical
Focus: Hematology
Purpose: The main purpose of this study is to elucidate the role of Src family kinases (SFKs) in platelet activation and functional responses. Whereas multiple SFKs are expressed in platelets and are known to regulate key functional responses of platelets, the molecular basis of this underlying redundancy and whether these individual SFKs regulate distinct functions of platelets is incompletely understood. Here we propose to evaluate the functional role of SFKs upon platelet activation. The long-term goal of these studies is to assess whether SFKs or the pathways

controlled by these important proteins would be targets for novel anti-thrombotic drugs.

- Title: Perfluorochemical (PFC) Liquid-Assisted Ultrasound Imaging of the Lung
Type of Research: Biomedical
Focus: Respiratory Sciences
Purpose: The purpose of this project is to use perfluorochemical liquids to increase the ultrasonographic visualization of the lungs in order to: 1) improve staging of lung cancer; 2) make endoscopic ultrasound guided fine needle aspiration (EUS FNA) possible in areas that are currently inaccessible; and 3) make ultrasonographic evaluation of the progression of the disease possible by measuring the volume of the tumor.

Thomas Jefferson University (\$3,674,642)

Research Projects:

- Title: Identification of a New Class of Genes that Contributes to the Development of Breast Cancer
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The proposed research will identify a new class of genes that contributes to the development of breast cancer. The researcher's studies of over 2,000 human breast cancer samples have shown the loss of the gene Dachshund predicts a substantially higher risk of death. Breast cancer cellular migration and metastasis are blocked by Dachshund and breast cancer cells are reverted to a precancerous phase. The researcher will characterize the function of this new class of genes to regulate breast cancer development. The researcher has developed a new mouse model which will allow the researcher to remove the Dach1 gene in breast cancer. These mice will allow the researcher to prove Dachshund can block the development of breast cancer. These mice will be valuable to test new therapies for breast cancer.
- Title: Role of the MYC Oncoprotein in Human Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Human cancer is caused by genetic mutations that occur in otherwise normal genes. The most commonly mutated gene in cancer is the MYC oncogene. MYC is mutated so frequently because it is a master regulator of the cell division. MYC accomplished this by controlling the activity of ~3000 other genes. While this number is too large to provide useful information about new drug targets or therapeutic strategies, recent data suggests that only a small subset of these 3000 genes play a direct role in cancer. Using new technology that allows the examination of all genes in a cell at once, the MYC targets actually required for transformation are being defined. The researcher has begun to decipher how these few critical targets participate in converting a normal cell to malignancy. Studies such as these should allow the rational design of new therapeutic strategies.
- Title: Stat5 Interaction with Androgen Receptor in Growth Promotion of Prostate Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: This project may validate Stat5a/b as a novel therapeutic target for androgen-independent prostate cancer. The outcome of the studies will increase the knowledge about the molecular mechanisms underlying androgen-independent growth of prostate cancer. The proposed studies may validate active Stat5a/b in

prostate cancer as a biomarker for poor response to androgen deprivation therapy. This project has a high impact on prostate cancer patients and for prostate cancer research. This is because there are currently no effective pharmacological therapies for hormone-refractory prostate cancer. Stat5a/b may provide a molecular target for new pharmacological therapy development. Specifically, pharmacological inhibition of Stat5a/b can be achieved by small-molecule inhibitors for dimerization or DNA binding of Stat5a/b.

- Title: Multidisciplinary Systems Approach to Predicting Response to Combination Therapy
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: This project is focused on developing the mathematical and experimental framework to determine the molecular mechanisms for the efficacy of cancer therapies based upon the combination of existing drugs. This model is important for not only predicting whether two drugs in combination will have synergy, but will also be used for determining the protein biomarkers of response for patients. The aim of this project is to find a mathematical model based on fuzzy logic that could accurately predict a patient's response to drugs in a clinical setting as it would facilitate the individualization of patient treatment and help to find some prognostic and predictive markers of breast cancer.
- Title: Cyclin D1 Regulation of Cellular Migration and Invasion
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: These studies aim to further understanding of how cyclin D1 collaborates in cellular invasion, migration and transformation. The abundance of the cyclin D1 gene product is rate-limiting in progression through the G1 phase of the cell-cycle and is required for transformation by Ras, ErbB2, Src, Stats, Wnt and mutations of the Apc gene. The researcher's laboratory has shown that cyclin D1 promotes DNA synthesis and cellular survival. Recent studies from our laboratory using cyclin D1^{-/-} mice and cyclin D1 siRNA have demonstrated that cyclin D1 regulates cellular migration and invasion. The proposed studies will determine the mechanism by which cyclin D1 regulates migration in cells and in vivo. Several novel technologies developed in this laboratory will be used in the proposed studies to provide high-resolution analysis of the mechanisms governing this process.

Treatment Research Institute (\$119,268)

Research Project:

- Title: WebSafePhilly: Alerting Parents to Narcotics on the Net
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this study is to examine the feasibility, acceptability, and impact of WebSafePhilly, a 90-minute workshop designed to: (1) inform parents about the availability of drugs and drug misinformation on the Internet, (2) provide parents with concrete prevention and monitoring strategies to protect their children from these threats, and (3) provide parents with specific strategies for recognizing and addressing problematic Internet use. Following the face-to-face training, continuing support, via a study-specific website and a toll-free parent hotline, will be provided to participants. Findings will be used to refine the curriculum, upgrade technological resources, and apply for federal funds to establish the effectiveness of this intervention in a large representative parent sample.

University of Pennsylvania (\$8,472,940)

Research Projects:

- Title: Health Services Research Data Center
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this project is to make administrative data available to researchers seeking to understand and improve the organization, delivery, financing, and management of health care, and the social forces that shape health. This project will coordinate the acquisition, storage, and analysis of data from private and government sources (e.g., Medicare, Medicaid, and others) and facilitate its use by researchers to answer important questions in health policy, the delivery of health care, and the effects of health care and other social forces on the health of individuals and populations. This is a multi-year project.
- Title: Role of Cancer Stem Cells in Tumor Progression and Response to Therapy
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Growing evidence indicates that the majority of cells within human cancers have a limited ability to divide and that only a minority of cells – termed cancer stem cells – have the ability to proliferate extensively and form new tumors. If true, these findings would have critical implications for the manner in which we treat cancer, since the properties of cancer stem cells are predicted to differ substantially from the majority of cells present in tumors. The purpose of this project is to understand the biology and response to therapy of cancer stem cells in common epithelial malignancies, such as carcinomas of the breast, colon, lung and prostate. Since eradicating cancer stem cells may be required to cure cancer, such studies are of paramount importance.
- Title: Tumor Tissue Bank for Cancer Research: Phase IV of a Research Infrastructure Project
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The purpose of this project is to support the establishment and development of an infrastructure for operations of a Tumor Tissue Bank and Biospecimen Repository. The Tumor Tissue Bank and Biospecimen Repository will foster and stimulate transdisciplinary research into the etiology, diagnosis and treatment of human cancer. This infrastructure project is a continuation of the 2005-06 project.
- Title: Nicotine Effects on Lung Cancer Promotion: From Cells to Patients
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The goal of this project is to examine the role of nicotinic receptor signaling in lung cancer progression and survival. This translational research program will: (1) characterize nicotinic acetylcholine receptor (nAChR) function in lung cancer cell lines, (2) examine nicotine effects on lung tumor growth and chemotherapy response in mouse models, and (3) to determine whether nAChR/ACh mRNA and protein expression in human lung tumors predicts patient response to chemotherapy and progression-free survival. The ultimate clinical goals of this project are to determine whether nicotine replacement therapies increase the likelihood of lung cancer recurrence and to identify novel molecular targets for drug development for lung cancer.
- Title: Inhibition of the PI3 Kinase Pathway in Leukemic Stem Cells
Type of Research: Biomedical
Focus: Hematology

Purpose: Acute myeloid leukemia or AML is a malignant disease of the blood that is still fatal in over half of patients who develop the disease. Recent advances in cancer biology have demonstrated that by understanding the molecular control of growth in malignant cells, new therapies can be developed that inhibits these growth regulatory mechanisms. The PI3 kinase pathway is critical for the survival of leukemic cells and leukemic stem cells. In this project, experiments will be performed to better understand the function of this and other pathways in leukemia cells. Tests will be performed of new therapies to inhibit these pathways in mouse models of leukemia. The aim is to develop clinical trials to improve the therapy of AML.

- Title: Clinical Trials of Novel Targeted Therapies in Patients with Advanced Cancers
Type of Research: Clinical
Focus: Oncological Sciences
Purpose: The treatment of the most common adult cancers, once they have become metastatic, is inadequate. Currently available systemic therapies, such as chemotherapy, rarely induce complete remissions, and partial remissions are followed by the emergence of tumors resistant to further therapy. Progress has been made in understanding the mechanisms by which cancers become established and spread to distant sites. The development of drugs that counteract these processes offers an approach that is unique compared to chemotherapy. The proposed project will focus on two elements of this biology: tumor blood vessel formation and the abnormal function of enzymes within the tumor cell. Clinical trials will be conducted evaluating novel strategies to inhibitor tumor blood vessel formation and, separately, to block the function of abnormal enzymes within tumor cells.
- Title: Acceleration of Umbilical Cord Blood (UCB) Grafts with Activated T Cells
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Hematopoietic Stem Cell Transplantation has emerged as a very promising therapy for a variety of life-threatening diseases. However, patients receiving UCB transplants performed up until now have proven to recover donor blood counts slowly, and in some cases incompletely. This slow engraftment results in a heightened risk of life-threatening infection. But if the problem of slow engraftment could be circumvented, UCB transplantation would become the dominant and, hopefully, decisively curative mode of blood stem cell transplantation. In this new program, we will take advantage of a newly developed approach to activate the T lymphocytes in the donor UCB graft as a technique for stimulating UCB stem cell engraftment. In 2009 this project was expanded in order to allow for the evaluation of cardiac stem cells in addition to cord blood stem cells for the development of novel therapies for human illness.
- Title: Vivarium – Research Infrastructure (Construction Phase III)
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The purpose of this vivarium construction is to breed and study specialized mice and other rodent models which have specific genes deleted, added or altered. Mouse models are our most important tool to study diseases with a genetic component and to understand normal body processes which may be altered to result in disease. Mice are the ideal model because they are mammals and share many similarities in basic body functions to humans, while they are small, breed rapidly and have been a major focus of scientific study. This project is a multi-year project including scope development, design, contract awards, construction and

commissioning. This infrastructure project is a continuation of a project supported by prior formula grants.

- Title: Novel Technologies for System Level Analysis of Complex Human Physiology and Diseases
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this project is to develop new technologies to aid the understanding of complex genomic basis of human physiology and diseases. The new technologies to be developed include computational analysis procedures for genome-scale datasets and high-throughput screening technologies for molecular, chemical, and morphological measurements. These new technologies are broadly grouped as 'systems biology' tools and include genetic, molecular, and computational tools that will allow for detailed characterization of physiology and disease conditions. These observations will be furthered by 'translational' technologies such as cell-based screening and applied to both target identification and validation.
- Title: Expansion of Biosafety Research Capacity – Research Infrastructure
Type of Research: Biomedical
Focus: Research Infrastructure Project
Purpose: The purpose of this research infrastructure project is to expand the University of Pennsylvania's biosafety laboratory capacity, both Biosafety Level 3 (BSL3) and Animal Biosafety Level 3 (ABSL3) to accommodate the rapid growth in NIH-funded research for emerging infectious diseases and biodefense that supports the work of a large number of Penn investigators. While both research and vivarium space have been greatly expanded in recent years, construction of new BSL3 and ABSL3 facilities have not kept pace with the unexpectedly rapid growth in research and research training on emerging infectious diseases and HIV at the University. At present, research at Penn on emerging infectious diseases and, to a lesser extent HIV, is greatly constrained by limited BSL3 and ABSL3 capacity.
- Title: Prevention of Nosocomial Infections
Type of Research: Biomedical
Focus: Infectious Diseases and Microbiology
Purpose: The purpose of this project is to develop proof-of-concept technology for preventing the transmission of antibiotic resistant bacterial infections in medical facilities. This technology is based on the antimicrobial activity of nitric oxide, and it will be embodied in a device that treats and disinfects the hands of staff and visitors before and after contact with patients. The efficacy and safety of nitric oxide disinfection has already been established in human studies. The first stage of this project will yield a prototype device that can deliver nitric oxide in a manner that is acceptable to potential users, and that enables us to determine optimal operating parameters for the device. Human testing of its efficacy against bacteria will occur in a subsequent stage of development and will be supported by a different source of funding.
- Title: Development of a Sleeve Introducer Device for Rapid, Safe and Easier Placement of Naso Gastric Tubes
Type of Research: Health Services
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: Nasoenteral tubes were originally designed to deliver therapy and are now also used for diagnosis, decompression, and feeding. Large bore enteral tubes are more often placed for decompression and function via a double lumen sump mechanism, while small bore tubes are softer single lumen tubes that are typically used for feeding and delivery of therapy. Despite a long history of nasoenteral

tubes, placement remains difficult and even dangerous for certain patients. Difficulty is frequently described for the placement of large bore tubes under general anesthesia, while some patients can get bleeding and infections from the placement of this semi rigid tube. Rarely the tube can end up infecting or even perforating the lung. Placement in the lung occurs almost one time in fifty. This project evaluates a new sleeve introducer device designed to make this process safer, faster and less dangerous for the patient.

- Title: RS Rearrangement Frequency: A Clinical Lab Test for Autoimmunity
Type of Research: Clinical
Focus: Immunology
Purpose: Systemic lupus erythematosus (SLE) is a debilitating and sometimes lethal autoimmune rheumatic disease that afflicts over five million individuals worldwide. Current medical therapy is given on a trial and error basis because the underlying immune defects are not known for individual patients. However, one clue is that nearly everyone with SLE makes antibodies that bind to self (this is due to aberrant function of B cells, white blood cells that produce antibodies). The purpose of this study is to develop a clinical lab test called RS rearrangement frequency that identifies B cells that have defective early development. Identifying the developmental timing of the B cell defect in SLE will lead to improved therapy, in which specific B cell subsets can be targeted.
- Title: Vibrotactile and Auditory Feedback for Robotic Minimally Invasive Surgery
Type of Research: Clinical
Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The purpose of this project is to determine whether tactile and/or auditory feedback of tool contact vibrations will improve the usefulness of minimally invasive robotic surgery systems. Commercial surgical robots such as the Intuitive da Vinci system enable the surgeon to see and manipulate structures deep within the body via tiny incisions. Though the robotic tools mimic one's hand motions, the surgeon cannot feel what the tools are touching, a striking contrast to non-robotic approaches. We have developed a new method for partially restoring this lost sense of touch; our VerroTouch system measures the vibrations caused by tool contact and immediately recreates them on the robot handles for the surgeon to feel and hear. This project's human subject study will measure how this additional feedback affects novice and expert surgeons during manual task performance.

University of Pittsburgh (\$8,472,940)

Research Projects:

- Title: Immune Assessment of a Novel Influenza Virus-Like Particle Vaccine
Type of Research: Biomedical
Focus: Immunology
Purpose: Public health officials predict that an influenza pandemic can cause more illnesses and deaths over a shorter period of time than any other natural health threat. The influenza virus is easily spread from person to person. Although vaccination is a useful and cost effective way to combat the threat of a flu outbreak, seasonal flu vaccines provide only partial protection, especially in the very young and the elderly. The goals of this project are to gain a deeper understanding of how the immune system responds to influenza and to develop better methods for evaluating the effectiveness of influenza vaccines.
- Title: DNA Repair Pathways and Their Influence on Tumorigenesis
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: The purpose of this project is to explore novel features of three DNA repair pathways involved in mediating cellular response to DNA damage. Characterization of DNA repair has important implications for the development of cancer and for understanding certain kinds of resistance to anticancer chemotherapy. It is hoped that, through a better understanding of this fundamental process, more effective prevention and treatment strategies can be devised.

- Title: Viruses and Cancer: Characterization of Host Cell-Virus Interactions
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: Kaposi's sarcoma (KS), a lymphatic endothelial cell tumor, remains a critical public health problem world-wide. While rates of this disease have declined in the U.S. since their peak in the late 1980s, KS is now the most commonly reported tumor in sub-Saharan countries. In the U.S., specific populations remain at high risk for mortality from KS, including solid organ transplant patients who have a 40-60% mortality rate after contracting KS and the majority of survivors lose the transplanted allograft. Finally, while KS is currently well-controlled among AIDS patients, when these patients age it is expected that a resurgence of severe KS will occur. Therefore, developing vaccines to prevent or control this disease remains an important public health priority.
- Title: Cancer Inflammatory and Immune Response - Novel Insights and Targets for Therapy
Type of Research: Biomedical
Focus: Immunology
Purpose: The experiments described in Aim 1 build upon the observation that the sera of patients with oral carcinoma contain tumor-derived membranous microvesicles (MV) that have been shown to induce death of activated immune cells and thus may contribute to immune dysfunction seen in these patients. The studies will characterize MV biology, importance for diagnosis, and prognosis of tobacco-related oral cancer. The experiments in Aim 2 extend observations related to how tumor cells die, examining the release of damage associated molecular pattern molecules (DAMPs) and their effect on inflammatory cells. The effect of DMAPs, coupled with MV, on treatment response may enhance future therapeutic strategies and improve survival rates for cancer patients.
- Title: Mechanisms for Antiestrogen Resistance in Breast Cancer
Type of Research: Biomedical
Focus: Oncological Sciences
Purpose: The estrogenic signaling pathway is the target of proven and effective tamoxifen (a selective estrogen receptor modulator; SERM) chemoprevention and treatment for breast cancer. However, it is suspected that some breast cancers contain mutations in the estrogen receptor, and the Nichols lab has isolated one from a breast cancer that appears to be activated, not inhibited, by tamoxifen. This finding raises the question of whether expression of such a receptor converts normally sensitive breast cancer cells to antihormone resistance. By studying how cancer cells are inhibited by tamoxifen or similar SERMs and how they escape that inhibition, one can define alternative or additional therapy to minimize its effect. This new knowledge should lead to more successful combination strategies for chemoprevention, therapy, and disease-free survival for breast cancer patients.
- Title: Oral Cancer and Chromosomal Instability: Finding Novel Cancer Prevention Targets
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: This project is designed around two major aims. The first aim seeks to determine how deregulation of cell cycle checkpoints leads to genomic instability in oral cancer cells. A significant subset of oral carcinomas is associated with high-risk human papillomaviruses (HPVs) and the HPV-16-encoded E7 oncoprotein will be used as a model system for further experiments. The second aim will focus on whether attenuation of the mitotic spindle checkpoint can be used to eradicate oral cancer cells. These projects will provide the framework for future translational studies to improve preventive approaches in patients at risk for HPV-induced oral cancer as well as nonvirus-induced oral carcinomas.

- Title: Evaluating the Effects of Stress on Spontaneous Tumor Development

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The purpose of this project is to evaluate how chronic stress affects the development and progression of breast cancer in mice that spontaneously develop mammary tumors in a model that mimics the development of breast cancer in women. The investigators will also study the effects of chronic stress on the ability of these mice to mount immune responses that target a receptor on the breast tumors which is also expressed on human breast tumors and which is already known to be an antigen available for inducing immune responses in ~25% of women with breast cancer. These studies will provide new insights into how stress responses affect the induction of antitumor immunity to breast cancer.

- Title: Hypermethylation of Genes in Secondary SCCHN in Relation to Smoking

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: Most cases of squamous cell carcinoma of the head and neck (SCCHN) are strongly associated with chronic smoking. Almost half of the survivors of first tumors continue smoking after treatment, and many of these patients develop a second primary tumor (SPT) within two decades of initial diagnosis. The basic biological mechanisms that connect smoking and secondary SCCHN are not well understood. The Garte research team is interested in understanding these mechanisms by linking exposure to smoking with one of the more exciting recent fields of research into molecular carcinogenesis—changes in the function of genes due to hypermethylation, a specific way that cells control gene expression. The hypothesis to be addressed is that cigarette smoking is linked to hypermethylation of specific genes involved in secondary SCCHN tumorigenesis.

- Title: Research Infrastructure: Vivarium Renovations for Barrier Facility

Type of Research: Biomedical

Focus: Research Infrastructure Project

Purpose: Despite a vivarium staff's best efforts to run a pathogen-free facility, communicable disease outbreaks will still occur. The best method to minimize these outbreaks is to develop specialized standard operating procedures (SOPs) for moving animals, personnel, and materials into the facility; moving animals between facilities; and limiting facility access for outside individuals (public and researchers). The design of the existing vivarium facility in the Biomedical Science Tower South (BSTS) prohibits rigorous SOP implementation, leaving the animals vulnerable to adventitious disease outbreaks. The purpose of this project is to renovate the existing animal facility into a barrier facility to minimize communicable disease outbreaks.

- Title: Research Infrastructure: Caging Installation at Bridgeside Point II Vivarium Facility

Type of Research: Biomedical

Focus: Research Infrastructure Project

Purpose: Bridgeside Point II (BPII) is a new research facility at the University of Pittsburgh. At this time, final fit-out of the core vivarium facility is being completed, and this project will provide necessary caging and related sanitary equipment. Because the facility is one mile from the heart of the main University campus, a fully equipped, on-site vivarium facility is essential for investigators working there.

UPMC McKeesport (\$58,248)

Research Projects:

- Title: Jameson Behavioral Health Cancer Counseling Research Project
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: As an extension of the Neighborhood Cancer Care Cooperative/Radiation Oncology Community Outreach Group collaboration (with UPMC McKeesport), Jameson Behavioral Health Services will provide a research based project with individual counseling, group counseling, family counseling, education and treatment programming for patients diagnosed within Jameson Health System Network, while proving that aforementioned counseling service assists cancer diagnosed patients to participate in medical treatment, live safely (i.e., what is considered medically proven safe living habits by documented information founded in former cancer research) and relieve mental/behavioral health stressors to a higher percentage than non-participating members in the program that were diagnosed and newly diagnosed within Lawrence County, PA.

Wistar Institute (\$ 1,363,886)

Research Projects:

- Title: The Immuno-protective Effect of K12/SECTM1 and CD7 Expression in Cancer Cells
Type of Research: Biomedical
Focus: Immunology
Purpose: We are attempting to understand how cancers can escape the normal mechanisms the body uses to permit normal growth control of cells. Cancers can grow independently of normal signals the body uses to control growth. Normally cells require growth factors to bind to cells to signal their division. Cancers have mutations in genes that make this unnecessary. Other factors bind to cells and block their division or migration. Cancers are either unresponsive to these growth control factors or secrete factors that permit them to migrate or spread to distant parts of the body. Our research is currently focused on determining the effect of over expression in breast and ovarian cancers of a novel factor, K12/SECTM1, on the ability of immune cells to attack and kill these cancers.
- Title: The Role of Micro RNA in Lung Cancer
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Lung cancer is the leading cause of cancer deaths worldwide, with 5-year survival rates of 15% and below, depending on the subtype. The reasons for these high mortality rates are the lack of early detection and inefficient treatments. The recent findings implicating micro RNAs (miRNA) in the pathogenesis of lung cancer identify potential new targets for the development of therapeutics for the treatment of lung cancer. The overall goal of this project is to identify miRNAs that promote tumorigenesis and metastasis, and to establish their function.
- Title: Molecular Basis for Telomere Replication and Maintenance
Type of Research: Biomedical

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

Purpose: In the past several years, significant links have begun to emerge between the integrity of eukaryotic chromosome ends, known as telomeres, and both aging and cancer. 80-90% of human tumors show high levels of activity of telomerase, the enzyme that replicates telomeres, when such activity is negligible from adjacent somatic cells. Studies have identified numerous proteins involved in replicating, and regulating, telomere length and stability. However, the function of these telomere maintenance factors and their role in human disease are far from fully established. The long-term goal of this research plan is to use structural, biochemical, and biophysical methods to understand how telomeric complexes mediate their replication and apply this information in pursuit of anticancer therapies.

- Title: Reference Plasma Proteomes for Validating Plasma Cancer Biomarker Candidates

Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: Systematic analysis of proteins in the blood of cancer patients has great potential to detect new indicators (biomarkers) of cancers that could detect cancer earlier or help doctors design better cancer treatments. However, it is difficult to systematically discover better cancer biomarkers because blood is very complex and cancer proteins are present at very low levels. To attack this "needle-in-a-haystack" problem, researchers at The Wistar Institute of Anatomy and Biology have recently developed a new 4-D protein profiling method and combined it with mouse cancer models to successfully detect many candidate cancer biomarkers. The purpose of the current project is to define the composition of proteins in normal human blood and normal mouse blood to serve as references for selecting the best candidate cancer biomarkers, which will then be validated in future studies.