

## **Health Research Formula Grants - State Fiscal Year 2005-06**

Forty organizations received health research formula grants for the state fiscal year 2005-06. Grants may support one or more research projects and research infrastructure projects. The grants started 1/1/2006 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 (\$165,620)**

#### **Research Projects:**

- Title: Implementing Automatic Speech Recognition in a Computerized Naming Program for Aphasic Adults  
Type of Research: Clinical  
Focus: Neurosciences  
Purpose: This project involves a computerized therapy system called MossTalk Words® (MTW). MTW was designed to improve word retrieval skills in individuals with aphasia – speech and language impairments resulting from stroke or other brain injury. This project aims to enhance the therapy system to maximize its usefulness to individuals with aphasia, clinicians and researchers and to ensure the likelihood of future funding. Specifically, we propose to (1) upgrade the software to make it compatible with current operating systems; (2) incorporate speech recognition in order to make it possible for MTW to determine and record the accuracy of the aphasic person's spoken responses and provide appropriate feedback; and (3) evaluate the stability of the upgrade and accuracy of the speech recognition feature.
- Title: Patient Participation in End of Life Decision-Making  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The purpose of this pilot study is to examine whether there are differences between African American and White patients around preference for involvement in end of life decision-making and perception of control over the decisions and to assess the feasibility of the research procedures. Data gathered from this pilot will be used to develop a larger study on this topic.
- Title: Non-Stimulant Pharmacotherapy in Aphasia  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: Aphasia refers to the loss of the ability to understand or produce speech that occurs when language areas of the brain are damaged. Individuals with aphasia commonly demonstrate limitations in attention and working memory that interact with and contribute to their impaired processing of language. The purpose of this project is to conduct a controlled short-term trial of a non-stimulant agent, atomoxetine hydrochloride (ATH), in aphasia to examine its influence on attention and memory processes engaged during speech processing. ATH, recently approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), may enhance cognitive processing and thereby facilitate new learning for individuals with aphasia.

### **Allegheny-Singer Research Institute (\$226,528)**

#### **Research Projects:**

- Title: Carotid Plaque Regression by Two LDL Inhibitors: An MRI Plaque Composition Study  
Type of Research: Clinical

Focus: Cardiovascular Sciences

Purpose: The purpose of this project is to 1) characterize carotid plaque using Cardiovascular Magnetic Resonance Imaging (CMR) derived total plaque burden vs. plaque specific components related to LDL changes following medication, 2) characterize and compare plaque morphology in a moderate to high risk patient population who are not at NCEP criteria following administration of Vytorin vs. Simvastatin over 12 months with serial CMR and 3) the primary goal, evaluate the nature and magnitude of physical properties of the carotid arterial vascular wall in response to treatment using phase velocity mapping by CMR and measure large and small systemic vascular compliance (C1 and C2) using a Windkessel model.

- Title: A Seizure Control System for Neocortical Epilepsy  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: The purpose of this project is to advance the development of a novel seizure prediction and medication delivery system that can be interfaced with the brain to prevent the occurrence of epileptic seizures. This system is being developed in an animal model of post stroke epilepsy, a type of neocortical epilepsy.

### **American Aging Association (\$1,699)**

#### **Research Project:**

- Title: Effects of Oxygen Tension on Oxidant Generation in Fetal Lung Fibroblasts  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Although required for life, even relatively low concentrations of oxygen are toxic to human cells. The underlying cause of oxygen toxicity is not established; however, it has generally been accepted that the toxicity results from increased rates of cellular generation of reactive oxygen species (ROS) such as superoxide radicals (an oxygen molecule with an extra unpaired electron) and hydrogen peroxide. Cells have natural defenses that remove reactive oxygen species, but these defenses do not appear to respond to changes in the ambient oxygen concentration. Conversely, chemicals that generate ROS stimulate the antioxidant defenses. This observation raises the question of whether oxygen toxicity actually results from increased intracellular ROS production. The purpose of this project is to assess whether elevated levels of oxygen increases cellular production of ROS.

### **American Association for Cancer Research (\$83,371)**

#### **Research Projects:**

- Title: In Vivo-like 3D System to Assess Stroma Permissiveness in Tumor Cell Invasion  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: There is an urgent need to identify new and better drugs for cancer treatment. This work arises from the growing scientific appreciation of the contribution of the cellular microenvironment to a developing cancer, which involves signaling between tumor cells and the extracellular matrix produced by surrounding stromal cells. We hypothesize that the response of cells to drug treatment is influenced by the microenvironment, and the effectiveness of drugs in cells grown within the matrices more accurately reflects the effectiveness of drugs in vivo. We will monitor tumor cell invasiveness through different classes of matrix, and then use this system to measure the ability of drugs to selectively inhibit invasion. Our

ultimate goal is to more accurately predict drug behavior in vivo, to reduce the cost and increase the efficiency of development of cancer therapeutics.

- Title: Contribution of Estrogen Synthesis and Detoxification Enzyme Expression to Tobacco Smoke-induced Lung Cancer  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: The purpose of this project is to study molecular alterations within lung tissue that could contribute to understanding the basis of the higher susceptibility to women to develop lung cancer. Local estrogen synthesis and carcinogen metabolism will be investigated due to their important role in cancer development. This project could facilitate the establishment of new biomarkers of risk and prognosis for adenocarcinoma of the lung, as well as guidelines for hormone use by female smokers.

### **American College of Radiology (\$2,590,126)**

#### **Research Projects:**

- Title: Biomarkers for Prostate Cancer Treatment with Radiation and Hormone Therapy  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: Some men with prostate cancer have an excellent prognosis and do not need treatment, while others succumb to the disease in a relatively short period of time. Since 1 in 6 men will develop prostate cancer in their lifetime, the need to better understand the biology of the disease is imperative. The identification of biomarkers that predict prostate cancer response to therapy will facilitate more accurate selection of appropriate therapy, lead to a greater appreciation of the molecular mechanisms that govern response and guide the administration of newer "targeted" therapies that are currently under investigation. The objectives are to bring into more routine use measurements of MDM2, p53, Ki-67 and p16 expression at the protein level and a host of other potential genes measured at the RNA level.
- Title: Assessing the Value Added of PROs in Cooperative Group Oncology Clinical Trials  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: Quality of life (QOL) during and after treatment is ever more important as cancer patient survival increases. The value added of patient-reported outcomes (PROs) has been questioned. With this study, we will examine the degree to which toxicity data is redundant with PROs and the number of cases that would be considered to have a positive outcome by each assessment method.
- Title: Identification of Barriers and Facilitators to RTOG Clinical Trials Recruitment  
Type of Research: Clinical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: It is well documented that only about 3-5% of new cancer patients participate in clinical trials. Despite considerable time, effort and expense, the proportion of patients recruited is frequently small. This study will assess barriers and facilitators to clinical trials recruitment within the context of patient-, clinician- and organizational-level factors. The data will provide evidence upon which to develop interventions for improvement of recruitment to Radiation Therapy Oncology Group (RTOG) clinical trials.
- Title: Missing Quality of Life Assessments in Radiation Therapy Oncology Group Studies  
Type of Research: Clinical

Focus: Oncological Sciences

Purpose: Quality of life (QOL) during and after treatment is ever more important as cancer patient survival increases. A major issue in QOL is missing assessments that complicate the analysis and interpretation of results. This project will describe patterns of missing QOL assessments in clinical trials that include radiotherapy and then investigate patient and disease characteristics that predict this missingness.

- Title: Dynamic Tumor Volumetric Regression Response Using Cone-Beam and PET/CT in NSCLC  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: To evaluate tumor response for non-small cell lung cancer (NSCLC) patients using PET/CT and Cone-Beam CT (CBCT) and determine parameters needed for adaptive radiotherapy. The parameters of interest are 1) Relationship between volumes determined using PET/CT and CBCT to determine which imaging modality is better to calculate clinical target volumes (CTV). 2) Volume of target (CTV) as a function of dose and time. 3) Three-dimensional motion of the target as a function of dose and time. 4) Margin needed for PTV as a function of dose and time. 5) Lung function after treatment with pulmonary function tests, including diffusion capacity (DLCO). 6) Correlation of imaging response with serum protein and peptide profiles with emphasis on signature effects of ionizing radiation.
- Title: Assessing Evidence to Support Quality Indicators for Radiation Oncology  
Type of Research: Clinical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The purpose of this project is to define quality indicators likely to be useful in measuring good quality care for patients treated with radiation oncology for cancer in several major sites and to use existing databases of national survey data to assess the strength of the evidence that these indicators actually show variations that can measure quality.
- Title: Emerging Imaging Technology Clinical Trials in PA: Part II  
Type of Research: Clinical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: This project represents the development and completion of clinical research trials involving the use of emerging imaging technology at selected Pennsylvania academic medical centers, aimed at advancing the role of imaging in the detection and/or treatment of disease. This research will 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 initial application (funded in 2004-2005) supports research on 1) the role of Dynamic Contrast Enhanced MRI (DCE-MRI) in assessing the effectiveness of drug interventions targeted at tumor vascularity and 2) the role of MRI in measuring the functional integrity of articular cartilage for the purpose of assessing the progress of arthritis.

### **Arcadia University (\$17,426)**

#### **Research Project:**

- Title: Neuromuscular Control of Force Production in Older Adults with and without Hip Fracture  
Type of Research: Clinical  
Focus: Musculoskeletal, Oral and Skin Sciences  
Purpose: A majority of older adult who have sustained a hip fracture fail to return to the pre-fracture functional status. Limitations in physical performance persist for at least one year after fracture. The rates of falls and new fractures are increased.

Many factors have been examined to account for this disability including depression, poor nutrition, and cognitive status; exercise programs have targeted therapeutic exercise. The level of disability, however, has not changed significantly as a result of these efforts. The purpose of this project is to investigate some of the mechanisms associated with muscle force production to determine if they are different in older persons with or without a hip fracture. The results will lead to development of a new treatment intervention.

### **Bryn Mawr College (\$9,544)**

#### **Research Project:**

- Title: New Tools for the Synthesis of Cyanthiwigin AC and Analogs  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: A novel synthetic chemistry sequence involving the Birch reduction-allylation and Cope rearrangement will be developed and applied to the synthesis of cyanthiwigin AC and related analogs. Cyanthiwigin AC has never been synthesized in a laboratory before and several structurally related natural products have demonstrated anti-cancer, antituberculosis and anti-HIV activity. Besides generating testable quantities of cyanthiwigin AC and related analogs, the synthetic chemistry tools developed in the project will assist other pharmaceutical researchers in their search for new therapeutics.

### **Carnegie Mellon University (\$737,186)**

#### **Research Projects:**

- Title: Developing Methods and Software for the Analysis of Large and Sparse Contingency Tables  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: Log-linear models are a powerful statistical tool for the analysis of categorical data. Their use has increased greatly over the past two decades with the compilation and distribution of large sparse databases, especially in the medical and biological fields. Such databases often take the form of high-dimensional contingency tables with a large number of empty cells, a situation for which most existing statistical procedures cannot be applied. The purpose of this project is to derive and implement new statistical methodologies for the analysis of large sparse contingency tables.
- Title: Changing Representational Codes in the Hippocampus  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: The hippocampus, located in the temporal lobe of the brain, plays an important role in memory formation, possibly by constructing compact representations for efficient coding of information by the cortex. The purpose of this project is to investigate computational theories of hippocampal coding in the rodent brain, in order to better understand how the hippocampus contributes to cognition.
- Title: Effort of Thinking - A Neuroscience Approach  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: Many common mental operations, e.g., conversation, reading, and listening, are not accompanied by a subjective feeling of effort. However, some do invoke a feeling of effort; moreover, they become increasingly difficult to sustain the longer one has engaged in them. What types of mental operations produce mental fatigue? Is mental fatigue associated with processing in specific brain regions? Why

are our brains engineered such that some mental operations are tiring, but not others? The proposed research will attempt to answer these questions. Given the increasing importance of mental effort in the workplace, this research could have implications for the formulation of work, in education and for understanding the cognitive effects of aging.

- Title: Monitoring and Feedback to Support Physical Exercise Awareness  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: Being physically active is a critical component of fighting obesity. Reviews of studies on exercise have revealed that two factors promote and maintain appropriate levels of physical activity: point-of-decision prompts and individual activity programs. Most work in supporting physical activity has concentrated on non-computer based solutions for these factors. Our work is focused on conducting a rigorous user-centered design and development process to build technological support to automatically monitor physical activity and provide effective feedback to encourage engaging in appropriate amounts of physical activity. In this project, we focus on sensing the activity levels of individuals dealing with obesity and use this information to sense patterns.
- Title: MRI Detection of Cardiac Rejection in a Pig Model  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: The purpose of this research initiative is to support a pilot project using MRI techniques to detect cardiac rejection using a large animal model (namely pigs). Scientists working at the Pittsburgh NMR Center for Biomedical Research (NMR Center) and the University of Pittsburgh Medical Center will be conducting the research.

### **Children's Hospital of Philadelphia (\$3,460,487)**

#### **Research Projects:**

- Title: Nerve Promoting Factors from the Early Embryonic Inner Ear  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: The cochlear implant is a remarkable electronic device that can restore hearing to profoundly deaf children. It works by bypassing the sound-sensitive tissues of the inner ear to provide direct electrical stimulation of the nerve of hearing, the auditory nerve. A child's success with a cochlear implant depends on maintaining auditory nerve cells, which can be diminished substantially by some forms of deafness. The purpose of this project is to characterize a critical nerve-stimulating substance called ODF, a mixture of unknown active proteins secreted by the inner ear during embryonic development. ODF has a powerful effect on nerve cell growth and survival, and so may have great clinical potential for stimulating nerve regeneration and possibly helping children perform better with cochlear implants.
- Title: Functional Imaging in 4 Dimensions: Magnetoencephalography (MEG)  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: Detection and recording of brain functional activity using magnetoencephalography (MEG) offers unique advantages over alternative methodologies (such as positron emission tomography and functional magnetic resonance imaging). In particular, MEG offers direct non-invasive recording of neuronal activity with sub-millisecond temporal resolution and no radiation risk. Consequently neuronal activity evoked by a stimulus presentation or by cognitive or

motor task performance, as well as spontaneous activity can be recorded. This project is to explore the fine structure of evoked responses, detected by MEG, and to define temporal signatures of normal and abnormal brain function, with a view to definition of electrophysiological phenotypes of developmental disorders such as autism, ADHD and learning disability.

- Title: Building a Multimodality Imaging Core Resource  
Type of Research: Biomedical  
Focus: Research Infrastructure  
Purpose: The goal of this research infrastructure project is to develop a multi-modality experimental animal imaging resource to support, expand and extend the preclinical research investigations of a large number of CHOP investigators as well as to develop and refine an integrated translational research effort, which will allow ready translation of experimental and preclinical advances to the clinical setting. To achieve this goal, we are customizing space within the rodent facility, acquiring state-of-the-art imaging equipment (both of these aspects of the project are being supported by institutional funds), optimizing the state-of-the-art experimental animal imaging protocols (including microMRI, microCT and microPET) and establishing a common image post-processing and quantitative analysis endeavor, sharing and expanding resources of clinical radiology.

### **Children's Hospital of Pittsburgh (\$722,169)**

#### **Research Project:**

- Title: Peptide Hormone Signaling in Pancreatic Beta-Cell Formation  
Type of Research: Biomedical  
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
Purpose: The overall goal is to better understand how hormones that are normally produced by the pancreas may lead to the development of cells that make insulin. A great deal is known about other growth factors that may cause stem cells to become pancreatic insulin cells, but given the fact that the pancreas produces peptide hormones, there is compelling evidence that hormones, such as glucagon, could particularly play a role in the creation of insulin-producing cells. A better understanding of the role of these hormones will help to influence the ability of stem cells, or other possibly adult progenitor cells in a Petri dish to become insulin cells. These engineered cells would have the potential to be given to patients with diabetes mellitus as a possible cure.

### **Donald Guthrie Foundation for Education and Research (\$21,219)**

#### **Research Projects:**

- Title: Sleep-Related Disorders during Pregnancy and Their Effects on Postpartum Mood Disturbances  
Type of Research: Clinical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The purpose of this project is to determine the incidence and prevalence of sleep-related disorders in women from their last menstrual period through parturition and concluding one year postpartum and to evaluate the effects of sleep-related disorders on the quality of sleep during this same period. Furthermore, the project will determine if a relationship between postpartum mood disturbances and sleep-related disorders in women is possible.
- Title: Genetic Basis for the Lack of Efficacy of Erbitux (anti-EGFR-1)  
Type of Research: Biomedical  
Focus: Oncological Sciences

Purpose: These data will help define patterns of gene expression differences responsible for phenotypic differences and possibly reveal the molecular mechanisms responsible for the lack of additional effect by Erbitux. Selected molecular markers will be identified and will be directly applicable to pre-screening patients for Erbitux/Herceptin therapy and may shed light on the anti-tumor mechanism.

## **Drexel University (\$1,055,561)**

### **Research Projects:**

- Title: The Role of Microtubule-Severing Proteins in Alzheimer's Disease (AD)  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The overall goals of the project are to first test the merits of the hypothesis using tightly controlled experimental conditions, and then to expand the project into animal models for neuropathies. Specifically, the plan is to (i) determine whether overexpressing tau and other neuronal microtubule (MT)-associated proteins in simple fibroblasts affords strong "protection" against MT severing by katanin and/or spastin; (ii) determine whether depleting tau from cultured neurons renders the MTs in the axon more sensitive to MT severing; and (iii) characterize MT-severing proteins in an animal model for AD.
- Title: Building a Model for Financing Local Health Departments in Pennsylvania  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: This project will develop an analytic model to produce economic projections needed to support responsible decisions about the financing of local health departments. While focusing on the specifics of Pennsylvania's populations, laws, and geography, this analytic model would also inform policy makers about the resources – local, state and federal – that are necessary to carry out public health activities effectively in other parts of the country as well.
- Title: Environmental Particulate and Deficient Dietary Effect on Child Asthma Severity  
Type of Research: Clinical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: Asthma's increasing prevalence and economic burden indicate the need for more effective public health control strategies. Common, but possibly limiting, intervention strategies focus on single exposure reduction rather than a fully integrated, total exposure reduction approach to asthma in inner-city children. Research to assess the combined effects of simultaneous exposures will be conducted to address the limitation. Expanded exposures will include broader behavioral/environmental factors. The project will focus on the interrelationships of four risk factors associated with increasing asthma severity: 1) inhalable particulate matter ( $\leq 10 \mu\text{m}$ ), 2) endotoxin, 3) dampness and 4) dietary deficiencies. The results will serve as a basis for updated, evidence-based risk-reduction recommendations and lead to the discovery of causal pathways and more effective prevention efforts.
- Title: Pathways for EGF Receptor Endocytosis via Multichannel Scanning Probes  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: The purpose of this project is the development of a new tool and method for the study of pathways of Endocytosis involving the transmembrane cell receptor Epidermal Growth Factor Receptor (EGFr). This receptor plays a critical role in cell differentiation and growth. Since overexpression and/or mutations of EGFr are

implicated in many cancers (breast, ovarian, colorectal) and antibodies to this receptor are being tested as drug therapies for these cancers, it is anticipated that clarifying the details of the pathways and mechanisms involved will potentially benefit many through the development of improved cancer therapies.

- Title: Large-Scale High-Resolution Automated Connectivity Mapping of the Human Brain

Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology

Purpose: The purpose of this project is to develop a high-resolution method for use with human postmortem material. This method will be used to test the hypothesis that schizophrenia is associated with a disturbance in connectivity between different brain regions, rather than abnormalities within the separate regions themselves. Mounting evidence for this hypothesis is from several key MRI studies using diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI). These studies have found white matter associated with schizophrenia as well as histological studies showing reduced neuropil, as would be anticipated in response to a reduced axonal input.

### **Duquesne University (\$82,990)**

#### **Research Projects:**

- Title: Identification and Use of Secreted Proteins of Enterobacter Agglomerans  
Type of Research: Biomedical  
Focus: Infectious Diseases and Microbiology  
Purpose: The purpose of this project is to develop systems that allow secretion of antimalarial proteins from strains of Enterobacter agglomerans. This project is part of a larger effort to develop strains of bacteria that can interfere with the transmission of disease causing agents from mosquitoes to humans.
- Title: Regulation of Steroid Sulfatase by Glucocorticoids in Human and Mouse Bone Cells  
Type of Research: Biomedical  
Focus: Musculoskeletal, Oral and Skin Sciences  
Purpose: The purpose of this project is to study the regulation of steroid sulfatase by glucocorticoids in human and mouse bone cells. Steroid sulfatase is an enzyme that converts inactive steroid hormones to their active forms. It is believed that steroid sulfatase plays a role in providing estrogen to bone cells in order to maintain proper bone density, particularly in postmenopausal women. Glucocorticoids are known to reduce bone density, and even to cause osteoporosis when used clinically. Glucocorticoid-induced osteoporosis (GIOP) has increased dramatically in the past few decades due to the introduction of synthetic glucocorticoids to treat inflammatory diseases. New data indicates that glucocorticoids affect steroid sulfatase levels in human bone cells. This project will further investigate the regulation of steroid sulfatase by glucocorticoids, using human and mouse bone cell lines. These data should provide important information on the steroid hormone regulatory processes that are involved in normal bone deposition and in osteoporosis.

### **Family Planning Council (\$12,184)**

#### **Research Project:**

- Title: Contraception Choices Amongst Adolescent Females  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: The purpose of this project is to provide information and recommendations on what adolescent females know about birth control methods and what factors are important when adolescent females decide which ones to use.

### **Fox Chase Cancer Center (\$3,001,121)**

#### **Research Projects:**

- Title: Improving Prostate Cancer Outcomes by Data Acquisition, Representation and Mining  
Type of Research: Biomedical and Clinical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: Prostate cancer is the second most common form of cancer among men in the United States, and it is the second leading cause of cancer-related death in males. The American Cancer Society estimates that approximately 230,000 new cases of prostate cancer will be diagnosed and 29,900 men will die of the disease in 2004. This project will develop a series of bioinformatics methods and tools to facilitate prostate cancer research. These tools will be applied to data collected on a large number of patients treated at Fox Chase Cancer Center (Fox Chase) to construct new prognostic models for early stage prostate cancer and to enhance our understanding of the cellular mechanisms, molecular markers, and natural history of this deadly disease.
- Title: Maintenance of Genomic Integrity at CpG Sites  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Cancer is caused by the accumulation of changes in the four DNA bases (A,C,G,T) that make up the sequence of genes. These changes, called mutations, are often caused by defects in the DNA repair machinery. One third of all cancer mutations are special changes, from CG to CA. Despite the importance of these mutations, both the causes of the high frequency of CG to CA changes in tumor cells, and the DNA repair systems that prevent them, are not well understood. The purpose of this project is to understand how CG to CA mutations take place and which DNA repair systems are involved in the prevention of these changes. We will use engineered cells and mice defective in DNA repair proteins to measure efficiency of DNA repair, rates of accumulation of mutations and tumor formations.
- Title: Effect of Resveratrol on Colonic Inflammation in a Mouse Model of Colitis  
Type of Research: Biomedical and Clinical  
Focus: Oncological Sciences  
Purpose: The purpose of the proposed research is to examine the possible mechanisms by which resveratrol, a naturally occurring polyphenol found in nuts, grapes and grape products such as red wine, inhibits colonic inflammation in both acute and chronic colitis and evaluate its ability to inhibit colitis-associated colorectal cancer.
- Title: Patterns of Gene Expression in Developing B Lymphocytes  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Antibody responses that provide immunity following immunization are produced by a specialized type of lymphocyte known as a B cell. B cells, a type of white blood cell, are generated from precursors in the bone marrow of humans and mice throughout life. These precursors have been classified into stages based on distinctive proteins expressed on the cell surface and these stages characterized in terms of their growth properties and functional properties. Specifically, there are

stages where genes, for the first one part (the heavy chain) and then the other part (light chain) of the antibody molecule, are assembled by precise rearrangements of DNA in the precursors. There is also a stage where the precursors undergo extensive proliferation, termed clonal expansion. While a great deal is known about a limited set of genes that participate in this process of B cell development, we plan to carry out a global analysis of gene expression in order to understand this process more completely. This type of analysis is now possible using a technique known as microarray analysis, wherein the level of expression of all genes is measured.

- Title: Mechanisms of Renal Tumorigenesis in Tuberous Sclerosis  
Type of Research: Biomedical and Clinical  
Focus: Oncological Sciences  
Purpose: Tuberous sclerosis complex (TSC) and Birt-Hogg-Dube syndrome (BHD) are inherited diseases associated with kidney cancer. This project will use biochemistry, cell culture, human specimens, and animal models to elucidate the cause of kidney disease in TSC and BHD. The cellular and biochemical pathways that cause kidney tumors in TSC and BHD are likely to be closely related to the pathways that cause kidney tumors in the general population. Understanding the cause of kidney cancer is likely to result in improved methods for prevention, early detection, and treatment.
- Title: Therapy of Chronic Hepatitis B Virus Infection  
Type of Research: Biomedical  
Focus: Infectious Diseases and Microbiology  
Purpose: - Patients with chronic hepatitis B virus infection have a 25-40% life time risk of death from cirrhosis or hepatocellular carcinoma. Chronic infection is common, afflicting 1.25 million in the US and 360 million worldwide. Therapy with nucleoside analogs such as lamivudine, which block virus reproduction, cures the infection in about 10-30% of patients, reducing the risk of death from hepatitis B. After a short-term remission, infection rebounds in the remaining patients due to emergence of drug resistant virus. The purpose of this project is to determine if vaccination with a cell based vaccine during the period when the infection is in remission will prevent a relapse by inducing the destruction of the residue of infected cells.
- Title: Role of Dyskerin in Translation Control as a Mechanism for Tumor Suppression  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Mutations in genes that encode components of the translation apparatus have been identified in tumor susceptibility syndromes. Dyskeratosis Congenita (DC) is a striking example of such a syndrome, in which mutations in the enzyme that modifies ribosomal RNA (rRNA) lead to cancer susceptibility. The gene mutated in DC, DKC1, is a pseudouridine synthase that mediates the conversion of uridine (U) to pseudouridine ( $\Psi$ ) in rRNA. We have previously generated hypomorphic DKC1 mutant mice (DKC1m), which recapitulate all the clinical features of DC including increased tumor susceptibility. Strikingly, more than 50% of all DKC1m mice develop carcinomas and B-cell lymphomas. This project is aimed at investigating the role of dyskerin, the protein encoded by DKC1 gene, in the regulation of protein synthesis as a mechanism for tumor suppression.
- Title: Epigenetic Basis of Breast Cancer Prevention  
Type of Research: Health Services  
Focus: Oncological Sciences  
Purpose: The risk of developing breast cancer is markedly decreased in women who have borne one or more children at a young age. The protection conferred by the

reproductive process is mediated by the induction of breast differentiation, which results in the conversion of undifferentiated Stem Cells 1 that are amenable to be transformed by carcinogens to Stem Cells 2 that are resistant. The purpose of this project is to determine whether the conversion of the Stem Cell 1 to Stem Cell 2 in the breast of women with an early pregnancy is the result of methylation of specific sets of genes that would become selectively silenced by this epigenetic mechanism, thus imprinting in the breast epithelium a genomic signature that confers protection. This novel approach will contribute to the development of innovative strategies for breast cancer prevention.

- Title: Poly ADP-ribose Polymerase in Chromatin and Transcriptional Regulation  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The vital roles of PARP1 protein in Drosophila development have been demonstrated during previous work. PARP1 enzymatic activity is required for transcriptional activation of heat shock-dependent, NF- $\kappa$ B-dependent, and ecdisteroid-dependent genes. Also demonstrated is the requirement of PARP1 for nucleolar function. Published data strongly suggest that PARP1 is involved in transcriptional regulation through induction of chromatin loosening at targeted genetic loci. These roles are distinct from the previously characterized role of PARP1 in DNA repair and apoptosis. The main purpose of this project is to investigate the PARP-dependent regulatory mechanisms that are involved in chromatin and transcription modulation during a eukaryotic organism development. In order to understand such mechanisms, it is essential to know: (1) how PARP protein is targeted to chromatin and regulated there; (2) which proteins are subjected to pADPr modifications.

### **Geisinger Clinic - Weis Center for Research (\$110,724)**

#### **Research Project:**

- Title: Translational Research Initiative  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The purpose of this project is to support research that brings to bear sophisticated scientific instrumentation and expertise to address an important clinical problem. An additional goal is to promote increased collaboration between laboratory and clinical investigators. Such "translational research", which strives to translate the scientific innovations into improved health, constitutes a major bottleneck, and was recently identified as the cornerstone of a new vision for biomedical research by the Director of the National Institutes of Health. The specific project to be undertaken will investigate mechanisms that underlie tumor resistance to killing by chemo-radiation.

### **Juniata College (\$9,495)**

#### **Research Projects:**

- Title: Use of Phage Display to Identify Bacterial Receptors for Abundant Plasma Proteins  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: The purpose of this project is 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: To 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 (\$244,328)**

#### **Research Projects:**

- Title: Methionine Restriction and Epithelial Barrier Function in a Cell Culture Model  
Type of Research: Biomedical  
Focus: Biology of Development and Aging  
Purpose: There are two well documented procedures that can increase the lifespans of animals by as much as 30%. The first is caloric restriction or simply reduction of the number of calories typically consumed. The second is to reduce the amount of specific amino acids in the diet, most notably methionine. Because the ability of epithelial tissues to keep foreign substances out of the vasculature is so intrinsic to health, we hypothesize that one of the mechanisms by which these lifespan-extending nutritional regimens achieve their goal, is to forestall age-related morbidities in a variety of major organs by enhancing the barrier ability of the epithelial linings. We plan to test this hypothesis in a very general way by examining the effects of methionine deprivation on the barrier ability of an artificially grown renal epithelium.
- Title: Preclinical Evaluation of Combining 1MT with Chemotherapy to Treat Metastatic Cancers  
Type of Research: Biomedical  
Focus: Immunology  
Purpose: Treatment with 1-methyl-tryptophan (1MT), a small molecule inhibitor of the enzyme indoleamine 2,3-dioxygenase (IDO) dramatically leverages the efficacy that can be achieved with standard cytotoxic chemotherapeutic agents in a transgenic mouse model of breast cancer. To move this novel combinatorial treatment strategy forward towards eventual clinical development, this project will address the critical need to demonstrate effectiveness against metastatic disease. Treatment parameters will initially be optimized in a mouse model of metastatic breast cancer. These optimized treatment conditions will then be applied to other models of metastatic disease representing different tissues of origin to provide an assessment of how widely applicable this therapeutic approach might be.
- Title: New Markers for Improved Prognosis of Small Ductal Carcinomas  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: Twenty percent of breast cancer patients identified as having good disease-free survival using current parameters will suffer recurrence and/or succumb to their disease. It is well understood that early aggressive treatment minimizes the risk of recurrence and death, which is why a correct prognosis is of importance. In a retrospective study, we have identified a set of markers that reduces the number of patients given the wrong prognosis with fifty percent. The project aims to verify the usefulness of these markers to better identify patients in need of early adjuvant therapy to reduce the risk of recurrence and death.

### **Lehigh University (\$130,662)**

#### **Research Project:**

- Title: Children with ADHD: Long-term Effects of Psychosocial Intervention  
Type of Research: Clinical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: There are two purposes to this project. First, long-term (18-24 months) follow-up data will be collected to determine whether short-term effects of academic and psychosocial interventions are maintained for children with attention-deficit/hyperactivity disorder (ADHD). Changes in behavioral, social, and academic functioning of two large samples of children with ADHD will be assessed. Second, the short-term effects of organizational skills training on the academic performance of middle school students with ADHD will be investigated. The academic achievement, homework completion, and study skills of a small sample of students with ADHD will be evaluated prior to and following the implementation of a 30 session, after school, study skills training program.

### **Lincoln University (\$20,913)**

#### **Research Project:**

- Title: Method Development of Nicotine and its Metabolites Using LC/MS  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: The purpose of this research is to design a robust LC/MS technique that will allow the quantitative detection of low concentrations of nicotine and its metabolites. The technique employed, High Performance Liquid Chromatography (HPLC) interfaced with Mass Spectrometry (MS), are separation and detection techniques that are becoming very popular in the scientific community, especially in the pharmaceutical industry. HPLC allows separation of mixtures of analytes into individual components. MS allows one to rapidly characterize and detect low amounts of chemical species present in a sample. MS also is used for structural characterization of analytes. Combined, the two techniques are very powerful and sensitive techniques that can be used in clinical settings that require high throughput analysis and rapid characterization of samples.

### **MPC Corporation (\$160,481)**

#### **Research Projects:**

- Title: Long-term Adjustment Among Young Breast Cancer Survivors  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: With previous NCI-funding, younger women with breast cancer were enrolled in a treatment project that was designed to enhance their psychological response to their diagnosis and treatment. The women who participated in the active intervention programs reported better physical functioning and less depression, compared to the standard care group. The purpose of this project, which reflects an outgrowth of activities of the Pittsburgh Mind-Body Center (an NHLBI-funded center jointly operated by the University of Pittsburgh and Carnegie Mellon University), is to collect data that will assess the feasibility of conducting a follow-up study of this same group of young breast cancer survivors, 5 to 9 years after their treatment program ended.
- Title: NMR Research Initiative  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: This research initiative will seek to advance the state-of-the-art in applications of in vivo magnetic resonance imaging (MRI) and spectroscopy (MRS) in order to understand tissue and organ function and to optimize these new research

methods for application by others. Scientists working at the Pittsburgh NMR Center for Biomedical Research (NMR Center) will be conducting the research.

- Title: Chronic Stress, Glucocorticoid Resistance and the Inflammatory Response  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: This project is an outgrowth of activities of the Pittsburgh Mind-Body Center (an NIH funded center jointly operated by the University of Pittsburgh and Carnegie Mellon University) and represents a supplemental protocol added to a recently NCI-funded study, which is designed to examine the efficacy of a multi-modal psychosocial intervention for children newly diagnosed with cancer and their families. The parent grant does not explore any biological factors, but presents an exceptional opportunity to begin to investigate whether a stress-management intervention known to reduce levels of psychological distress among a highly stressed population also benefits the hormonal and immune responses that typically accompanies chronic stress and is postulated to result in adverse physical health outcomes.
- Title: Flavoprotein Autofluorescence Imaging for Functional Brain Mapping  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: Flavoprotein autofluorescence imaging (FAI) is a method that allows investigators to view the activity of cortical neurons in vivo by measuring cellular metabolic rate. This technique can measure both spatial and temporal changes in brain activity and has the potential to analyze an individual neuron. The technique also has advantages because it measures natural changes in cellular metabolic rate rather than introducing a dye or other chemical for visualization, thus avoiding possible cellular toxicity. Furthermore, the FAI may be utilized in research models of development, aging, stroke, and cancer because tissue metabolic activity is a critical indicator of various physiological and pathological conditions. The purpose of this study is to examine the feasibility of FAI for functional brain mapping in advanced research models.

### **Madlyn and Leonard Abramson Center for Jewish Life (\$35,639)**

#### **Research Project:**

- Title: Individualizing Care to Frail Elders: Refining the Preferences for Everyday Living Inventory  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: This health services research project focuses on aiding the assessment and integration of psychosocial preferences for everyday living for frail elderly individuals who receive long-term care services. Psychosocial preferences include such things as amount and type of social contact, leisure activities, and daily routines. A small, growing body of literature highlights the positive impacts of integrating these preferences into care delivery for frail elders. The Preference for Everyday Living Inventory (PELI) is a rigorously developed assessment instrument fielded in a previous study of over 500 randomly selected elderly home health care recipients. The current project seeks to expand this line of research through a series of secondary analyses with the goal of refining the amount of individual preference information provided to a caregiver.

### **Magee-Womens Health Corporation (\$600,197)**

#### **Research Projects:**

- Title: Gene Targeting for Paraganglioma Mouse Model

Type of Research: Biomedical

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

Purpose: The purpose of this project is to produce recombinant DNA molecules (vectors) that will be used to generate a mouse model to study human paraganglioma tumors. Paragangliomas are rare tumors that often develop in the head, neck and abdomen. Paragangliomas can cause significant health problems because they can damage important nerves and vessels in the head and neck region or they can cause high blood pressure by secreting certain hormones. A significant fraction of paragangliomas is 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. In this project, we will produce DNA molecules that carry mutations in mouse paraganglioma genes with the eventual goal of generating a paraganglioma mouse model.

- Title: Mechanisms of Endothelial Progenitor Dysfunction in Preeclampsia

Type of Research: Biomedical

Focus: Cardiovascular Sciences

Purpose: The hypertensive pregnancy syndrome preeclampsia is a leading cause of maternal death and increases fetal death five-fold. This pilot project will test the hypothesis that placental sVEGFR-1 also causes EPC dysfunction, a line of investigation that may offer new therapeutic approaches to preeclampsia.

- Title: Effect of Leptin on Placental Amino Acid Transport: Relationship to Fetal Growth

Type of Research: Biomedical

Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences

Purpose: The purpose of this project is to investigate the role of the hormone leptin on placental amino acid transport. Amino acids are an important nutrient during fetal development. The fetus is almost entirely dependent upon the placenta to transport most amino acids across the placenta from the maternal circulation, amino acid uptake is in excess of fetal protein synthesis requirements, and amino acids are estimated to comprise as much as 20 to 40% of the energy supplied to the fetus and placenta. Leptin is an important hormone in pregnancy and metabolism, and is reported to increase placental amino acid transport. Intrauterine growth restriction (IUGR) is a serious complication of pregnancy associated with increased neonatal morbidity and mortality; placental amino acid transport is decreased in IUGR and therefore is likely contributing to the reduced fetal growth.

- Title: Development and Characterization of HIV/STD Co-infection Explant Cultures

Type of Research: Biomedical

Focus: AIDS and Related Research

Purpose: Infection with human immunodeficiency virus (HIV) remains a public health concern. The highest proportions of newly infected people are women; the majority is in Africa and Asia. Having a sexually transmitted disease (STD) makes you more likely to be infected with HIV when exposed. People infected with HIV and an STD (co-infection) pass HIV to their sexual partner more often than people without an STD. The purpose for this project is to use women's reproductive tissues to develop tissue explant cultures to study the co-infection process. Understanding the interactions between HIV and STDs, in a controlled setting, will improve our ability to prevent these infections.

- Title: Alterations in Airway Cell Differentiation in Response to Nicotine

Type of Research: Biomedical

Focus: Respiratory Sciences

Purpose: COPD (emphysema) is a progressive, incurable disease and is a major cause of hospitalization and death in the United States. In this project, we determine if nicotine alters the ability of the lung to regenerate in an animal model. We determine if nicotine changes the ability of non-human primate (nhp) stem cells to become differentiated lung cell types. If nicotine does change the ability of lung stem cells to regenerate, this could be one of the mechanisms by which COPD occurs, and will be a new model of the disease. Specifically, during COPD, the increased proliferation of airway fibroblasts takes place while numbers of bronchial epithelial cells decrease. This decreases the elasticity of the lungs and contributes to the decline in function. The project determines if the cause of these changes are due to the effects of nicotine on normal healing mechanisms.

### **Medical Diagnostic Research Foundation (\$50,384)**

#### **Research Project:**

- Title: Women's Personal Health Care Scanner (WPHCS)  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: The purpose of this project is to construct and test a hand-held self-operated breast cancer scanner. This device will give an audible or visual signal of the detection of cancer and its localization by indicating a low tone or green light on one side of the suspected cancer and a high pitch (tone) or red light on the other side. It is expected that this will afford a novel and economical outreach to underserved and high-risk, under-40 year old populations for early breast cancer detection.

### **Monell Chemical Senses Center (\$281,629)**

#### **Research Projects:**

- Title: Sweet Taste Analgesia in Women  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The purpose of this research project is to determine whether smoking alters sweet preferences and the ability of sweet tastes to reduce pain in women during different phases of the menstrual cycle. The information gleaned from this research may enable us to develop new and effective strategies to reduce smoking in women.
- Title: Naltrexone and Food Craving in Abstinent Alcoholics  
Type of Research: Health Services  
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences; Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: This research will lead to a better understanding of the mechanisms for craving food and alcohol. It will help us to understand whether food and alcohol cravings have any similarities in neuropharmacological mechanisms. This work will enable us to evaluate whether naltrexone, a medication that has been approved for the treatment of alcoholism and other drug addictions, could be useful in the treatment of obesity.
- Title: Improving Human Chemosensory Research Infrastructure at the Monell Center  
Type of Research: Biomedical  
Focus: Research Infrastructure  
Purpose: An adequate, flexible and multi-user research facility for investigation of the response by humans to chemical stimuli using the senses of taste and smell is critical to expanding knowledge on the functions and malfunctions of the chemical senses. The continued development and careful planning of a Human Chemosensory

Research Facility for the Monell Chemical Senses Center will ensure seamless interfacing of the scientists, construction engineers and the construction company to realize a well-organized and appropriately equipped laboratory.

### **National Disease Research Interchange (\$55,546)**

#### **Research Project:**

- Title: Genetic Epidemiology of Diabetic Complications: Family/Genetic Contribution to Type 1 Diabetes  
Type of Research: Health Services  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The HBDI database, the largest collection of clinical data on families identified through Type 1 Diabetes (T1D) patients, will be analyzed to determine which family or genetic factors predispose to the diabetic complications of neuropathy, nephropathy and retinopathy. Such factors include the presence of diabetes in a parent, whether another sibling has T1D and whether another sibling has complications. We will also test whether factors such as the age of onset of T1D can be familial and should be considered as modifiers of the risk to develop complications. The precision of prior findings will be increased by updating clinical information. This will increase the reliability of risk assessments of factors such as age of onset and severity of the complication, and the development of complications in other family members since the original data were collected.

### **National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation (\$1,588,633)**

#### **Research Projects:**

- Title: Gene Expression Profiling of BCPT Cancer Events for NSABP Genomic Database  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: Sharing of the NSABP clinical trials data has contributed significantly in improving the outcome of breast and colon cancer. Effective sharing of more complex data from genomics studies requires development of a new mechanism (the NSABP Genomic Database). The purpose of this project is to perform gene expression profiling of tamoxifen-resistant tumors procured in the NSABP Breast Cancer Prevention Trial in order to initiate the NSABP Genomic Database. Description of molecular differences between tamoxifen-resistant versus naturally occurring breast cancer will provide unique scientific resources for a better understanding of the mechanism of tamoxifen resistance.
- Title: Prediction of Trastuzumab Response in Breast Cancer  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: This project is aimed at validating a set of genes that are found to be predictive of degree of benefit from trastuzumab added to adjuvant chemotherapy in the treatment of breast cancer. Trastuzumab was originally developed to target HER2 protein over-expressed on the cancer cell surface. However, only half of HER2-positive tumors respond to trastuzumab. Furthermore, trastuzumab, when added to chemotherapy reduced the recurrence rate of even HER2-negative tumors in NSABP clinical trial B-31. These results suggest that there are molecular determinants of tumor response to trastuzumab other than HER2. Whole genome expression analyses of 400 tumors from NSABP B-31 identified many candidate genes that predict benefit from trastuzumab. If validated, the predictive test will help many women who have breast cancer to get the right treatment.

### **Oncology Nursing Society (\$32,860)**

#### **Research Project:**

- Title: Symptom Clusters Experienced by Women Across the Ovarian Cancer Disease Trajectory  
Type of Research: Health Services  
Focus: Oncological Sciences  
Purpose: Women with ovarian cancer are known to experience a high number of co-occurring symptoms. The study of symptom clusters, defined as three or more concurrent symptoms that are related to and influence one another, has been identified as a high priority by the National Institute of Nursing Research and the Oncology Nursing Society. To date, no studies have evaluated symptom clusters experienced by women with ovarian cancer. The purpose of this exploratory, secondary analysis is to identify and compare symptom clusters experienced by women with ovarian cancer at different phases of the disease trajectory.

### **Pennsylvania College of Optometry (\$52,203)**

#### **Research Project:**

- Title: Mechanisms of Signal Transduction in Vertebrate Photoreceptors  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: Vertebrate photoreceptors respond to light stimuli by altering their membrane potential, resulting from a complex network of biochemical reactions involving multiple protein components. Alterations in the normal signaling pathways lead to visual abnormalities and often to complete blindness. The long-term purpose of this project is to elucidate the mechanisms of photoreceptors action and pathology by directed inactivation of the components for rod and cone signal transduction. The immediate goal for the proposed pilot project is to provide the foundation for development of new genetic models by creating new constructs for gene disruption by homologous recombination and transgenic expression. In particular, it will focus on disruption of a gene, GUCY2f, involved in production of a signal messenger in rods.

### **Pennsylvania State University (\$7,845,194)**

#### **Research Projects:**

- Title: Role of Transient Receptor Potential (TRP) Channels in Cardiac Ischemia  
Type of Research: Biomedical  
Focus: Cardiovascular Sciences  
Purpose: The purpose of the project is to evaluate the role of TRP ion channels in mediating heart protection during low blood flow states (ischemia) and increased heart cell growth (hypertrophy) of the surviving heart cells after a heart attack (myocardial infarction). Virtually nothing is known about the function of TRP channels in the heart. We have preliminary evidence that TRPC4, TRPC5 and TRPC6 channels in the heart are increased after a heart attack, and that TRPC channels mediate calcium ion entry into cells. Understanding how TRP channels function in the heart, both in healthy and diseased states, will offer novel and rational therapeutic strategies for the treatment of both acute and chronic heart ischemia.
- Title: Research Center on the Molecular Aspects of Obesity and the Metabolic Syndrome  
Type of Research: Biomedical and Clinical  
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences

Purpose: Improvements in obesity-related sleep apnea, satiety/appetite, and diabetes occur rapidly after gastric bypass (GBP) surgery and are not explained by significant weight loss or decreased food intake alone. The goals of this project are to: 1) Identify animal models of obesity that mimic the improvements in appetite, sleep and metabolic syndrome observed after GBP surgery; 2) Investigate the mechanisms by which appetite, satiety, sleep, and diabetes are improved after GBP; 3) Collect and bank tissue before and after GBP surgery in patients for proteomic/functional genomic analysis, and 4) Apply this information to test specific hypotheses in knockout/ transgenic mice and obese patients. We believe that understanding how GBP surgery improves appetite, sleep, and diabetes will elucidate new targets, develop less invasive treatments for obesity, and provide important information on the pathogenesis of obesity and obesity-related medical co-morbidities.

- Title: Functional Elements in the Genomes of Human and Mouse, Phase 2  
Type of Research: Biomedical and Health Services  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The DNA sequences of virtually all the genetic material in humans, mice and other species have been determined, but only a small fraction appears to be needed for proper function (e.g., growth, development, cognition). Computational and experimental approaches developed in the PSU Center for Comparative Genomics and Bioinformatics are used to find these critical sequences. This project will continue support of this Center to (a) improve bioinformatic servers so that they facilitate translation of the data to improve understanding of human development and disease and (b) apply new sequencing technology to find functional sequences, such as the DNA sequences bound by particular proteins in the nucleus.
- Title: Biochemical Mechanisms that Contribute to HIV Transcriptional Latency  
Type of Research: Biomedical  
Focus: AIDS and Related Research  
Purpose: The goals of this project are to understand the biochemical mechanisms that permit HIV to establish latency. Latently infected cells do not actively express HIV and, because they are not sensitive to current anti-viral treatments, they are important reservoirs for virus late in AIDS or when treatments are interrupted. The project will use novel experimental systems to study how latency is established, including what proteins are associated with the HIV DNA. These studies will provide insights into ways to eradicate HIV from all infected cell populations.
- Title: Ceramide Liposomes for Combinatorial Drug Delivery of Chemotherapeutics and siRNA  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: The purpose of the project is to utilize nanotechnology to encapsulate pharmacological and molecular agents to synergistically treat cancers. The project will optimize and validate ceramide-incorporated nanoliposomes as a treatment modality for breast cancers, melanomas and leukemias. Our nanoliposomes (70-80nm in size) have the potential to target cancerous lesions without activating the body's defense mechanisms.
- Title: Mouse Metabolic Phenotyping Center for Diabetes  
Type of Research: Biomedical  
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
Purpose: Type 2 diabetes is characterized by altered metabolism and insulin resistance and leads to complications affecting organs including heart, kidney, and eyes. To determine the underlying mechanism, gene targeting techniques have been

applied to develop transgenic mouse models of diabetes and obesity. The goal of this project is to develop an interdepartmental investigator-initiated Penn State Mouse Metabolic Phenotyping Center (MMPC) that will perform an array of novel and sophisticated experiments using the state-of-the-art equipment for the purpose of investigating transgenic mice potentially useful for understanding diabetes and its complications. The MMPC consisting of multiple Cores will provide important insights into identifying the candidate genes of diabetes and potential therapeutic targets in the treatment of diabetes and its complications.

- Title: Center for Molecular and Cellular Neuroscience  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: Penn State is in the midst of a significant expansion in its Neuroscience research and education enterprise. This expansion includes the establishment of a Center for Molecular and Cellular Neuroscience. The different research groups of the Center share the use of molecular, genetic, electrophysiological, immunohistochemical and animal behavior techniques to investigate different aspects of synaptic transmission and animal models of neurological disorders. As part of this joint effort, a pilot research program will use gene targeting of GABA-A receptor subunit genes in mice. Our laboratory has developed an animal model of anxiety-driven depression that replicates the hallmarks of anxiety-driven depressive disorders including i) selective vulnerability in early life, ii) behavior indicative of anxiety-driven depression, iii) and an adult deficit in hippocampal neurogenesis. The project hypothesizes that these mice are suitable to further analyze the molecular and cellular substrate of anxiety-driven depression.
- Title: Hemispheric Lateralization for Unilateral Reaching Movements  
Type of Research: Biomedical and Clinical  
Focus: Neurosciences  
Purpose: The purpose of this project is to test a hypothesis that the left and right brain hemispheres are differentially specialized in controlling different features of movement. To test this hypothesis, we will examine the effect of unilateral brain damage on the performance of the ipsilesional arm of stroke patients with hemiparesis during simple reaching movements made toward multiple target directions, and also during adaptation to novel dynamic conditions. Findings from this project will lead to a better understanding of the functional deficits of the ipsilesional arm in stroke patients, which may be useful to improve rehabilitation techniques for stroke patients.
- Title: Assembly of Nipah Virus-Like Particles  
Type of Research: Biomedical  
Focus: Infectious Diseases and Microbiology  
Purpose: Nipah virus is a recently emerged, highly pathogenic paramyxovirus. Like H5N1 avian influenza virus, Nipah virus spreads poorly between humans, and the disease is spread to humans primarily via contact with infected livestock. In the case of Nipah virus, transmission results from contact with infected pigs, and the mortality rate in humans is about 40%. The purpose of the research project is to develop an experimental system by which Nipah virus biology can be more easily studied. An additional purpose of the research project is to develop a vaccine that can protect pig-handlers and their livestock from Nipah virus infection.
- Title: DNA Repair and Susceptibility to Tobacco-Induced Cancer  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: The long-term goal of this research is to identify high-risk subgroups that are susceptible to cancer and might benefit disproportionately from screening or chemoprevention interventions. We hypothesize that reduced DNA repair capacity increases susceptibility of tobacco-induced lung cancer. The current protocols that test DNA repair capacity of an individual are not adequate to determine whether an individual is at risk.

- Title: Human Retinal Pigment Epithelial Cell (hRPEC) Mediated Ex-vivo Gene Therapy in Parkinson's Disease  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: Parkinson's Disease (PD) is a devastating neurological illness that affects 1 million Americans and the health of a large population of senior citizens in Pennsylvania. hRPEC transplants are a novel and newly emerging technique that has enormous promise in helping PD patients. hRPEC transplants into the brain of parkinsonian animals and in 6 PD patients have shown significant amelioration of parkinsonism with minimal side effects. In this project we will test the mechanisms through which hRPEC mediates its effects, explore methods to enhance such beneficial effects and use hRPEC as a tool to "prevent" or "retard" the progression of PD. Results from these studies would further elucidate the biology of hRPEC transplants and its use in the PD patients and also in other major medical illnesses that could benefit from cell therapy, such as diabetes and macular degeneration.
- Title: Center of Excellence (COE) on Nutrigenomics: BOLD Effects on Established and Emerging Cardiovascular Disease Risk Factors  
Type of Research: Biomedical and Clinical  
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
Purpose: The field of nutrition, as well as many others, is moving in a direction where global analytical methodologies such as genomics, proteomics, and metabonomics are providing important new insights into health and disease processes. "Nutrigenomics" describes the use of cutting-edge molecular technologies to understand diet-gene interactions and human or animal health. The present project will provide continued support for the Center of Excellence in Nutrigenomics (CEN) at Penn State University with the ultimate goal of obtaining multi-investigator extramural support. As part of this effort, a pilot research program that fully utilizes the CEN's infrastructure and expertise will be initiated where the hypothesis being tested is that a heart-healthy diet, including lean beef (the BOLD diet), will reduce Cardiovascular Disease (CVD) risk.
- Title: Research Infrastructure for a Center for the Treatment, Prevention and Cure of Cancer  
Type of Research: Biomedical, Clinical and Health Services  
Focus: Research Infrastructure  
Purpose: To design and construct a new building for the Penn State Cancer Institute that will bring together patient care, 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. Formula funds from the 2003, 2004 and 2005 grants will be used for this project because the entire project cost is estimated to be ~\$100 million.
- Title: Longitudinal Examination of the Structural, Metabolic and Functional Brain Changes Associated with Moderate and Severe TBI  
Type of Research: Biomedical, Clinical and Health Services  
Focus: Neurosciences

Purpose: There are few investigations using advanced MRI techniques to examine both short-term and long-term consequences of moderate and severe traumatic brain injury (TBI). This project will examine recovery following brain trauma at several weeks after injury and several months after injury. At both time points, data will be collected about the patient's recovery as it is observed by physicians and through the use of advanced MRI techniques. By integrating information about changes in the brain (using MRI) with information about changes in patient behavior (as observed by physicians), recovery from TBI can be better characterized. With an improved understanding of brain changes after TBI, future medical treatments and interventions can be tested to treat not only changes that can be observed, but also those changes in the brain that are not immediately apparent to clinicians.

- Title: Center for Magnetic Resonance Imaging and Spectroscopy  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: Penn State University (PSU) has recently established a Center for Magnetic Resonance on the University Park campus. The purpose of the center is to develop new magnetic resonance measurement and imaging techniques which can be used by numerous animal researchers on campus. As part of this effort, a pilot research program will develop new hardware, software and imaging methods for very rapid imaging of cardiac function and structure in mouse models of disease. This will result in significant advances in the amount of information that is available from such studies, and will be applicable to many other studies at PSU.
- Title: Function of PAD4 and Histone Arg Methylation in Cell Differentiation and Cancer  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: The overall goal of this project is to understand how PAD4 activity and histone citrullination is regulated during transcription by other protein factors, how PAD4 complex efficiently regulates gene expression by incorporating multiple histone/chromatin modifying activities, and how PAD4 and histone Arg methylation regulates a fundamental cell differentiation process, the X chromosome inactivation in mouse female embryonic stem cells.
- Title: Identification of Ubiquitination Events in CL Leukemia as Targets for Therapy  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: Chronic Lymphocytic leukemia (CLL) is a common form of lymphoid cancer, accounting for approximately 25% of all leukemias. Although some effective treatments are available, the disease remains incurable with the occurrence of relapses and drug resistance. Thus, there is a need for novel therapies. The purpose of this project is to identify ubiquitin-mediated proteolysis events (UMPEs) in CLL cells, which, when interrupted, could be clinically beneficial. An UMPE is a signal that instructs the cell to degrade certain proteins that perhaps, may be considered targets for therapeutic intervention. An important objective of this project is to identify novel targets that could lead to the development of new drugs for CLL.
- Title: The Role of Osteopontin in the Alteration of Tight Junction Complex in Metastatic Colon Cancer  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: The objective of this project is to identify pathways through which the tight junction proteins and osteopontin intersect which affect the metastatic potential of colon cancer cells. Osteopontin is a protein in cancer cells that becomes more active as colon cancer progresses, possibly aiding in the spread to other organs, or

metastasis. One way it aids in metastasis is that it causes cells not to stick together. Since cells must release their attachment to the parent tumor if they are to metastasize, it is important to recognize the changes in proteins that normally exist between the cells that maintain the integrity of the tissue. The tight junction complex is located between epithelial cells and has a role in cell-cell adhesiveness and permeability. A study of the tight junction protein complex will help in the understanding of how cells become metastatic.

- Title: Adoptive Cellular Immunotherapy for EBV and CMV Disease  
Type of Research: Biomedical  
Focus: Immunology  
Purpose: The purpose of this study is to investigate new ways to present viral and tumor antigens to the immune system. We will study the use of B-lymphoblastoid cell lines (BLCL) derived from bone marrow donors to present viral proteins to immune cells (T cells) derived from that same donor. We will stimulate these donor T cells to become specific for cytomegalovirus and Epstein Barr virus (CMV and EBV), two common viruses that can cause complications following a stem cell transplant. In this study we will be infusing stem cell transplant patients with these virus specific T cells post-transplant for the prevention of viral reactivation.
- Title: What Makes Fatty Food "Irresistible"? Relating Food Structure and Eating Behavior  
Type of Research: Biomedical  
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
Purpose: - Heart disease and diabetes accounted for about 31.5% of all cause mortality in the United States in 2003. Dietary fat intake is a key factor thought to increase risk for both of these diseases. Yet in spite of repeated health messages to reduce fat in the diet, per capita fat intake has increased. Fat brings many qualities to food (e.g., texture, flavor, calories) and there must be some combination of these that stimulates consumption and makes fatty foods "irresistible". In this project fat emulsions will be created in which the flavor and caloric content vary. Rats will be used to identify which emulsions: (i) promote the largest intakes, (ii) promote binge-eating, and (iii) have rewarding qualities. If the "irresistible" properties that trigger excessive fat intake can be identified, then appealing low-fat foods can be developed that will help people stick to a healthy diet.

### **Philadelphia FIGHT (\$29,970)**

#### **Research Project:**

- Title: Evaluating 10-year Coronary Heart Disease (CHD) Risk and Risk Reduction Opportunities for HIV+ Patients  
Type of Research: Clinical  
Focus: AIDS and Related Research  
Purpose: The purpose of the study is to develop a greater understanding of the relationship between smoking and 10-year coronary heart disease (CHD) risk in HIV infected patients on boosted-protease inhibitor (PI) regimens. Research has tended to focus more generally on protease-inhibitor-induced increases in cholesterol in the context of evaluating overall risk for CHD. However, high rates of smoking in our practice suggest that smoking is an important risk factor for coronary heart disease. As part of this investigation, low, medium, and high-risk categories will be defined and the benefits of smoking cessation in each category will be examined.

### **Philadelphia Health Management Corporation (\$6,505)**

#### **Research Project:**

- Title: Adult Sex Offender Characteristics, Treatment and Recidivism

Type of Research: Health Services

Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: The purpose of this project is to identify characteristics of adult sexual offenders and degree of engagement in treatment associated with sexual reoffending. This project will examine the association between client characteristics and treatment engagement and recidivism (sexual offending) among adult sexual offenders referred to a Philadelphia outpatient treatment program between 2001-2004. Administrative data extracted from client treatment records and from Philadelphia's automated police parole and probation department database will be combined to create an aggregate file for data analysis. This file will not include any personal identifying information.

### **Pittsburgh Tissue Engineering Initiative (\$26,589)**

#### **Research Project:**

- Title: Cell-Seeded ECM Scaffolds for Esophageal Reconstruction  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: Extensive preliminary work has shown that biologic scaffolds composed of naturally occurring extracellular matrix (ECM) can induce constructive remodeling/healing of the esophagus with minimal or no scar tissue formation. A recent collaboration with a tissue engineering company in Tokyo, Japan, provides an opportunity to explore the combination of two promising technologies to solve the current biggest problem of esophageal surgery; specifically, the formation of intractable scar tissue with even the most minimally invasive procedures. The current surgical therapy of choice for esophageal disease is complete removal of the esophagus: a procedure associated with high morbidity and unacceptable 5-10% mortality. A successful regenerative medicine approach to esophageal reconstruction would fill a critical unmet medical need.

### **Temple University (\$2,034,995)**

#### **Research Projects:**

- Title: A Novel Approach for Targeting Drugs to Tumors  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology  
Purpose: Cancer patients are often treated with radiotherapy, chemotherapy or a combination of both. In most cases, using modern clinical radiotherapeutic techniques, radiation damage can be limited to the tumor and the immediate normal tissue surrounding it. Similarly, it would be ideal for a chemotherapeutic agent or a gene to be delivered only to the cancerous and not to healthy tissue. This project seeks to explore the feasibility of targeting drug carrying particles carrying molecules on their surfaces, which preferentially adhere to other molecules expressed on the vasculature of irradiated tumors. The immediate goal of this project is to provide proof that this therapeutic approach is feasible in animal models of cancer. The long-term goal is to develop a drug delivery scheme to selectively target drug/gene carriers to irradiated tumors in cancer patients.
- Title: A Novel Method for Obesity Control by Fat Cell Apoptosis  
Type of Research: Biomedical  
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
Purpose: The goal of this project is to control the growth and/or cause the death of fat cells in the body by targeted drug delivery. Because fat cells produce enzymes that signal the body to save energy or eat more, most overweight persons who engage in dieting are unable to maintain their weight loss, leading to yo-yo weight

behavior. The solution may be to cause the death of fat cells, resulting in a reduction of the production of these enzymes. A current procedure at Temple University, which shows promise in targeting the death of cancer cells, will be adapted to look for methods of killing fat cells. Animal models will be found for in-vivo tests of these methods.

- Title: Serotonin Neuromodulation of Feeding Behavior in Young, Adolescent, and Adult Rats  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The purpose of the present experiments is to compare the role of serotonin (5-HT), specifically 5-HT<sub>2C</sub> receptors, in the development and maintenance of overeating (hyperphagia) and weight gain in weanling, adolescent, and adult rats. It is hypothesized that serotonin compounds will differentially alter weight gain and hyperphagia across the lifespan. Furthermore, the rewarding effects of food in adulthood will be greater in rats that were repeatedly treated with antagonists that block serotonin receptors throughout the weanling and adolescent months.
- Title: The Role of Exposures during Gestation and Subsequent Child Health  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The goal of this investigation is to determine if cigarette smoking during pregnancy, confirmed by urinalysis results, is an independent risk factor for obesity in the offspring. If significant findings are reported, these data will provide additional evidence for fetal life as a critical period in the development of obesity. In addition, evidence of the role of maternal substance use during pregnancy as a risk factor for obesity in the offspring may be a strong motivator to stop smoking before or during pregnancy. This may lead to tremendous public health benefit, both for the children and the mother.
- Title: Electrophysiological Correlates of Action Perception and Imitation in Children  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: A current theory in psychology is that when someone observes an action carried out by someone else, particular brain areas in the observer are activated that are associated with planning or carrying out that same action. This "mirror neuron system" may enable people to understand another person's actions by mapping those actions onto their own stored representations of the same actions. Recent research has suggested that the activity of specific parts of this system may be dysfunctional in individuals with autism. The project aims to test this hypothesis in autistic children using electroencephalographic (EEG) techniques. If this hypothesis is confirmed, this may help to explain the neurobiological and psychological basis of certain aspects of the social deficits that are exhibited by many autistic children.
- Title: Electronic Research Administration Infrastructure Project: Phase II - Proposal Development and Laboratory Animal Management  
Type of Research: Biomedical, Clinical and Health Services  
Focus: Research Infrastructure  
Purpose: This project represents the second phase in establishing a new electronic research administration system to meet all new and emerging Federal requirements for electronic commerce in grants administration, as well as to improve the efficiency and functionality of the University's current research enterprise, including proposal development, award tracking, budgeting, compliance, and regulatory processes.
- Title: Interactions of AIF-1 with Signal Transduction Proteins  
Type of Research: Biomedical  
Focus: Cardiovascular Sciences

Purpose: Our laboratory has shown that AIF-1 is a protein not present in normal arteries, but is expressed at high levels in injured and atherosclerotic human arteries. Through experiments over the last several years, we have developed a hypothesis that AIF-1 is an inflammation-responsive signaling protein that plays a central role in regulation of VSMC activation and development of neointimal hyperplasia.

- Title: Role of Tyrosine Kinase Src in the Regulation of Bone Formation and Differentiation  
Type of Research: Biomedical  
Focus: Musculoskeletal, Oral and Skin Sciences  
Purpose: The non-receptor tyrosine kinase Src is one of the key regulators of cell proliferation, migration and differentiation. Deletion of Src gene in mice results in osteopetrotic phenotype (increase in bone mass) suggesting, that Src plays an important role in bone biology. The role of Src kinase is well characterized in osteoclastic bone resorption; however, there is increasing evidence that Src family kinases are also involved in osteoblast function. The proposed study will undertake a comprehensive analysis to evaluate the role of Src kinase in osteoblast function by determining Src kinase activity and expression during normal course of bone formation in mice and by evaluating the role of Src kinase activity in osteoblast differentiation.
- Title: Mechanism of E. coli Termination Factor Rho  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The broad goal of this work is improved understanding of a fundamental process in gene expression. Transcription termination protein Rho from the intestinal bacterium Escherichia coli is a homohexameric protein that releases newly synthesized RNA from transcription complexes. Rho acts through ATP-fueled, directional travel along nascent RNA, achieved by coordination of the RNA-dependent ATPase activity of Rho with RNA binding and release. The molecular mechanism of travel by Rho along RNA is not understood. The goal of this work is to identify critical amino acids in the ATP hydrolysis site of Rho and their roles in the catalytic mechanism. Analysis of selected mutant proteins will establish the identities of active site residues whose roles are suggested by comparison with other ATPases.
- Title: Interactions of Cocaine and Opiates on Addiction Relevant Behaviors in the Rat  
Type of Research: Biomedical  
Focus: Neurosciences  
Purpose: The abuse of cocaine and opiate combinations represents a growing subset of intravenous drug abusers. Results from published literature indicate that as many as 63% of intravenous drug abusers report self-administration of both cocaine and opiates such as heroin, morphine, or methadone. Co-administration of cocaine and heroin goes by the street name of 'speed-ball'. This project will investigate the interaction of cocaine and morphine on several addiction relevant behaviors in a rat model. The ability of prior exposure to cocaine to alter the behavioral response to morphine will be determined, as will the ability of prior exposure to morphine to alter a subsequent response to cocaine. In addition, co-administration of cocaine and morphine will be investigated in order to determine if co-exposure results in synergistic behavioral responses.
- Title: Role of Tiam1 in the Effects of c-Cbl on Cells Transformed by Abl Oncogene  
Type of Research: Biomedical  
Focus: Oncological Sciences

Purpose: The protooncogenic protein c-Cbl exerts a transformation-suppressing effect on cells transformed by Abl, a protein tyrosine kinase oncogene. Our recent studies have identified several other proteins involved in these effects of c-Cbl. One of these is Tiam1, a small GTPase critically involved in the regulation of cell spreading and migration. Neither the contribution of Tiam1 to the effects of c-Cbl nor the molecular basis of the involvement of Tiam1 in the effects of c-Cbl is clear. Given the importance of transformation-suppressing effects of c-Cbl for understanding cancer transformation and treatment, it is critical to decipher the molecular basis of the effects of Tiam1 on c-Cbl-dependent signaling in Abl-transformed cells. This study should advance our understanding of these effects and may suggest novel therapeutic approaches targeting Tiam1.

- Title: Chemokines and Chemokine Receptors in the CNS: A Neuro-Immune Link  
Type of Research: Biomedical

Focus: Neurosciences

Purpose: The purpose is to evaluate the role of chemokines and chemokine receptors in providing a link between the immune and nervous systems through modulating neurotransmitter and neuropeptide systems within the brain. This will provide a better understanding into the cellular mechanisms of chemokine effects in the brain and further our knowledge regarding neuroinflammatory conditions.

- Title: The Role of Cbl in Platelet Activation

Type of Research: Biomedical

Focus: Hematology

Purpose: The major problem being studied is the mechanism of platelet activation by collagen. Collagen activation of the circulating blood cell, the platelet, is a step in blood clotting. Inappropriate activation of platelets can lead to stroke and heart attack. We hypothesize that the protein regulator Cbl plays a key regulatory role in platelet activation by collagen. We will test this hypothesis by complementary biochemical, pharmacological, molecular genetics and cell biological approaches. We will assay activation of platelets using several biochemical and physiological tools. By fully understanding the pathways that lead to platelet activation, new therapies can be developed that will decrease the risks associated with unwanted platelet activation.

- Title: Characterization of Phosphatases Regulating Pocket Proteins

Type of Research: Biomedical

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

Purpose: The pocket protein family consisting of the retinoblastoma tumor suppressor protein (pRB), p107 and p130 negatively regulates the cell cycle progression, in a manner dependent on tight regulation of their phosphorylation status. We have found that a protein phosphatase 2A (PP2A) holoenzyme plays a role in modulating the phosphorylation status of pocket proteins by reversing the action of CDKs throughout the cell cycle. However, the variable B subunit(s) of the PP2A holoenzyme that targets pocket proteins is/are not known. The goal of this project is to identify and functionally characterize the pocket protein PP2A (pp-PP2A) holoenzymes or subsets of pp-PP2A holoenzyme that play a role in a dynamic equilibrium with CDKs in the control of the phosphorylation state of pocket proteins during the cell cycle.

- Title: Characterizing the Regenerative Potential of the Adult Human Heart

Type of Research: Biomedical

Focus: Cardiovascular Sciences

Purpose: Heart disease is the leading cause of mortality in the U.S. causing more than 700,000 deaths annually. The discovery that stem cells can become cardiac

myocytes has opened the possibility for cellular therapy as a treatment for heart failure. This project will assess the potential of human cardiac stem cells (CSCs) to differentiate into functional cardiomyocytes. Also, different sized myocytes will be studied to determine if they provide clues about cardiac regeneration in the adult heart. The goals of the project will involve 1) cloning and differentiating CSCs expressing the surface receptor c-kit from normal and failing myocardium; 2) molecular characterization of c-kit+ CSCs to assess their proliferative capacity; and 3) electrophysiologic assessment of CSCs and myocytes for specific ion currents, calcium cycling, and gap-junctional communication with other cells.

- Title: The Role of Implicit Smoking Attitudes and Motivations in Smoking Behavior  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: A number of models of drug use suggest that automatic or implicit processes play an important role in smoking and drug related behavior. The project will examine a model of implicit social cognition and behavior that combines implicit evaluative and implicit motivational information in the prediction of smoking behavior. Implicit liking of smoking is expected to predict cigarette use (i.e., to discriminate between smokers and non-smokers), while among smokers, implicit wanting to smoke is expected to predict the degree of cigarette addiction (i.e., to discriminate between light smokers and heavy smokers) and to predict cravings for smoking. These predicted findings have implications for both smoking prevention and smoking cessation programs.
- Title: Pilot Project to Examine Environmental Effects on Heritable Epigenetic Traits  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The purpose of the study is to determine whether assisted reproduction technology ("ART"; in vitro fertilization or intracytoplasmic sperm injection) increases the possibility of deregulated expression of genes involved in early development. We will examine a type of modification to DNA (DNA methylation) that is involved in regulating gene expression. We will examine DNA methylation over the whole genome by using a "whole genome gene chip." The incidence of abnormal DNA methylation will be compared between DNA samples from placentas of children conceived by ART and children conceived in the traditional fashion.
- Title: The Treatment of Child and Adolescent Obesity Using a Family Intervention Model  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The purpose of this preliminary pilot study is to measure the effect of a Temple family therapy intervention on the BMI of overweight or obese youth and to explore potential mechanisms of change. It is hypothesized that overweight and obese youth participating in this family therapy intervention will decrease their BMI more than a matched control receiving primary care physician intervention as usual.
- Title: Behavioral Mechanisms of Cue Exposure Treatment for Smoking Relapse Prevention: A Feasibility Trial with Bupropion  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: Nicotine dependence is characterized by multiple cessation attempts and high rates of relapse well after the withdrawal phase of a quit attempt. This study is designed not only to test the feasibility of an innovative application of behavioral strategies to lower smoking relapse risk, but also to improve our understanding of mechanisms of action of Bupropion (Zyban™) on factors known to relate to smoking

relapse. Data from this study would lead to a full scale treatment outcome study with potential to improve long-term smoking abstinence rates.

- Title: Role of Tissue Factor-Factor VIIa Signaling in Pulmonary Epithelial Cell Function  
Type of Research: Biomedical  
Focus: Respiratory Sciences  
Purpose: Tissue factor is a membrane-bound protein that is the principal initiator of blood coagulation. Recently, roles for this protein have been shown in physiologic and pathologic processes other than blood coagulation that include inflammation, cellular signaling, angiogenesis, and tumor metastasis. Tissue factor is expressed in normal lung tissue and its expression is increased in lung diseases associated with inflammation. The role of tissue factor in lung epithelial cell function is not known. The purpose of this project is to study the tissue factor signaling pathway in lung epithelial cells. The overall hypothesis for this study is that the tissue factor signaling pathway modulates lung epithelial cell function and mediates an inflammatory response.
- Title: Effects of Yoga Program on Postural Stability in the Elderly Female: A Pilot Study  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The main goal of this project is to explore effects of a classical Iyengar yoga exercise program on postural sway in elderly females. This is based on an idea that Iyengar Yoga -- by promoting stretching, strengthening, and improving overall awareness of posture and locomotion -- may improve postural sway and reduce the risk of falls in the elderly female.
- Title: Nutrition Education Outreach in Philadelphia Public Schools / Healthy Corner Store Initiative  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The proposed research will evaluate the efficacy of an intervention in urban corner stores, surrounding 10 Philadelphia elementary schools. Community-based, environmental manipulation of corner stores is an understudied area and represents the next step in understanding and improving the nutritional intake of school students to prevent obesity.

### **Thomas Jefferson University (\$4,262,076)**

#### **Research Projects:**

- Title: Regulation of the Immune Response to Colorectal Cancers  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: A subgroup of colorectal cancers caused by deficiencies of a DNA repair mechanism called DNA mismatch repair is characterized by dense lymphocytic inflammation surrounding invading tumor cells. The biological behavior of this subgroup of tumors is typically less aggressive than of the usual colorectal cancer. This project attempts to elucidate the molecular mechanism underlying the inflammatory response by analyzing different types of cells in and around the tumor. Up- and down-regulation of molecules involved in the inflammatory response at the transcription level will be studied using expression microarrays. Co-culture experiments will address the effect of the different types of cells on each other's growth. An understanding of the inflammatory host response could help to develop immune-modulatory treatment.

- Title: Characterization of FFR Function in Obesity, Diabetes Mellitus and Heart Diseases  
 Type of Research: Biomedical  
 Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
 Purpose: The ability to modulate lipid metabolism can have profound clinical implications in humans because a variety of human diseases are associated with abnormal lipid metabolism, such as obesity, diabetes mellitus, and cardiovascular diseases. FFR is a newly discovered gene that has been shown to impair lipid metabolism when it is mutated. The mechanisms involved in FFR mutation and its role in lipid metabolism are poorly understood. This project will use molecular, biochemical, and animal models to better understand the mechanisms that regulate lipid metabolism through manipulating FFR levels and functions. The long-term objective of this project is to provide novel therapeutic strategies for preventing or treating obesity, diabetes mellitus, and cardiovascular diseases.
- Title: Core Equipment for Physiological Research – A Research Infrastructure Facilities Renovation Project  
 Type of Research: Biomedical  
 Focus: Research Infrastructure  
 Purpose: The purpose of this project is to establish a core facility containing state-of-the-art analytical equipment to facilitate the research objectives of the Department of Physiology of Jefferson Medical College.
- Title: Characterization and Modulation of DNA Damage Response in Vertebrates (Zebrafish)  
 Type of Research: Biomedical  
 Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
 Purpose: This project focuses on novel approaches to define at the molecular level the response of cells to DNA damaging agents including radiation or chemotherapy, both commonly employed modes of cancer therapy. The proposed studies will benefit cancer patients by guiding efforts to maximize tumor control while minimizing damage to normal tissues associated with anti-cancer therapies.
- Title: The Role of Cyclin D1 and Androgen Receptor (AR) Mutations in Prostate Cancer  
 Type of Research: Biomedical  
 Focus: Oncological Sciences  
 Purpose: The goals of this project are to determine the mechanisms of escape from cyclin D1 repression by mutant ARs found in patients with prostate cancer. The possibilities are systematically examined, including regulation of AR transactivation, nuclear translocation and DNA binding. As DHZT-induced AR activity is linked to direct acetylation it is proposed that cyclin D1 may directly inhibit acetylation of wild type AR, but fail to inhibit the mutant ARs. This project aims to determine the role of cyclin D1 and androgen receptor (AR) mutations in prostate cancer cellular growth.
- Title: Caveolin-1 in Prostate Cancer: Translational Research Employing Mouse Models  
 Type of Research: Biomedical  
 Focus: Oncological Sciences  
 Purpose: The long-term objective of this project is to understand the role of caveolae and caveolin-1 in 1) advanced prostate cancer and 2) metastasis. Caveolae are “little caves” at the surface of cells that function both in vesicular trafficking and signal transduction. Caveolin-1 is the principal oligomeric structural protein of caveolae membranes that are found in most cell types.

- Title: Molecular Mechanisms that Govern Cell Differentiation of Breast Cancer  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: The project goal is to identify molecular mechanisms that govern cellular differentiation of human breast cancer. Loss of differentiation is required for progression from solitary tumors to metastases, and the mechanistic knowledge gained from this project will be used to develop new breast cancer therapies.

### **Treatment Research Institute (\$97,407)**

#### **Research Project:**

- Title: Feasibility of Behavioral Parent Training for Mothers in Drug Treatment  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: Drug and alcohol abuse and dependence are associated with parenting problems. As a result, mothers in drug treatment have unique needs requiring interventions for recovery from addiction combined with interventions for effective parenting. Thus, the importance of effective parenting interventions specifically tailored to these mothers is crucial. The purpose of this project is to first ask mothers in drug treatment to identify what help they need related to parenting and get their ideas about the best way to deliver this help. Behavioral parent training is known to be effective with other populations. Using the information from mothers in drug treatment, an existing behavioral parenting training intervention will be adapted and then tested with mothers receiving substance abuse treatment and their children.

### **University of Pennsylvania (\$9,229,640)**

#### **Research Projects:**

- Title: Effects of Nicotine Deprivation and COMT Genotype on Cognitive Performance  
Type of Research: Clinical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: Identify the neural and genetic substrates of cognitive deficits experienced during nicotine deprivation in dependent smokers.
- Title: Developing Effective Gene Silencing Agents for Human Malignancies  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: Advance the development of messenger RNA (mRNA) "silencing" molecules for the treatment of hematologic malignancies. When an mRNA is silenced the information it contains can no longer be used to instruct the cell's machinery to make the specific protein it encodes. If the proper mRNA targets are selected a cell's ability to grow, or survive, could be greatly compromised. Accordingly, this strategy should be very effective in the treatment of many different types of malignancies.
- Title: Genetic Determinants of Bone Loss and Ovarian Failure in Breast Cancer Survivors  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: Identify genetic variants in reproductive hormone and vitamin D pathways that are associated with premature ovarian failure and/or bone loss in survivors of breast cancer who received adjuvant chemotherapy. By identifying patients at risk for these late effects of therapy, interventions will be developed to prevent or ameliorate these potentially devastating long term effects of curative breast cancer therapies, decrease symptoms that adversely impact quality of life and prevent long-term skeletal and other complications that reduce function and productivity in this population.

- Title: Research Infrastructure to Establish a State-of-the-Art Tumor Tissue Bank  
 Type of Research: Biomedical  
 Focus: Research Infrastructure  
 Purpose: To establish a state-of-the-art Tumor Tissue Bank to provide immediate and long-term access to properly processed and maintained malignant and normal tissue for current and future cancer research. The infrastructure funds will allow renovation of dedicated space that will meet the requirements of the facility to properly collect, process, monitor, and store (long and short term) tissue samples and blood components.
- Title: Research Infrastructure: Developing a Stem Cell Research Facility at the Penn School of Veterinary Medicine  
 Type of Research: Biomedical  
 Focus: Research Infrastructure  
 Purpose: The Department of Animal Biology at the Penn School of Veterinary Medicine (SVM) wishes to build vigorous stem cell research as part of a proposed University wide Center for Stem Cell Biology and Regenerative Medicine. Our objective is to stimulate research on the treatment of neurodegenerative disease (Alzheimer's, Parkinson's), dilated cardiomyopathy, osteoporosis, diabetes, cancer, and hematopoietic and reproductive disorders by consolidating our existing strength in this area and by the recruitment of additional faculty. The purpose of this application is to develop research infrastructure by renovating about 4400 square feet of space into a modern research laboratory and core facility for stem cell research. Funds will be used for outfitting 4400 square feet of space in the Rosenthal Building of SVM with a modern research laboratory and stem cell core facility for cell derivation, maintenance and cryopreservation.
- Title: Outcomes of an Exercise Program for Older African American Women in a PACE Model  
 Type of Research: Health Services  
 Focus: Health of Populations, Behavioral and Biobehavioral Processes  
 Purpose: In this project we will learn whether a 16-week structured exercise program given three times a week for older African American women enrolled a program in Philadelphia called Living Independently For Elders, which provides services to avoid moving to a nursing home, will improve the participants' strength and endurance, help participants avoid becoming depressed, and improve their memory and thinking. We will also learn if blood pressure and weight, for those who are overweight, are lowered and sleep improves for those who participate. This will help support funding for more community-based exercise programs which improve the health and well being of older African American women.
- Title: Vivarium – Research Infrastructure (Construction Phase II)  
 Type of Research: Biomedical  
 Focus: Research Infrastructure  
 Purpose: 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 both 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 and construction.
- Title: Diagnostic Serology Laboratory for University Laboratory Animal Resources - Research Infrastructure  
 Type of Research: Biomedical

Focus: Research Infrastructure

Purpose: To improve turn-around time, optimize reliability, and optimize use of resources for routine and "outbreak" serologic testing which is essential to maintain the health of more than 70,000 experimental rodents used on our campus.

- Title: Computational Cell Biology of Human Diseases  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Many human diseases arise as a result of a dysfunction of cellular processes. For example, cancer is the result of dysregulation of cell growth and cell death. Similarly, certain neuropsychiatric diseases such as autism and schizophrenia can be traced to the loss of control of cell-to-cell communication processes in the brain. The purpose of this project is to develop new computational approaches and genome-scale measurement technologies to understand the molecular control of cell processes and how the loss of such control leads to human diseases.
- Title: Effects of Clinical Research Regulatory Auditing and Management on Compliance Findings  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: This study will assess the effect of applying a quality improvement oversight and management effort to clinical research studies in the School of Medicine and Health System at the University of Pennsylvania. The goal is to see if there are year-to-year changes/improvements in the types and severity of any regulatory compliance gaps noted on research regulatory audit.
- Title: Roles of ATR, H2AX and DNA-PKcs in Genome Maintenance and Tumor Suppression  
Type of Research: Biomedical  
Focus: Oncological Sciences  
Purpose: Evidence suggests that mutations of the proteins ATR, H2AX and, likely, DNA-PKcs are risk factors for development of human cancers. Understanding the functional interaction between ATR and DNA-PK/H2AX (a signaling pathway) and their role in suppressing chromosomal translocations and the development of tumors has broad significance in cancer etiology, prognosis and treatment. This project examines whether two distinct pathways in genome maintenance may be linked, and whether or not these distinct pathways act cooperatively in suppressing the mutations and genomic rearrangements that cause cancer.
- Title: A Propensity Score to Evaluate the Impact of Haplotypes on Cancer Incidence  
Type of Research: Biomedical  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: The primary purpose of this project is to develop statistical methods that will allow cancer researchers to better estimate the effect of genes on the risk of cancer incidence. Statistical models that investigate the association between single nucleotide polymorphisms (SNPs) or multiple adjacent SNPs (haplotypes) with cancer incidence will be developed. These methods will allow the comparison of cases and controls and the presence and absence of a particular genotype or haplotype after taking into account the differences in non-genetic patient characteristics that may influence their cancer risk. These methods will be applied to data from a large prostate cancer study where three genes (CYP3A4, CYP3A5, and CYP3A43) will be studied in 622 incident prostate cancer cases and 396 controls.
- Title: Anti-Her2/neu Polymersomes for Breast Cancer Diagnosis and Therapy  
Type of Research: Biomedical  
Focus: Bioengineering, Surgical Sciences and Technology

Purpose: Early detection of breast cancer is critical for successful treatment. Tumor detection by, non-radioactive, optical imaging is a new opportunity to detect and diagnose early breast cancers in a cost-effective manner. Her2/neu and EGF receptors are validated therapeutic targets for breast cancer therapy. Anti-Her2/neu peptidomimetics (AHNP) are small antibody-like molecules that bind to Her2/neu receptor and limit tumor growth in mice similar to the anti-Her2/neu monoclonal antibody, Herceptin®(Genentech, Inc). In this project, nanoparticles consisting of the small anti-Her2/neu antibody-like peptidomimetic (AHNP) conjugated to polymersomes with near-infrared emitting fluorescent (NIRF) probes will be used to visualize breast tumors in mice. In addition, the therapeutic efficacy of the anti-Her2/neu nanoparticle will be studied in mice.

- Title: Role of Daxx in Tumorigenesis  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The tumor suppressor p53 exerts its anti-proliferation function through the induction of growth arrest and apoptosis in response to various cellular stresses. Nearly 50% of human tumors have mutations in the p53 gene, and in the tumors with wild type p53, its function is often compromised through the alterations in its regulatory proteins or targets. The function of p53 is inhibited by Mdm2, and the inactivation of p53 can be accomplished by the overexpression of Mdm2 in tumors. We have recently found that a cellular protein known as Daxx is required for the function of Mdm2 and that Daxx may also be overexpressed in a substantial number of tumors. This project will investigate the possibility that Daxx is an oncogene through the inhibition of p53. This work will likely reveal an important regulatory mechanism of p53 and may identify a novel target for cancer therapy.
- Title: Oncogenic Kras and Cox2 in Pancreatic Tumorigenesis  
Type of Research: Biomedical  
Focus: Digestive Sciences  
Purpose: Pancreatic cancer is the most deadly malignancy in the western world, and the fourth most common cause of cancer-related mortality in the United States. The extreme mortality of pancreatic cancer is attributable to a lack of effective early detection methods and the poor efficacy of existing therapies for advanced disease. To investigate new approaches to pancreatic cancer detection and therapy, a mouse model of this malignancy was generated. Using this model system, Cox-2, an enzyme important in cell proliferation, was discovered to be present at high levels in early and advanced pancreatic cancer specimens. This project will determine whether Cox-2 is required for pancreatic cancer development by using genetic and pharmacological methods to inhibit Cox-2. If Cox-2 is important in the model of pancreatic cancer, a clinical trial will be proposed.
- Title: Lactic Acid as a Predictor for Severe Sepsis in the Hematologic Malignancies  
Type of Research: Clinical  
Focus: Oncological Sciences  
Purpose: To determine if serum lactic acid levels are predictive of severe sepsis in the hospitalized, hematologic malignancy patient population with a strong clinical suspicion of infection.
- Title: Identification of Barriers and Facilitators to Oncology Clinical Trials Recruitment  
Type of Research: Health Services  
Focus: Health of Populations, Behavioral and Biobehavioral Processes  
Purpose: It is well documented that only about 3-5% of new cancer patients participate in clinical trials and that almost 80% of adult studies suffer from

recruitment issues. Despite considerable time, effort and expense, the proportion of patients recruited is frequently small. This study will assess barriers and facilitators to clinical trials recruitment at the University of Pennsylvania within the context of patient-, clinician- and organizational-level factors. The data will provide benchmarks against which to evaluate the effectiveness of future interventions and evidence upon which to develop interventions for improvement of recruitment to oncology clinical trials.

## **University of Pittsburgh (\$9,229,640)**

### **Research Projects:**

- Title: Structural and Biochemical Characterization of Peptergents with Membrane Proteins  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Knowledge of membrane protein structure is critical for advancements in drug discovery. This project aims to develop methods to enhance three-dimensional membrane protein crystallization, which will ultimately increase the number of known membrane protein structures. Current methods employed for expression, solubilization, and crystallization of membrane proteins have been notably unpredictable and inconsistent for obtaining the diffraction-quality crystals needed for atomic resolution structural studies. Early results show that it may be possible to design crystal lattices with specific dimensions and symmetries; proteins imbedded in these lipid lattices will maintain their native configuration. These imbedded membrane proteins, which have been solubilized in a novel lipid-mimic, amphiphilic peptide detergent are called "peptergents."
- Title: Structure and Assembly of Icosahedral Virus Capsids  
Type of Research: Biomedical  
Focus: Infectious Diseases and Microbiology  
Purpose: The capsid is a complex protein shell that contains the genome of a given virus and interacts directly or indirectly with cells for infection purposes. It is also dynamic; it assembles into a precise geometry from many subunits, undergoes several transformations that modify the subunits' sizes and positions, packages the genome, and binds additional stabilizing proteins. Understanding these processes is important for identifying opportunities to interfere with the virus life cycle in a safe but effective manner. Structural analysis will focus on capsids of herpesvirus 3, or varicella zoster virus (VZV), which is responsible for chickenpox and shingles. In particular, the goal of this analysis will be to gain insight into differences with respect to other herpesviruses and capsids of a herpes-like bacteriophage, SPO1, that share important and unique morphological similarities.
- Title: DNA Repair Proteins and Response to Genotoxic Stress  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: The purpose of this project is to characterize the role of several DNA repair proteins 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: Monitoring Biologic Response to Gain Insights for Improved Cancer Therapy  
Type of Research: Biomedical

Focus: Oncological Sciences

Purpose: The primary goal of this study is to identify host proteins that either decrease or activate immune function. In Aim 1, new assays will be developed to identify damage-associated marker pattern molecules (DAMPs) released from melanoma tumor cells, and the effect of DAMPs on immune cell activation will be determined. Aim 2 will biochemically characterize microvesicles (MV) from patients with oral cancer, and the molecular mechanisms for MV-mediated immunosuppression will be explored. The goal of these experiments is to better characterize host-tumor responses; to identify new targets for improved therapy; to characterize important cellular proteins involved in tumor cell immune recognition; and to discover new biomarkers to improve cancer detection, diagnosis, and prognosis.

- Title: Mechanisms of Viral Induced Carcinogenesis

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 disease have declined in the United States since their peak in the late 1980s, specific populations remain at high risk for mortality from KS. These high-risk populations include solid organ transplant patients, who have a 40 to 60 percent mortality rate after contracting KS; the majority of survivors lose the transplant. While KS is currently well-controlled among AIDS patients, as 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: Research Infrastructure: Regional Biocontainment Laboratory

Type of Research: Biomedical

Focus: Research Infrastructure

Purpose: The Regional Biocontainment Laboratory (RBL) is a space in which researchers can work on developing vaccines and treatments for infectious agents, including both naturally occurring agents as well as those intended for use in acts of bioterrorism. The RBL will be housed on an entire floor of the new Biomedical Science Tower Three (BST3) at the University of Pittsburgh. Available to approved researchers within and outside of the University, the RBL will enable the expansion of vaccine research and augment existing hospital, state, and regional laboratories, thus providing rapid access to trained personnel, laboratory facilities, and specialized equipment in the event of a public health emergency. This research infrastructure project will include the construction and fitout required to complete the RBL facility.

### **Wills Eye Hospital \$8,591)**

#### **Research Project:**

Title: Wills Eye Hospital Corneal Dystrophy Registry Pilot Project

Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology

Purpose: This project will study the feasibility and appropriate design of a model disease registry for corneal dystrophies at Cornea Service of Wills Eye Hospital. The purpose of this project is to produce a reference document for the design and use of a successful registry, defining standards and best practices and create a model registry to test the use of clinical data for exploratory analysis. The overall goal of the registry is to benefit patients with corneal dystrophies and their families through improved diagnostics, treatments, and quality of life enhancements.

## **Wistar Institute (\$ 1,474,006)**

### **Research Projects:**

- Title: Studies on Tumor Progression Using Whole-body Imaging Technology  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Cancer remains the number two killer in the U.S. Cancer mortality is largely the result of metastatic disease, occurring when tumor cells escape the primary tumor mass, avoid immune surveillance and eventually adhere and grow in distant sites. The metastatic process is dependent upon the tumor microenvironment and changes in the genetic program of tumor cells. This project will employ whole-body imaging to identify new metastatic tumor lines, identify genes controlling tumor dormancy, study the role of host stromal cells in tumor metastasis and explore mechanisms required to enhance immunosurveillance of metastatic cells. Thus, emerging imaging technology will be combined with state-of-the-art molecular genetics to study tumor progression, regression and recurrence in real time in genetically defined host and tumor systems.
- Title: Genetic Models of Early Development and Cancer  
Type of Research: Biomedical  
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
Purpose: Mouse genetics and molecular biology will be used to investigate three major pathways that are thought to be important in the development and progression of tumors. The first involves a family of proteases important in the patterning of cells within the brain with the goal of understanding how changes in neural organization and patterning result in various neural pathologies. The second examines a signaling pathway controlling the proliferation of early hematopoiesis and lymphopoiesis with the goal of understanding how perturbations of this pathway can lead to the development of lymphomas and leukemias. The third pathway being investigated controls cell migration and adhesion. Studies concerning this pathway will focus on events leading to the aberrant expression of growth factor and adhesion receptors resulting in abnormal cell growth and movement.