Health Research Formula Grants - State Fiscal Year 2004-05

Thirty-nine organizations received health research formula grants for the state fiscal year 2004-05. Grants may support one or more research projects and research infrastructure projects. The following list of grants provides the name of the grantee, amount of the grant award, grant period, contact person 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 ($182,685) - 3 Projects
Grant Period: 1/1/2005 – 6/30/07
Contact:

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Albert Einstein Healthcare Network
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Research Projects:

- Title: Corazon Saludable: Healthy Heart
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to examine the impact of 2 independent classes (nutrition/cooking class and salsa aerobics class) on improving cardiovascular risk factors and psychosocial well-being in urban Latino women. These 16-week classes are taught by bi-lingual instructors and are focused on the issues and barriers faced by urban Latinas. Outcomes variables will include: blood pressure, body mass index, waist-to-hip ratio, depression, social support, and knowledge of heart disease. These variables will be assessed before the sessions begin and at the end of the 16-week session.
- Title: PTX1-Induced Apoptosis in Prostate Cancer Cells
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this research project is to study the mechanism of action of a novel tumor suppressor gene named PTX1 in the induction of cell death in prostate cancer cells. PTX1 has been shown to arrest the growth of human prostate cancer cells. Recently, it has been shown that it also induces cell death in these cells. This property may be utilized to kill and eliminate potential cancer cells. Therefore, it will be important to understand the mechanism of action of PTX1 in invoking the cell death processes. The results of the project will provide us a better understanding of the mechanism of action of this tumor suppressor, which will lead to design the means of intervention to combat advanced prostate cancer in the future.
- Title: An Exploratory Study of Amphetamine Effects on Auditory Processing in Aphasia
  Type of Research: Health Services
  Focus: Neurosciences
  Purpose: Attentional deficits that commonly co-occur with aphasia secondary to stroke have been cited as significant variables mediating progress in rehabilitation and the ability to return to work. Attentional defects that are neurodevelopmental in origin are often successfully treated with stimulant medications, such as

dextroamphetamines. To date, this form of treatment has not been systematically studied in adults with aphasia. We intend to conduct an exploratory study of stimulant medication effects on auditory attention and speech processing in subjects with aphasia. This study will assess the effects of a 20 mg dose of a dextroamphetamine medication (Adderall XR) on performance of tasks requiring attention to speech. Knowledge gained from this study may advance our understanding and rational use of medications to enhance recovery from aphasia.

Allegheny-Singer Research Institute ($209,634) - 2 Projects
Grant Period: 1/1/05 – 12/31/08
Contact:

Alison M. Sylvester, M.P.A.
Manager, Office of Grants and Contracts
Allegheny-Singer Research Institute
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Research Projects:

- Title: Cerebral Blood Flow Regulation in Stroke and Hypotension in Transgenic Mice
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this study is to further knowledge of stroke and hypotension using a physiologically controlled mice preparation and transgenic mice.
- Title: A Pilot Clinical Trial to Assess Percutaneous Segmental Mastectomy in Women with Malignant Tumors < 1.0 cm
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: A Pilot Clinical Trial to Assess Percutaneous Segmental Mastectomy in Women with Malignant Tumors < 1.0 cm - The purpose of this study is to determine if small invasive carcinomas of the breast can be completely and safely removed in a closed percutaneous fashion with a large core vacuum assisted electrosurgical biopsy device as would be expected from an open surgical mastectomy procedure.

American Aging Association ($1,706) - 1 Project
Grant Period: 1/1/05 – 6/30/05
Contact:

Robert G. Allen, Ph.D.
Research Director
American Aging Association
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(610) 565-3300

Research Project:

- Title: Effects of Ambient Oxygen Tension on the Growth and Proliferative Potential of WI-38 Cells Exhibiting Diminished p53 Expression
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: The p53 gene is activated in damaged cells and in precancer cells; if functioning normally it kills defective cells before they can become transformed into cancer cells. p53 is known to activate genes that increase the production of oxidants in cells. The purpose of the proposed study is to determine how the concentration of oxygen in tissue culture flasks influences the growth rate and the proliferative

lifespan (total number of divisions possible) in human fetal lung fibroblasts that have been treated to decrease their expression of p53. It is predicted that loss of p53 as well as low oxygen will increase growth rate and lifespan.

American Association for Cancer Research ($89,360) - 1 Project
Grant Period: 1/1/05 – 6/30/07
Contact:

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Chief Executive Officer
American Association for Cancer Research
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Research Project:

- Title: Functional Identification of Chromosome Arm 11q Genes Contributing to the Development of High-Risk Neuroblastoma
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this research is to identify one or more 11q genes involved in the development of the high-risk neuroblastoma phenotype that would lead to an improved risk-stratification system, uncover proteins and/or pathways that could serve as therapeutic targets, and may have implications to other human cancers.

American College of Radiology ($2,372,081) - 3 Projects
Grant Period: 1/1/05 - 12/31/08
Contact:

Harvey L. Neiman, M.D.
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American College of Radiology
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Research Projects:

- Title: Conducting Biomarker, Genomics, and Proteomics Correlative Research in the Radiation Therapy Oncology Group
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project will collect tissue and perform translational and microarray analyses of potentially prognostic biomarkers and evaluation of gene expression in multiple cancer disease sites including cervical cancer, lung cancer, head and neck cancer, bladder cancer, prostate cancer, rectal cancer, brain tumors, and cancer of the esophagus, pancreas, and anal canal. The purpose of this research is to identify and statistically correlate biomarker expression levels and genetic and proteomic profiles with patient outcomes and so advance the goal of individualized treatment for cancer patients based on genetic makeup.
- Title: Imaging Practice Patterns for Pulmonary Embolism in Pennsylvania
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The overall objective of this study is to identify current practice patterns in the diagnostic approach to the large number of patients with suspected acute

pulmonary embolism in the Commonwealth of Pennsylvania, and to determine the major factors responsible for local differences in the diagnostic work-up being used for this common and clinically important pulmonary vascular disorder.

- Title: Emerging Imaging Technology Clinical Trials in Pennsylvania
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: This proposal represents the development and completion of clinical research trials involving the use of emerging imaging technology at selected Pennsylvania accademic medical centers, aimed at advancing the role of imaging in the detection and/or treatment of disease. This research will leverage existing federally-funded clinical trials infrastructure operated by the American College of Radiology (ACR) in order to evaluate the role of Dynamic Contrast Enhanced MRI (DCE-MRI) in assessing the effectiveness of drug interventions targeted at tumor vascularity and 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.

Bryn Mawr College ($9,536) - 1 Project
Grant Period: 1/1/05 – 4/30/08
Contact:

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Research Project:

- Title: An Evaluation of Ready, Willing & Able-Philadelphia (RWA-P), Phase 2
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This new project extends work on the evaluation of Ready, Willing & Able-Philadelphia (RWA-P), a long-term, residential, work-based treatment program for substance-abusing homeless men. The previous phase of this project evaluated only the program's implementation. Now that RWA-P is fully implemented, this study focuses on rates of client retention, return-to-shelter, and predictors of these outcomes.

Carnegie Mellon University ($822,602) - 5 Projects
Grant Period: 1/1/05 - 12/31/07
Contact:

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Research Projects:

- Title: Comparative Systems Biology: Identifying the Core Set of Cell Cycle Genes

Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: One of the major causes of cancer is the loss in the control of the cell cycle system. Recent advances in high-throughput biological techniques provide a large-scale view of cellular activity. These techniques have been used to study the coordinated activity of genes during the cell cycle, and how the control of the cell cycle system is achieved in a number of organisms including healthy and cancer human cells, mouse, yeast, plants and bacteria. Here we propose to identify the core set of cycling genes by comparing the cell cycle expression programs in these various organisms. Genes that are identified to participate in the cell cycle in all, or most, of these organisms represent a conserved subset of the cell cycle genes and are likely to play an important role in the control of the cell cycle. These genes represent promising future targets for cancer research.

- Title: Engineering Cell Responses to 3D Solid-Phase Patterns of FGF-2
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Three dimensional (3D) immobilized ("solid-phase") patterns of FGF-2 in fibrin matirices, including concentration gradients of FGF-2 and controls with uniform distributions of FGF-2, will be synthesized with a novel ink jet printing process. The ability of gradients to direct cell migration, both in vitro and in vivo, will be investigated. The overall goal is to determine if this solid-phase, spatially directed growth factor delivery paradigm would be relevant for future therapy development in clinical tissue engineering application
- Title: Smoking as a Risk Factor: A Methodology for Assessing the Rupture Potential of Native Abdominal Aortic Aneurysms
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this project is to develop a methodology for non invasively assessing the rupture potential of abdominal aortic aneurysms (AAAs). We will combine clinical imaging with computational methods to reconstruct patient-specific AAA models and evaluate their risk of rupture by means of numerical prediction of wall stresses. The methodology is expected to greatly enhance the presurgical planning capabilities of vascular surgeries and endovascular therapies in the future management of cardiovascular diseases.
- Title: Nanostructured Bio-Ceramic and Bioceramic-Polymer Composite Gels for Non-Viral Gene Delivery
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The overall objective of this project is to engineer a safe and versatile plasmid gene delivery system for tissue engineering. Our goal is to demonstrate that the synthesized nanostructured bioceramic and bioceramic-polymer composite gels will enhance both the in vitro and in vivo transfection efficiency of plasmid DNA (pDNA) by increasing the uptake and expression of marker genes (Luciferase and/or GFP). The present project will only focus on in vitro assessment of transfection due to time and budget constraints.
- Title: Determining Human Hand Control Strategies for Natural Reanimation
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: 2.4 million Americans suffer from conditions limiting hand function while preserving cognition. Ideal treatment will require functional electrical stimulation of muscles to create the patient's intended movement. While there has been

considerable effort in determining the intended movement, the relationship between muscle activity and dynamic movements is largely unclear. The goal of this work is to determine neural control strategies of hand manipulation. Predicting these strategies given the intended movement will return natural hand movements to paralyzed individuals.

Children's Hospital of Philadelphia ($3,451,163) - 6 Projects
Grant Period: 1/1/05 - 12/31/08
Contact:

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Vice President, Research Administration
Children's Hospital of Philadelphia
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Research Projects:

- Title: Development of a Large Animal Preclinical Model for In Utero Hematopoietic Cell Transplantation
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: In Utero Hematopoietic Cell Transplantation (IUHCT) is a promising approach for the treatment of a large number of congenital hematologic disorders. We have been utilizing the murine model for investigation of the transplantation biology and immunology of IUHCT and have identified successful strategies for achievement of therapeutic levels of donor cell engraftment in allogeneic (immunologically mismatched) recipients. The successful translation of these murine studies to a large animal model is a necessary step prior to clinical application. We propose the development of a canine model of IUHCT to rigorously confirm the efficacy and safety of strategies developed in the mouse, prior to human application.
- Title: Generation of Mature Neural Cells from Fluorescently Labeled Totipotent and Multipotent Stem Cells
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: A very promising new approach to therapy of neurodegenerative diseases is the transplantation of totipotent embryonic stem cells (ES cells) or multipotent neural stem cells which are then capable of proliferation, migration to areas of degeneration, differentiation into neurons and glia, and seamless neural repair. Our goal is to move this promise closer to reality, by high throughput in vitro and in vivo studies employing mouse ES cells and multipotent neural progenitors, which we have genetically engineered to express fluorescent proteins.
- Title: Emergency Department Reliance as a Quality Indicator for Child Health
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Evidence suggests that when a considerable portion of children's care takes place in the emergency department (ED), medical care is less coordinated and overall health may suffer as a result. It is thus advantageous to study quality of care for children by focusing on the use of services in the ED; the measure referred to as ED reliance (the proportion of all outpatient health care visits occurring in an ED), developed at CHOP, offers a promising approach in this area. The primary goal of this project is to engage in a collaborative research effort centered on a new quality measure – specifically, emergency department reliance – that will be valid and broadly applicable to child health care.

- Title: Suppression of Translocations and Tumors by Histone H2AX
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: DNA double strand breaks (DSBs) are among the most hazardous cellular lesions and among the most difficult to repair. The proper repair of these lesions is critical for the suppression of cancers, such as lymphoma. We have recently demonstrated that histone H2AX, a protein around which DNA is packaged, is required for proper DSB repair and the suppression of translocations that cause lymphoma in mice. The purpose of these proposed experiments is to elucidate the molecular mechanisms through which H2AX promotes normal DSB repair and prevents the generation of translocations and tumors. This mouse model will generate a greater understanding of the molecular pathways that lead to cancers and will be ultimately be applicable in humans.
- Title: Redox Regulation of Protein-Protein Interactions
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Cells are frequently confronted with abrupt changes in their environment. An example is the first exposure of a newborn infant to oxygen in the lungs. To cope with such dramatic changes, existing proteins are modified chemically to alter their functional state. Recently, it has been shown that changes in the oxidation status of key amino acids in several important proteins occur in response to a variety of environmental changes. This pilot program will explore, using advanced proteomic and cell biological tools, the concept that such modifications function as "biological switches", controlling diverse cellular reactions. This concept has broad ramifications for pathologies of the immune system, the nervous system, pulmonary airways and many other tissues.
- Title: Expanding the Animal Research Program at CHOP
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: Through this research infrastructure project, the Children's Hospital of Philadelphia (CHOP) will renovate its Laboratory Animal Facility (LAF). The proposed renovations will allow the LAF to provide additional housing and procedural space to meet the growing needs of the research community at CHOP.

Children's Hospital of Pittsburgh ($700,355) - 1 Project
Grant Period: 1/1/05 - 12/31/07
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Research Project:

- Title: Inborn Errors of Metabolism Research Program: Laboratory Study of Acyl-CoA Dehydrogenases
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: This program will provide funding for investigation of genetic diseases leading to serious metabolic disturbances in children.

Donald Guthrie Foundation for Education and Research ($34,542) - 1 Project
Grant Period: 1/1/05 - 12/31/06
Contact:

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Medical Director.
Basic and Clinical Research
Guthrie Foundation Medical Research
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Research Project:

- Title: Genetic Basis for the Diverse Effects of Herceptin on Breast Cancer Cell Lines
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The expression of the gene Her2 in breast cancer has been associated with a poor prognosis. Treatment of patients with the monoclonal antibody Herceptin has been shown to dramatically increase survival times in some but not all Her2 expressing patients. Similar results have been obtained for Her2 breast cancer cell lines in vitro. In this study we will identify the mechanism of growth inhibition of susceptible cell lines. We will also identify the genetic differences between the susceptible, and those that are resistant.

Drexel University ($1,100,707) - 6 Projects
Grant Period: 1/1/05 – 6/30/07
Contact:

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Office of Research and Graduate Studies
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Research Projects:

- Title: Nanoencapsulated Live Influenza Virus Vaccine Development
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this research is to develop a vaccine against influenza virus that can be used in the event of a newly emerged pandemic of influenza virus. We are proposing to develop a novel live virus vaccine delivery technology which is safe, cost-effective and can be rapidly produced at the large amounts required to vaccinate the population in the event of a pandemic. If a pandemic strain were to emerge, it would take an estimated 6 months to develop a vaccine against the new strain with the existing current technology. The vaccine we are developing uses very low doses of virus and allows for large quantities of vaccine doses to be prepared very rapidly before the spread of a potential pandemic. The purpose of this proposal is to develop such a novel vaccine.
- Title: Validation of a Sleep Questionnaire in a General Pediatric Population and Application to Detect Abnormalities of Sleep in Specialized Pediatric Populations, Specifically, Children with Sickle Cell Disease

Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: The purpose of this study is to help develop a simple questionnaire about children's sleep habits and patterns from minorty populations that can be completed by parents and/or their children. We hope to use this information to assist us with identifying those children who may have possible sleep problems and finding out difference between them and children from a middle class caucasian population. We will also use this information to find out if sleep problems may be impacting their health and/or quality of their life and if the children might benefit from a referral to a sleep specialist to determine if treatment is necessary. We also hope to identify the extent of sleep problems in children with sickle cell disease.

- Title: Nanotechnology Meets Neuroscience: The Use of Microgrippers to Study the Molecular Motor Mechanics of Axonal Growth
  Type of Research: Health Services
  Focus: Neurosciences
  Purpose: The purpose of this project is to quantify the contributions of cellular proteins such as actin, tubulin, dynenin, and kinesin in maintaining nerve cell mechanical integrity. This research will use recently developed micro- and nanomanipulation technologies to mechanically load individual living nerve cells for the purpose of understanding growth and repair kinetics at the cellular, molecular, and protein level. This work has broad impacts in understanding how the peripheral and central nervous systems develop, maintain, and repair themselves.
- Title: One-Dimensional Nano Plasmonic Terahertz Sensors for Biomedical Imaging and Diagnostics
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: We will produce a class of nanoscaled, tunable detector devices for biomedical imaging technologies. These sensors will feature ultrasensitive detection of terahertz (THz) radiation based on the fabrication of one-dimensional (1D) clouds of strongly correlated and spatially confined electronic charge carriers within coaxial semiconducting nanowires. As sensor arrays, this technology permits biomedical imaging systems to operate in the time-domain, and at significantly reduced cost. These nanostructured devices with sub-picosecond response times will be important in a new generation of biosensing devices which combine imaging and vibrational spectroscopy for identification of biomolecular species within bone, teeth, fatty and thin slices of non-fatty tissue to aid in the early detection and diagnosis of heart disease.
- Title: Protein Interaction Networks in Human Disease
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: At the most fundamental level proper cellular function relies on specific protein interactions. With the completion of the human genome project we now have, if you will, a complete parts list of human cells. The challenge we are now faced with is determining how these parts interact and work together in normal cells and what interactions are compromised in human disease states. The purpose is to identify key protein interaction networks that underly normal human development as well as human disease.
- Title: Can Ultrasound Contrast Agents Operate Effectively in the Nano Range?
  Type of Research: Biomedical
  Focus: Oncological Sciences

Purpose: The purpose of this project is to develop an ultrasound (US) contrast agent (CA) that is injected in the patient just prior to a scan. The CA accumulates in the blood vessel bed of a solid tumor, and there produces a strong ultrasound image to aid in detection of smaller masses and to distinguish between benign and malignant masses. Ultrasound CA consist of stabilized gas bubbles. Malignant tumors develop aberrant, highly leaky blood vessels to bring nutrient to the rapidly dividing tumor cells, and a CA in the nanometer size range could be forced through these pores by the US pressure wave. However, reduction in CA size could compromise the imaging ability, although preliminary data indicate very promising results. The agent we are developing has a highly flexible wall which resonates in the US wave, enhancing the resulting image.

Duquesne University ($89,469) - 2 Projects
Grant Period: 1/1/05 - 12/31/06
Contact:

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Dean, Bayer School of Natural and Environmental Sciences
Duquesne University
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Research Projects:

- Title: Development and Evaluation of Surface Coatings to Resist Thrombosis for Cardiovascular Stents
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Cardiovascular stents are tube-like implants, constructed of stainless steel or nitinol, that are placed in the artery after angioplasty surgery to keep the artery open ensuring the free flow of blood to the heart. The insertion of the stent elicits a biological response that can lead to the encapsulation of the implant and subsequent reclosure of the artery. Additionally, platelets can adhere to the inner surface of the stent and blood clots can form. These complications can lead to additional surgeries or even death. This project aims to mitigate these complications by chemical modification of the implant surface to resist the adhesion of scar tissue and platelets to the stent.
- Title: Microbial Transformation of Nitrates Derived from Tobacco
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The nitrate found in tobacco products can be transformed by bacteria into nitrogen compounds that are more toxic to humans. The purpose of this project is to investigate the conversion of nitrate to nitrite by bacteria that normally reside in the digestive tract of humans. We will 1) develop a biochemical probe (antibody) to detect the specific enzyme (nitrate reductase) that these bacteria use and 2) study the enzyme that is specifically made by Camplyobacter species (bacteria known to inhabit the mouth and intestine) by producing it in Escherichia coli. The biochemical probe will be a useful tool for detecting nitrate-reducing bacteria while the production of the enzyme will allow us to study the range of nitrogen compounds it can transform.

Family Planning Council ($14,582) - 1 Project
Grant Period: 1/1/05 - 12/31/05
Contact:

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Associate Director, Research Department
Family Planning Council
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Philadelphia PA 19102
(215) 985-6769

Research Project:

- Title: Qualitative Evaluation of Advance Provision of Emergency Contraception
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to provide information and reccomendations on what aspects of clinical care and other factors are most likely to encourage advance emergency contraception (EC) distribution.

Fox Chase Cancer Center ($3,195,298) - 21 Projects
Grant Period: 1/1/05 - 12/31/06
Contact:

Robert C. Young, M.D.
President
Fox Chase Cancer Center
333 Cottman Avenue
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(215) 728-2781

Research Projects:

- Title: Developing Bispecific Single-Chain Fv Molecules to Alter Signal Transduction in Breast Cancer
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this project is to develop and test new agents that may directly lead to the death of cancer cells or increase the impact of chemotherapy or radiation therapy on cancer. These agents are engineered antibody-based molecules that bind to two targets on the surface of cancer cells that direct the cells to grow and ultimately make the cells resist current treatments.
- Title: Myeloperoxidase Gene (MPO) in Lung Cancer Protection
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: In Pennsylvania, more people die of lung cancer than of colon, breast, and prostate cancers combined. Lung cancer will strike over 15,500 Pennsylvanians this year with about 12,600 attributable deaths. Our long term goal is to confirm that a single copy of the A variant of the Myeloperoxidase gene (MPO) is associated with reduced risk of lung cancer. Ongoing studies have determined that the MPO has consistently shown protection in lung cancer confirming previous reports. We have screened 130 lung cancer cases and 130 controls to test our hypotheses that the -463 A MPO variant is protective in lung cancer. We need 100 case-control pairs to complete the study.
- Title: A Novel T Cell Vaccine Against HER2 Cancer Cells
  Type of Research: Biomedical and Clinical
  Focus: Immunology

Purpose: The purpose of this project is to establish a novel vaccination procedure that induces a strong and specific cellular immune response against cancer cells that over-express the protooncogene HER2. HER2 is a cellular growth receptor that is frequently over-expressed in cells of human cancers including breast, ovarian and colorectal carcinoma. Considering that colon cancer causes the second most deaths for cancer in the US and that every year more than 2,300 Pennsylvania women lose their lives to breast cancer, there is an urgent need for novel therapeutic procedures. The development of a potent vaccine targeting HER2 over-expressing cells would be highly desirable to be applied as a direct therapy or during follow-up treatments of surgery to prevent relapses of the disease.

- Title: Telomere Maintenance Mechanisms in Sarcoma
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: Maintenance of telomeres, structures that provide stability to chromosome ends, is essential for the continued cellular proliferation that is a hallmark of cancer. In most tumors, telomeric DNA is replicated and maintained by telomerase, a specialized enzyme. In contrast, sarcomas often utilize a telomerase-independent pathway for telomere maintenance, termed Alternative Lengthening of Telomeres (ALT). Thus, a substantial subset of sarcomas will be refractory to treatment with inhibitors targeted against telomerase. This project is focused on identification of novel targets that may inhibit the growth of telomerase-negative tumors.
- Title: Assessment of Clinical, Genetic and Behavioral Factors in Men at Increased Risk for Prostate Cancer
  Type of Research: Health Services and Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Numerous studies show that heredity exposure, ethnicity and behavioral factors increase the risk of prostate cancer. The purpose of this project is threefold: 1) to identify clinical factors that may predict the risk of being diagnosed with cancer in the FCCC High-risk Prostate Cancer Risk Assessment Program (PRAP); 2) to evaluate genetic markers that may predispose men at high-risk to develop prostate cancer; and 3) to assess behavioral factors that may influence decision making in men at hish risk for prostate cancer.
- Title: Restoration of Beta-Catenin Signaling by Perillyl Alcohol
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This study will determine the ability of perillyl alcohol (POH), a naturally occurring monoterpene, to modulate the signaling pathway of adenomatous polyposis coli (APC)/beta-catenin, the gatekeeper of colorectal cancer formation.
- Title: Enabling Clinical Research in Pennsylvania Community Hospitals - Phase II, An Expanded Approach
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: The purpose of this research project is to increase the number of cancer patients enrolled in clinical research studies at Pennsylvania community hosptials and physician medical oncology practices.
- Title: Novel Predictive Indicators in Breast Cancer and Preclinical Validation of Combined mTOR and BCL-2 Targeting
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: This project will determine whether an abnormal change (phosphorylation at Serine 167 of the estrogen receptor alpha = pERalpha) occurs at the target site needed for anti-estrogen therapies such as tamoxifen to work – thereby making

these tumors resistant to these therapies. Two new molecularly targeted drugs, thought to be lethal to breast cancer cells, will be tested with the hope that this particular combination might one day work to treat breast cancer patients.

- Title: Predicting the Effects of Disease-Associated Missense Mutations on Protein Stability and Interactions
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetic
  Purpose: Individuals inherit small variations in their genomes that lead to changes in the chemical makeup of proteins that are produced by the body. In most cases, these changes are harmless but in some cases, these changes lead to differences in protein structure and function. These changes are likely to affect proteins in two ways: by decreasing the stability of the folded structure of proteins and by altering the interactions of proteins with other molecules. The purpose of this project is to develop a database and software to predict the effects of protein mutations on stability and interactions that may deleteriously affect function leading to disease.
- Title: Cetuximab-Sensitizing EGFR Mutations in Colon Cancer
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: This study will improve the effectiveness of developing cancer therapies by treating patients based on the specific characteristics of their tumors. Recent insight into the study of cancers has found that certain changes, which tumor cells acquire and allow them to grow without regulation, can fortuitously serve as their Achilles' heel for cancer therapy. Clinical trials of new anticancer therapies often are considered less than effective if only a small portion of the patients experience clinical benefits. However, for those patients whose tumors respond favorably to treatment, the drug is effective and may even lead to the cure of their disease. Therefore, the goal is to determine why some patients with colorectal cancer respond and others do not to similar treatment regimens.
- Title: Loss of Vitamin A Metabolism in Ovarian Oncogenesis
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Ovarian cancer is the leading cause of death from gynecological cancer in Pennsylvania and in the United States. In year 2004, approximately 25,580 new cases were diagnosed with 16,090 women in the US and 700 in Pennsylvania dying from the disease. It is well known that nutritional factors are important in many types of cancer, although this is not established for ovarian cancer. The purpose of this study is to determine if vitamin A (retinol) protects women from getting ovarian cancer.
- Title: Histone Deacetylase Inhibitors for Cancer Therapy
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Genes (encoded by DNA) control the growth of cells in the human body. Some genes act as "cellular brakes" that keep cells from dividing too rapidly. If such genes are damaged (by DNA mutations), the cell may grow uncontrollably and become cancerous. Recently, it has been found that genes can lose activity (become "silent") without sustaining DNA mutations. Furthermore, it is believed that certain drugs ("histone deacetylase inhibitors") can reactivate such silent genes and restore controlled cellular growth in certain cancer cells. The proposed research is aimed at understanding how a specific drug, "SAHA", is able to restore normal cell growth.

- Title: Preclinical Cancer Models of Furin Inhibition
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Furin is an enzyme involved in activating other enzymes responsible for the destruction of tissue components that allow cancer cells to invade surrounding tissues. Furin also activates growth factors that regulate cancer cell division. The furin inhibitors, PDX and CMK, have been successfully used to decrease growth of certain cancer cells in culture. We will develop a technology to administer PDX as a drug and test its efficacy on cells and animals. A similar approach will be followed with the synthetic furin inhibitor CMK.
- Title: Synthetic Lethal Screening for Agents that Kill Methylthioadenosine Phosphorylase Deficient Tumor Cells
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to identify small drug molecules that can specifically kill methylthioadenosine phosphorylase deficient cells, but are not harmful to normal cells that have methylthioadenosine phosphorylase activity.
- Title: 4-Methylthio-2-Oxobutanoic Acid as a Chemopreventive Agent
  Type of Research: Biomedical and Health Services
  Focus: Oncological Sciences
  Purpose: 4-methylthio-2-oxobutanoic acid (MTOB) is a naturally occurring compound that can kill human cancer cells in cell culture. 4-methylthio-2-hydroxybutanoic acid (MTHB) is a related compound used as a supplement in poultry farming. Many human cancer cells have genetic alterations that prevent MTOB from being produced. The purpose of this project is to determine if oral administration of MTOB or MTHB could eliminate or reduce cancer incidence in a mouse model for colon cancer. These studies will establish the potential for using MTOB and MTHB as a chemopreventive agents, and if successful may lead to the initiation of human trials.
- Title: High-Throughput Screening and Pre-Clinical Evaluation of Allosteric, Chemical Inhibitors of Pak1 in Tumorigenesis
  Type of Research: Biomedical and Clinical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Pak1 is a protein whose activity is increased in breast and colon cancers and tumors derived from neurofibromatosis type II, a disease currently with no effective treatments. This project seeks to find new drug-like molecules that inhibit the protein Pak1 and slow the growth of cancer cells.
- Title: Expression Profiling of Metastatic Prostate Cancer
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Prostate cancer is the second most common cancer affecting American men and as such represents a major public health issue. Spread (metastasis) of prostate cancer is arguably one of the most significant events in the progression of disease; to date there is no cure for advanced prostate cancer. It is well known that prostate cancer tends to metastasize to bone, yet the reason for this is unknown. This work will identify proteins that are necessary for the spread of prostate cancer to bone and isolate antibody-based molecules that bind to those proteins. Such antibodies will serve as a starting point for the development of agents that will both block the ability of prostate cancer to spread to bone as well as treat already existing bone tumors.
- Title: Cyclin C-Cdk8 Function as a Tumor Suppressor

Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: This project focuses on how cells regulate a self-destruction mechanism termed programed cell death or apoptosis. The ability to selectively trigger this program can lead to targeted destruction of tumor cells. To achieve this goal, the underlying regulatory system controlling programmed cell death must be determined. Specifically, the role of a conserved protein called cyclin C in the control of apoptosis will be examined in tumor cells. If successful, the identification of cyclin C as a previously unknown regulator of programmed cell death may provide a new target for drug therapies that induce apopotosis in cancer cells.

- Title: Basis for Lymphoma Formation in Myr-Akt2 Transgenic Mice
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: Akt2 is a signaling protein that regulates the activity of many cellular processes by transferring phosphate molecules to protein targets. While Akt2 is frequently overexpressed and/or activated in human tumors, this is not sufficient to initiate tumor development and other cooperating events are required to drive tumor formation. Characterization of the lymphocyte tumors (i.e., lymphomas) arising in a mouse model that overexpresses activated Akt2 will enable identification of other cellular proteins that cooperate with Akt2 in tumor formation. We propose that the proteins that cooperate with Akt2 to generate lymphomas in our mouse model may serve as therapeutic targets useful for treating human lymphomas, as well as other Akt2 expressing human tumor types.
- Title: Diet and Breast Density in U.S. Chinese Women
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project will investigate whether acculturation is associated with mammographic density, a marker for breast cancer risk, in US Chinese women in the Philadelphia region, and to examine if the effect of acculturation is due to diet and other lifestyle factors.
- Title: Analysis of the Role of Werner Syndrome Protein in Cancer Cells
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: Werner syndrome is a genetic disorder associated with premature aging and proneness to cancer. The gene defective in Werner syndrome encodes a protein that plays an important role in facilitating genome duplication. Cancer cells often duplicate genome abnormally and, furthermore, many cancer chemotherapeutic drugs act by interfering with genome duplication. This project proposes to investigate the potential role of Werner syndrome protein in cancer development and therapy. The major objective is to determine if the Werner syndrome protein is over expressed in cancer cells and if disabling this protein renders cancer cells more sensitive to cancer drugs.

Geisinger Clinic - Weis Center for Research ($128,587) - 1 Project
Grant Period: 1/1/05 - 12/31/06
Contact:

David J. Carey, Ph.D.
Director and Senior Scientist
Weis Center for Research - Geisinger Clinic
100 North Academy Avenue
Danville, PA 17822-2600

(570) 271-6659

Research Project:

- Title: Molecular Medicine Initiative
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This project supports the application of cutting-edge laboratory technology to the study of human disease. These technologies, gene microarray analysis and proteomic profiling, can rapidly and with high sensitivity provide information on the molecular repertoire of biological samples. This information can provide important insights into disease risk or response to particular treatments. The funds will support the application of these technologies in two pilot projects: a study of medical treatments for abdominal aortic aneurysms using an animal model and a study of risk factors for liver disease in severely obese patients.

Lankenau Institute for Medical Research ($287,621) - 4 Projects
Grant Period: 1/1/05 - 12/31/05
Contact:

George C. Prendergast, Ph.D.
President and CEO
Lankenau Institute for Medical Research
100 Lancaster Avenue
Wynnewood, PA 19096
(610) 645-3475

Research Projects:

- Title: Age-Dependent Stromal Alterations that Promote Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to explore age-related "activation" of cells in the stromal compartment of the skin that are found underneath the outer epithelial cells. As we grow older, activation of stromal cells can stimulate the epithelial cells to develop into tumors.
- Title: Evaluating the Impact of Bin3 Loss on Promoting Tumor Immune Escape through Dysregulation of IDO
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Our work established an important cancer connection between the Bin1 gene, which is implicated in allaying cancer development, and the IDO gene, which can prevent the immune system from operating effectively. Bin3 is a gene that is closely related to Bin1 and our preliminary evidence suggests that it too may be able to exert regulatory control of IDO. The primary goal of this project is to investigate the hypothesis that dysregulation of IDO as a result of Bin3 loss might contribute to the ability of cancerous cells to form tumors in host animals that have a normal immune system but not in those in which the immune system is compromised. This information will contribute to our efforts for developing better chemotherapies that exploit this finding.
- Title: A Screening Method for Detecting Patients With Barrett's Esophagus
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: This project seeks to determine if the transepithelial leak of the disaccharide, sucrose, can be used as a safe, inexpensive screening method to detect those patients with chronic gastroesophageal reflux disease (GERD) who also harbor

Barrett's Esophagus. The latter metaplastic condition would present with symptoms indistinguishable from GERD, but would increase the risk of esophageal adenocarcinoma by 50-fold. This test is meant to essentially triage those GERD patients who would be most likely to have Barrett's esophagus, and therefore have the greatest need to undergo upper endoscopic examination, and not merely be treated with proton pump inhibitors.

- Title: Identifying a DNA-End Binding Protein and Its Role in Chromosome Repair and Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Throughout our life the cells in our bodies are continually exposed to damaging agents in sunlight, x-rays in the soil, chemicals in the water, and even oxygen in the air. The cell's chromosomes are especially important structures since they contain the genetic information necessary for normal cell function. To prevent this information from being altered, our cells have developed accurate repair mechanisms that restore the information in a damaged chromosome. Patients who have an inherited defect in one of these repair mechanisms often have extremely high rates of cancer, an abnormal immune system and neurological disorders. The purpose of this project is to identify a protein that specifically binds to the ends of broken DNA in the chromosome. We believe this protein plays an important role in repairing chromosome breaks and preventing diseases such as cancer.

Lehigh University ($131,021) - 1 Project
Grant Period: 1/1/05 - 12/30/05
Contact:

Stefan W. Maas, Ph.D.
Assistant Professor
Department of Biological Sciences
Lehigh University
111 Research Drive
Bethlehem, PA 18015
(610) 758-6276

Research Project:

- Title: Proteomics and Genomics Approaches to Study Complex Biological Processes in Health and Disease
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: In the human body, all biological components—from individual genes to entire organs—work together to promote normal development and sustain health. This amazing feat of biological teamwork is made possible by an array of intricate and interconnected pathways that facilitate communication among genes, molecules, and cells. The purpose of the proposed, highly collaborative project is to study how collections of genes or proteins work together to carry out complex biological processes with relevance for health and disease.

Lincoln University ($22,412) - 1 Project
Grant Period: 1/1/05 - 12/31/05
Contact:

Derrick J. Swinton, Ph.D.
Assistant Professor
Department of Chemistry

School of Natural Sciences and Mathematics
Lincoln University
Wright Hall, Room 223
1570 Baltimore Pike
Lincoln University, PA 19352
(610) 932-8300 Extension 3470

Research Project:

- Title: Quantitative Analysis of Nicotine and its Metabolites Using HPLC
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this research is to design a robust HPLC method that will allow the quantitative detection of low concentrations of nicotine and its metabolites. The technique employed, High Performance Liquid Chromatography (HPLC), is a separation technique commonly used in the pharmaceutical industry to characterize and quantitate drug ingredients and their degradation products. Statistical techniques will be employed to confirm the validity and accuracy of the HPLC technique's ability to measure low concentrations of nicotine and its metabolites.

MPC Corporation ($193,969) - 2 Projects
Grant Period: 1/1/05 - 12/31/06
Contact:

Mark Kamlet, Ph.D.
President
MPC Corporation
607 Warner Hall
Carnegie Mellon University
Pittsburgh, PA 15213
(412) 268-6684

Research Projects:

- Title: Cortical Contributions to Basal Ganglia Disorders
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: There is growing evidence that the brain's basal ganglia (BG) participate in multiple "loops" with many cortical areas, including regions of motor, premotor, prefrontal, cingulate, and posterior parietal cortex. These circuits could provide the BG with the neural substrate to influence motor, cognitive, emotional and perceptual domains of behavior. Likewise, abnormal activity in BG loops with the cerebral cortex could lead to a broad range of motor and neuropsychiatric symptoms like those associated with Parkinson's and Huntington's diseases, Tourette's syndrome, attention deficit hyperactivity disorder, obsessive-compulsive disorder, and depression. The overall goal of these experiments is to link the attention deficits associated with BG dysfunction to the cortical areas responsible for their expression.
- Title: Integrative Computational Modeling of the Primate Visual System
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Normal function of our visual system relies on the successful coordination and integration of information from many different visual areas of the brain. The purpose of this project is to understand the computational principles and neural mechanisms underlying the coordination of these areas in bringing about the development of object recognition capability in the visual system.

Madlyn and Leonard Abramson Center for Jewish Life ($39,055) - 1 Project
Grant Period: 1/1/05 - 12/31/05
Contact:

Nancy A. Hodgson, Ph.D., R.N.
Senior Research Scientist
Polisher Research Institute
Madlyn and Leonard Abramson Center for Jewish Life
1425 Horsham Road
North Wales, PA 19454-1320
(215) 371-1896

Research Project:

- Title: Perceived Barriers to Palliative Care Services in Pennsylvania Nursing Homes
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The aim of this project is to advance the understanding of palliative care delivery in the long term care setting by developing a theoretical model of the perceived barriers to the provision of these services. If we can understand how barriers to palliative care programs are perceived in nursing homes, we are in a better position to develop models of palliative care that most nearly address these barriers and reflect the needs of the participants involved in it.

Magee-Womens Health Corporation ($631,282) - 3 Projects
Grant Period: 1/1/05 - 12/31/05
Contact:

Robert G. France, M.H.A., M.B.A.
Administrative Director, Magee-Womens Research Institute
Magee-Womens Health Corporation
204 Craft Avenue
Pittsburgh, PA 15213
(412) 641-5268

Research Projects:

- Title: Endothelial Function and Insulin Resistance Following Pregnancy Complicated by Gestational Diabetes
  Type of Research: Clinical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Women with gestational diabetes (GDM), glucose intolerance first recognized during pregnancy, have a 50% lifetime risk of developing type 2 diabetes. The goals of this project are to investigate the relationships of endothelial function and insulin resistance, which play important roles in type 2 diabetes, in women diagnosed with GDM to better understand the potential long-term health implications for women.
- Title: Relaxin: A Vascular-Derived Relaxing and Compliance Factor
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Although traditionally associated with the function of reproductive organs in gestation, the protein hormone, relaxin (Rlx), which emanates from the ovary during pregnancy, is emerging as an important player in vascular function. We previously showed that circulating Rlx induces systemic and renal vasodilation, and increases arterial compliance. Here, we hypothesize that Rlx is also a vascular-derived, locally acting relaxing and compliance factor.
- Title: Producing Monkey Blastocysts after Somatic Cell Nuclear Transfer for Deriving Nonhuman Primate Embryonic Stem Cells

Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: Somatic cell nuclear transfer [SCNT] in nonhuman primates [NHP's] can answer basic and preclinical challenges in developmental biology such as fundamental discoveries on nuclear reprogramming mechanisms, developmental origins of primate embryos before and after implantation, the production of limited numbers of identical NHPs for biomedical research, and answer urgent stem cell biology problems, i.e. whether SCNT NHP embryonic stem cells are immune-matched with the donor NHP's.

Medical Diagnostic Research Foundation ($58,488) - 1 Project
Grant Period: 1/1/05 - 12/31/05
Contact:

Britton Chance, Ph.D., D.Sc.
President
Medical Diagnostic Research Foundation
39 Northwoods Road
Radnor, PA 19087-3759
(610) 688-8952

Research Project:

- Title: Women's Personal Health Care Hand-Held Breast Cancer Detector
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this project to construct a hand-held self-operated breast cancer scanner. This device will give an audible signal of the detection of cancer and its localization by indicating a low tone on one side of the suspected cancer and a high pitch (tone) on the other side. It is expected that this will afford a novel outreach to underserved and high-risk populations.

Monell Chemical Senses Center ($302,317) - 3 Projects
Grant Period: 1/1/05 - 12/31/05
Contact:

Gary K. Beauchamp, Ph.D.
Director and President
Monell Chemical Senses Center
3500 Market St.
Philadelphia, PA 19104-3308
(215) 898-8878

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 mensutral cycle. The information gleaned from this research may enable us to develop new and effective strategies to reduce smoking in women.
- Title: Food Craving in Abstinent Alcoholics
  Type of Research: Health Services
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences

Purpose: This research will lead to a better understanding of mechanisms for craving for food and for alcohol. It will help us to understand whether food and alcohol cravings have any similarities and whether alcoholism changes desire for food. This work should lead to improved methods for the treatment of alcoholism.

- Title: Research Infrastructure: Matching Funds for Development and Construction of the Molecular Genomics / Proteomics Facility
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: An adequate multi-user research facility for investigation of the early events in taste and smell is critical to expanding knowledge of the chemical senses. The continued development and construction of this Facility interfaces the scientists, construction engineers and the construction company to realize a well-organized and appropriately equipped laboratory. This is a continuation of the research infrastructure project funded in the 2003-04 grant.

National Disease Research Interchange ($59,884) - 1 Project
Grant Period: 1/1/05 - 12/31/05
Contact:

John T. Lonsdale, Ph.D.
Research Director
National Disease Research Interchange
1628 JFK Boulevard
Eight Penn Center
Philadelphia, PA 19103
(215) 557-7361 extension 271

Research Project:

- Title: Use of Genetic Association and Linkage Analysis to Examine Whether Any Identified Type 1 Diabetes-Related Loci Affect the Course of Retinopathy
  Type of Research: Health Services
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This study will focus on the use of both genetic association and linkage analysis to examine whether any of the already identified Type 1 diabetes-related loci affect the course of retinopathy. Single nucleotide polymorphism (SNP) analysis will be used to determine the association of already-identified Type 1 diabetes loci with retinopathy, comparing the "fast progressors" and "slow progressors" to retinopathy, with controls and with each other.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation ($1,856,715) - 1 Project
Grant Period: 1/1/05 - 12/31/07
Contact:

Donna Szczepankowski
Director of Finance and Sponsored Projects
NSABP Foundation, Inc.
Four Allegheny Center, 5th Floor
Pittsburgh, PA 15212
(412) 330-4610

Research Project:

- Title: Comprehensive Survey of Clinical Significance of Amplified Genes in Breast and Colon Cancer
  Type of Research: Biomedical and Clinical

Focus: Oncological Sciences
Purpose: Gene amplification has been shown to have a profound effect on gene expression levels in breast cancer cells as examplified by HER2 gene amplification. However, a comprehensive survey of amplified genes as to their correlation with clinical outcome has not been attempted due to technical barriers. We have established a robust proprietary method to rapidly develop fluorescence in situ hybridization probes for any known amplified genes. When combined with tissue microarrays constructed from the NSABP tissue bank, we are able to screen thousands of cases for all commonly amplified genes in breast and colon cancer. This project will allow us to identify gene amplifications that are prognostic, predictive, and/or can be new treatment targets in breast and colon cancer.

Oncology Nursing Society ($31,527) - 1 Project
Grant Period: 1/1/05 – 12/31/06
Contact:

Gail A. Mallory, Ph.D., R.N., C.N.A.A.
Director of Research
Oncology Nursing Society
125 Enterprise Drive
Pittsburgh, PA 15275-1214
(412) 859-6308

Research Project:

- Title: Symptom Clusters in Patients with Chronic Disease and Cancer as a Comorbidity
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: A symptom cluster is three or more concurrent symptoms that are related to and influence one another. As the number of cancer survivors increases, it is important to know how a past diagnosis of cancer influences the symptom clusters experienced with other chronic health problems. To date, no studies have documented symptom clusters in patients with chronic health problems who have cancer as a comorbid condition. The purpose of this exploratory, secondary analysis is to identify and compare symptom clusters in individuals with chronic health problems with cancer as a comorbidity versus individuals with chronic health problems who do not have cancer as a comorbidity.

Pennsylvania College of Optometry ($45,969) - 1 Project
Grant Period: 1/1/05 – 4/30/06
Contact:

Alexander M. Dizhoor, Ph.D.
Professor
Pennsylvania College of Optometry
8360 Old York Road
Elkins Park, PA 19027
(215) 780-1468

Research Project:

- Title: Molecular Mechanisms of Retinal Signaling and Degeneration
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Various types of congenital rod and cone degeneration, such as retinitis pigmentosa or Leber congenital amaurosis, result in blindness by eliminating photoreceptors, the light-sensitive neurons of the retina. The purpose of this pilot

study is to convert secondary neurons of the mouse retina to light-sensitive cells in order to mitigate the loss of light perception caused by congenital retinal photoreceptor degeneration. We will explore the possibility of imparting the light-sensitivity directly to the second-order retinal neurons in order to partially restore the ability of the retina to respond to light and to transmit the signal from the second-order to the third-order retinal neurons.

Pennsylvania State University ($8,225,637) - 19 Projects
Grant Period: 1/1/05 - 12/31/08
Contact:

Eva J. Pell, Ph.D.
Vice President for Research and Dean of the Graduate School
The Pennsylvania State University
110 Technology Center
University Park, PA 16802-7000
(814) 863-9580

Research Projects:

- Title: Center of Excellence in Nutrigenomics: Dietary Fatty Acids and Health: Characterization of the Omega-3 Fatty Acid Non-Responder Phenotype
  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 in the understanding of diet-gene interactions and human or animal health. The present project will provide continued support for 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, in the area of dietary fatty acids and human health, will be initiated.
- Title: Center of Competence in Neuroscience: The Function of Palmitoyltransferases in Modulating Neurotransmission
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Penn State has been very successful recently in hiring several promising young scientists working in the area of molecular neuroscience. Specifically, five different research groups whose laboratories are physically located in the Life Sciences Building at University Park are using molecular and electrophysiological techniques to investigate different aspects of synaptic transmission using analysis of diverse model organisms from flies (Drosophila) to mice. The present project will provide support for the development of this group into a Center of Competence in Neuroscience (CCN) at Penn State University. As part of this joint effort, the above pilot research program that fully utilizes the center infrastructure and expertise in the area of molecular neuroscience, will be initiated.
- Title: Center of Excellence in Metallobiochemistry
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The mission of the Center is to establish a program of research and education for the purpose of elucidating the mechanisms of iron and oxygen homeostasis in cells. Iron is an essential co-factor for biologically important

reactions, yet elevated levels are toxic. Consequently, iron homeostasis is highly regulated. Aerobic organisms utilize dioxygen as the terminal electron acceptor in the respiratory chain and have evolved sophisticated respiratory and cardiovascular systems to ensure adequate delivery of oxygen. Elevated levels of oxygen, however, are also toxic and result in oxidative damage to cells. The present project will enable support of pilot projects for the Center with the ultimate goal of obtaining extramural support for developing drug therapy against disease and defensive strategies against bioterrorism.

- Title: Receptor Tyrosine Kinases in AIDS-Associated Central Nervous System Diseases
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: Macrophages play a critical role in establishing HIV infection and its progression to AIDS. Infected macrophages produce inflammatory cytokines that compromise host-defenses against opportunistic pathogens contributing to AIDS-associated diseases such as Pneumocystis carinii pneumonia and HIV encephalopathy. How HIV disrupts normal signals that usually control inflammation is not understood. Specifically, this project will focus on a single protein RON, which is a critical regulator of inflammation. Studies will determine how RON impacts HIV replication, and mechanisms of RON action as well as how HIV targets this molecule.
- Title: Structural Biochemistry of Retrovirus Proteins
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: The long-term goal of this research is to benefit human health by developing ways to interfere with retrovirus replication. Retroviruses not only cause cancer in humans and animals, but also serve as a model system for studying genetic recombination. The objective of this project is to learn how certain critical retroviral proteins interact during the virus life cycle. The unifying central hypothesis is that products of the adjacent pol and gag genes interact during the virus life cycle and that these interactions orchestrate crucial events required for virus replication.
- Title: Penn State Program in Biomedical Devices and Functional Tissue Engineering
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: This project will continue and expand our efforts to establish a Program in Biomedical Devices and Functional Tissue Engineering at the Pennsylvania State University. The purpose of the Program will be to facilitate collaborative research among clinical scientists, basic scientists (cell and molecular biologists), and material scientists and engineers, at both the University Park and Hershey campuses of Penn State, in applications directed toward treatment of disease.
- Title: Center for Excellence in Diabetes: Intracellular Signaling Pathways and Diabetic Complications
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: New experimental techniques for interfering with the production of specific gene products are providing important new in- sights into disease processes such as diabetes mellitus and its life-threatening complications. To take advantage of these new techniques and to fully utilize the diverse expertise of the research community represented at Penn State University, we have formed a Center of Excellence in Diabetes. A pilot research project will be initiated with a goal of gaining greater insight into how alterations in intracellular signaling pathways contribute to the development of diabetic complications particularly diabetic retinopathy.
- Title: Genomic and Proteomic Evaluation of Organ Failure

Type of Research: Biomedical
Focus: Cardiovascular Sciences
Purpose: Our long-range goal is to understand the mechanisms involved in functional defects leading to chronic failure of the heart, lung, and kidney. The objective of this project is to identify potential mediators and targets involved in the dysfunction of distant organs during chronic heart and kidney failure. The central hypothesis of this project is that failure of either heart or kidney provokes a chronic inflammatory response which leads to the dysfunction and/or injury of distant organs.

- Title: Imaging Signal Transduction Pathways in Zebrafish
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This project proposes to establish a Center of Excellence for Zebrafish Functional Genomics. This Center will combine unique imaging capabilities of the Zebrafish Life-span Atlas project with new high-resolution 3D, DIC and fluorescence microscopy imaging on a motorized, inverted microscope. The core will provide embryo production, microinjection, and imaging, and personnel for production and expert interpretation of preliminary data for collaborative grant applications.
- 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: The purpose is 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: SP-A and SP-D Genetic Variants Associated with Preterm Birth
  Type of Research: Biomedical and Clinical
  Focus: Immunology
  Purpose: Parturition, whether term or preterm, involves inflammatory mediators. Activation of these mediators, initiated by a bacterial infection, is a recognized cause of pre-term labor. Marked individual differences in the pattern of inflammatory responses to bacterial challenges are largely genetically determined. Our overall hypothesis is that innate immune proteins SP-A and SP-D participate in parturition, and women who carry variant SP-A and SP-D alleles are at increased risk for spontaneous pre-term birth. The link between SP-A, SP-D and labor are the macrophages, known targets of these proteins. The hypothesis predicts that distinct alleles associate with distinct risks for pre-term birth, such as bacterial vaginosis. This information will form an initial link between inflammatory challenges interfering with placentation and with pre-term labor. These experiments form the basis of a future study of innate immune mechanisms involved in pre-term birth.
- Title: The Effects of Obesity on Human Reproduction
  Type of Research: Biomedical and Clinical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The purpose of this project is to identify adverse effects of obesity on female and male reproduction and examine the effects of weight loss strategies using a unique multidisciplinary team. We hypothesize adverse and unrecognized effects of

obesity on human reproduction, and marked improvements with weight loss. We hypothesize that aromatase activity in peripheral tissues, most commonly adipose tissue, contributes to reproductive dysfunction.

- Title: Role of Iron Transport Factor Genes in Iron Absorption: Functions of Hephaestin and Ferroportin-1 in Intestinal Iron Absorption
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The primary purpose of this project is to understand and define functions of hephaestin and ferroportin1 in the intestinal iron absorption processes.
- Title: Functional Elements in the Genomes of Human and Mouse
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Gene
  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 provide continued support of this Center with the goal of obtaining extramural support. In particular, this project will develop bioinformatic servers that facilitate interpreting the data to improve understanding of human development and disease, and it will implement new sequencing technology to find functional sequences.
- Title: Innovative Technology Research in Development of Therapeutics to Prevent Lung Metastasis
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Currently, no effective treatment exists to prevent metastasis of melanoma cells to the lungs or to inhibit metastatic tumors growing at this site. This is due, in part, to a lack of therapeutic approaches specifically designed to inhibit melanoma metastasis to the lung. The research proposed should lead to development of experimental therapeutic approaches to prevent colonization of the lungs by melanoma cells as well as growth and survival of these cells at this site. The proposed innovative approach will significantly establish an inter-disciplinary and cross-campus research partnership at Penn State.
- Title: Nanofibrous Materials for Cardiovascular Applications
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: This project seeks to investigate the biomedical utility of surfaces composed of very small polytetrafluoroethylene (Teflon or PTFE) fibers (nanofibers) formed in a novel "jet blowing" process. Of particular interest is the utility of such surfaces for cardiovascular applications. Current vascular grafts have a high failure rate. The failure modes of such grafts are strongly influenced by the the nature of the protein and cell adhesion to the graft material. Thus there is a need for new graft materials that will allow for selective adhesion of desired cell types. New types of jet blown PTFE surfaces that will allow for selective adhesion of desired cell types will be fabricated. These materials may prove useful for cardiovascular device applications.
- Title: Genomic and Evolutionary Influences on Inactive X Chromosome Expression
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: Genes carry the information specifying how we work and are encoded by DNA distributed over 23 pairs of chromosomes, but gene sequences account for only ~2% of all DNA. Neighboring DNA can influence gene expression, but is not completely understood. A special example of this is seen in the female sex chromosome (X) where most, but not all, genes on the second X must be silenced. Identification of sequences that regulate genes on the X is important for understanding normal development, for determining how a gene's expression is disrupted in disease and also may create new targets for genomic medicine. The purpose of this project is to identifty and directly test DNA sequences that regulate gene expression on the X chromosome.

- Title: Research Development in Diabetic Retinopathy
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this project is to develop preliminary data to explore the hypothesis that IR/IGF-1R function is important for normal retinal cell maintenance and survival, and result in grant applications to the National Eye Institute and Juvenile Diabetes Research Foundation for additional funding. Therefore, it is essential to better understand the molecular mechanism of the basal IR kinase activity and its alteration in diabetes. This work will combine fundamental principles of IR signaling that are well established in peripheral tissues with a neurobiological approach to diabetic retinopathy.
- Title: UDP Glucuronosyltransferase: Role in Cancer Susceptibility and Treatment
  Type of Research: Biomedical and Clinical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The project seeks to develop an interdisciplinary model for translational molecular studies examining the role of UDP-glucuronosyltransferases (UGTs) in cancer etiology and treatment. It is our hypothesis that functional genetic variations in genes that encode relevant UGTs play an important role in individual susceptibility to certain cancers, and an individual's response to specific treatments. This hypothesis will be tested in three projects: Project 1: to characterize important, common genetic variants for the UGT2B17 enzyme; Project 2: to examine the importance of this deletion in lung cancer risk; Project 3: to examine the role of genetic variations in UGTs in patient response to the chemotherapeutic agent, irinotecan.

Philadelphia FIGHT ($42,916) - 1 Project
Grant Period: 1/1/05 - 6/30/06
Contact:

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1233 Locust Street, 5th Floor
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Research Project:

- Title: Take Charge ADHERE
  Type of Research: Clinical
  Focus: AIDS and Related Research
  Purpose: This project will be conducted to determine effective interventions to encourage patients to adhere to their medication plan. We will assess specific adherence support interventions to determine their effectiveness. We will measure

the effectiveness of the interventions by monitoring and analyzing biological outcomes, including viral load and immune system function.

Philadelphia Health Management Corporation ($11,489) - 1 Project
Grant Period: 1/1/05 - 12/31/05
Contact:

Lisa Bond, Ph.D.
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260 South Broad Street, 18th Floor
Philadelphia, PA 19102
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Research Project:

- Title: Predictors of High-Risk Sexual Practices in a Multi-Ethnic Sample of Men Who Have Sex with Men
  Type of Research: Health Services
  Focus: AIDS and Related Research
  Purpose: This project will utilize existing data gathered from a multi-ethnic sample of 451 men who have sex with men in the Philadelphia region. The purpose of analyzing these data is to identify the factors that are associated with engaging in certain high risk sexual practices that are known to increase men's risk for HIV infection, including anonymous sex, sex trading, and engaging in unprotected sex. Factors that will be analyzed include sociodemographic characteristics such as age and socioeconomic status, sexual identity constructs such as sexual orientation identity (e.g., gay, bisexual, straight) and level of "outness", drug use history, beliefs and attitudes about HIV infection, perceived risk for HIV, sexual relationship variables, and HIV status.

Pittsburgh Tissue Engineering Initiative ($23,447) - 1 Project
Grant Period: 1/1/05 - 6/30/06
Contact:

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100 Technology Drive
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Research Project:

- Title: Vascularization of Tissue Engineered Lymphoid Structures
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: We will establish strategies and methods for the development of blood vascular channels and lymphatic vascular channels within a tissue engineered lymph node or lymphoid tissue equivalent (LTE). In brief, these studies will determine the appropriate conditions for cell culture work in which endothelial cells can be separated by their preferential differentiation toward a lymphatic type of endothelial cell versus a blood vessel type of endothelial cell. The overall objective or purpose of this work is to develop an artificial immune system suitable for the development of vaccines to protect at-risk populations against diseases that presently cause high morbidity and mortality such as HIV, small pox, and hemorrhagic fever. Importantly, a side benefit of this project is the development of international collaborative teams to address problems of global significance.

Swarthmore College ($7,697) - 1 Project
Grant Period: 1/1/05 – 12/15/05
Contact:

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Research Project:

- Title: Regulation of the E. coli Genotoxic Stress Response by the Universal Stress Protein
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This project will investigate the mechanisms by which one particular gene and the protein it encodes regulates the ability of Escherichia coli to repair DNA damage or mutation (i.e., genotoxicity). Experimental strategies include genetic analysis, biochemical characterization and assays of several aspects of bacterial physiology. Through such studies a better understanding of the power and limitations of DNA damage (mutation) repair will emerge. The research will be conducted undergraduate students who are supervised by an experienced microbiologist with expertise in bacterial stress response.

Temple University ($2,165,659) - 17 Projects
Grant Period: 1/1/05 - 12/31/08
Contact:

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Director, Sponsored Research Projects
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University Services Building, Suite 406
Temple University
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Philadelphia, PA 19122
(215) 204-7467

Research Projects:

- Title: Enhancing the Quality of Emotional Care for Multicultural Inpatients with Cancer or Heart Disease: Determining Emotional Support and Coping Needs
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to assess the emotional support and coping needs of multicultural inpatients with cancer or heart disease in a large, inner city hospital.
- Title: Assessment of the Primate Virus Herpesvirus Saimiri as a Human Pathogen
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Herpesvirus saimiri is a virus, which causes deadly cancers of white blood cells in monkeys and can, under experimental conditions, transform human while blood cells to cancerous growth. Therefore, this virus has a potential to be a human pathogen, but this potential cannot be revealed under normal conditions, because

there is no natural way to transmit this virus from the squirrel monkey, a natural host of this virus, to humans. However, the situation may change dramatically, if Herpesvirus saimiri is deliberately changed by targeted genetic modifications. This project is designed to assess the potential danger of Herpesvirus saimiri for humans by determining the ability of Herpesvirus saimiri-transformed human T cells to induce cancer in mice.

- Title: Pseudotyped HIV-1 as a Bioterrorist Weapon: Advancing Strategies for Rapid Prevention and Response Treatment
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: HIV-1 is a lethal pathogen spread via direct contact with infected blood or fluids. Current CD4-CXCR4/CCR5 receptor restriction of HIV-1 infection prevents environmental transmission; however, the severe impact of widespread infection can be observed in populations where transmission rates are high. Therefore, genetic engineering of the HIV-1 genome in such a way to overcome receptor restriction could represent a bioterrorism agent with catastrophic consequences. One example of this type of alteration is a pseudotyped HIV-1 with the envelope of respiratory syncytial virus (RSV) or vesicular stomatitis virus (VSV) which, with widespread cellular tropism, would facilitate respiratory transmission. HIV-1 pseudotyped with VSV may be particularly dangerous since the human population, unlike with RSV, does not have naturally occurring antibody titers to VSV. Prophylactic as well as therapeutic strategies against pseudotyped HIV-1 of this nature will be examined.
- Title: Creative, Culturally-Informed Approaches for Addressing Emotional and Physical Parameters, Quality of Life and Hospital Satisfaction of Multicultural Inpatients with Cancer or Heart Disease
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The study's purpose is to examine the effects of this approach on physical parameters, emotional parameters, quality of life and hospital satisfaction in multicultural inpatients with cancer or heart disease.
- Title: Examination of Inflammatory Markers and Endothelial Function in Patients with COPD
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This research will examine the influence of Chronic Obstructive Pulmonary Disease on the risk for cardiovascular disease. Common inflammatory mediators present in Chronic Obstructive Pulmonary Disease are also found in chronic cardiovascular disease and are known to cause endothelial cell injury, and to propagate the atherosclerotic process. In this study, patients with Chronic Obstructive Pulmonary Disease will be tested for inflammatory markers that are known to cause injury to blood vessels. These markers will be related to measures of endothelial dysfunction that initiate atherosclerosis.
- Title: Creative Approaches for Reducing Burnout in Medical Personnel
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to test a new and innovative approach to the treatment of physical/emotional exhaustion and lack of motivation stemming from prolonged stress on medical staff.
- Title: Electronic Research Administration Infrastructure Project: Phase I - Protocol Development and Tracking for Submissions to University Review Boards
  Type of Research: Biomedical, Health Services and Clinical
  Focus: Research Infrastructure

Purpose: Funds will be used to purchase computers and software for this project which represents the first 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: GPCR Signaling in the Genesis and Progression of Pancreatic Adenocarcinoma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Recent studies have indicated a role for G-protein coupled receptors (GPCR) in autocrine/paracrine loops that are involved in the genesis and progression of pancreatic cancer. In particular, there is evidence that indicates that the GPCR ligands gastrin and lysophosphatidic acid (LPA) are of biological importance to this progression, mediating proliferation and migration, respectively. However, the signal transduction mechanisms underlying these responses remain unclear. The goal of the project is to gain insight into the pathogenesis of this cancer so that novel diagnostic, prognostic, and/or therapeutic targets associated with the disease can be identified.
- Title: Novel Pathways Activated by Lysophosphatidic Acid (LPA) in Ovarian Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Ovarian cancer is the fourth leading cause of fatal cancer in women, and carries a 53% 5-year survival rate. Lysophosphatidic acid (LPA) is found at elevated concentrations in the serum and ascites of women with ovarian tumors, and is a crucial growth factor in the development of this disease. LPA activates multiple tumor-promoting pathways, but many details regarding its mechanism of action remain unclear. Therefore, we have begun a search for novel LPA-responsive signaling molecules that are amenable to targeted anticancer therapies. A mechanistic understanding of LPA signaling will provide crucial information for translation to the clinical management of ovarian carcinoma.
- Title: The Role of Connective Tissue Growth Factor (CTGF) as a Mediator of Cellular Condensation of Mesenchymal Stem Cells Induced by Transforming Growth Factor - Beta1 (TGF-β1)
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: The use of stem cells as a possible therapy to treat skeletal diseases holds much promise; however, a limited knowledge of skeletogenesis or how a stem cell differentiates into cartilage and bone prevents the implementation of stem cells for therapy. To realize the potential for stem cell therapy, we intend to study the initial stage of skeletogenesis in a process called cellular condensation. Cellular condensation is essential for bone and cartilage development and an understanding of how this process occurs will pave the way for stem cell therapy to treat skeletal diseases such as osteoporosis and osteoarthritis.
- Title: PBX Proteins and Neuronal Cell Differentiation
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Vitamin A plays a critical role in mammalian reproduction and embryonic development. A deficiency or excess of Vitamin A results in a variety of congenital malformations involving a number of different organ systems including the nervous system. PBX proteins function as partners with several other proteins called homeobox proteins to mediate gene expression during development. The level of PBX proteins are regulated by vitamin A. This work will focus on the understanding

of the role of PBX proteins in mediating the RA-dependent events involved in differentiation of neuronal cells.

- Title: Studies on the Immunopathogensis of Systemic Sclerosis
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Systemic Sclerosis (SSc) is a devastating autoimmune disease. Our studies will answer the important question of whether a particular kind of T cells, designated γδ TCR+, plays an important role in the pathogenesis of the disease. Another objective of these studies is to identify predictor molecular signatures using DNA microarrays and proteomics with the objective to distinguish between diffuse and limited SSc; to identify SSc patients at risk in developing progressive pulmonary fibrosis, acute renal crisis, and heart involvement; and to predict early overall survival. The current treatment modalities for patients with SSc leave much to be desired. New therapeutic approaches are urgently needed and their development requires better understanding of the pathogenesis of SSc. The studies proposed here will significantly improve this understanding.
- Title: Pro- and Anti-Apoptotic Proteins, Dihydrodiol Dehydrogenase and Cisplatin Resistance
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Increased expression of Dihydrodiol dehydrogenase 1 and 2 (DDH1 and DDH2) has been demonstrated to induce cisplatin/carboplatin resistance in human ovarian carcinoma cells. Furthermore, decreased generation of reactive oxygen species in the cisplatin resistant cells has been observed. Since reactive oxygen species have been shown to induce the expression of certain pro-apoptotic (apoptosis = programmed cell death) proteins and decrease the expression of certain anti-apoptotic proteins, this study aims to decipher the expression of these proteins and involvement in the DDH1- and DDH2-mediated cisplatin resistance phenotype in human ovarian cancer cells.
- Title: Mechanism of GEC1-Induced Enhancement in Expression of the Kappa Opioid Receptor In Vitro
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Activation of the kappa opioid receptor produces analgesia, dysphoria and water diuresis. It has been demonstrated recently that the kappa opioid receptor interacts with GEC1, an early estrogen-regulated gene and expression of GEC1 enhances the level of the receptor in vitro, which may in turn regulate signal transduction. The purpose of the project is to investigate the mechanisms underlying gec1-induced enhancement in kappa opioid receptor by examining the subcellular localization of GEC1, the portion and amino acid residues of GEC1 involved in the interaction with the kappa receptor and the step in the biosynthetic or recycling pathway involved in the GEC1 effect.
- Title: Perfluorochemical Augmented Intratracheal Delivery of Antioxidant Enzymes and Genes to Attenuate Oxidative Stress-Induced Lung and Respiratory Muscle Dysfunction
  Type of Research: Biomedical
  Focus: Respiratory Sciences
  Purpose: Despite improvement in clinical course and survival due to new treatment modalities, the incidence of acute and chronic lung disease (i.e. bronchopulmonary dysplasia - BPD) in preterm infants has not been substantially affected. BPD has been hypothesized to begin with acute inflammatory changes that occur secondary

to the use of large amounts of oxygen and the mechanical stress of mechanical ventilation. In this project, we will use breathable liquids (perfluorochemicals) to deliver antioxidant proteins and gene products to protect against lung and respiratory muscle injury due to high oxygen and to facilitate the maturation of the intrinsic anti-oxidant system in appropriate experimental models.

- Title: The Role of Osteoactivin (OA) on Mesenchymal Stem Cells Differentiation
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: The use of mesenchymal stem cells as a possible therapy to treat skeletal diseases holds much promise; however, there is limited knowledge of skeletogenesis or how a mesenchymal stem cell differentiates into cartilage and bone. Identification of new factors that regulate the differentiation of these cells will add more valuable information for the potential use of stem cell therapy. The purpose of this study is to examine the role of OA on mesenchymal stem cells differentiation; this will include its role of cell proliferation, migration and differentiation into osteoblasts. An understanding of how this process occurs will pave the way for stem cell therapy to treat skeletal diseases such as osteoporosis and osteoarthritis.
- Title: Emergency Preparedness in Pennsylvania's Retail Food Safety Industry: Assessing the Gaps
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to assess the current policies and procedures in place within the retail food industry in Pennsylvania to respond to an emergency food situation, such as a natural disaster or an intentional attack on the food supply. Beyond the written policies of each organization, the project is also intended to assess the level at which employees within each of these organizations are aware of such policies and the degree to which these policies are being implemented.

Thomas Jefferson University ($4,700,818) - 21 Projects
Grant Period: 1/1/05 - 12/31/08
Contact:

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Research Projects:

- Title: Completing the Construction for the Center for Translational Medicine
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: The purpose of this project is to complete the construction for the Center for Translational Medicine, a total space of 30,000 square feet. The construction of this space will emphasize collaboration not only within the Center for Translational Medicine and Department of Medicine but also throughout the university. The Center for Translational Medicine houses shared facilities and equipment as well as several cores to promote scientific collaboration across departments and disciplines. Nearly 18,000 square feet has already been completed. The current request will increase research capacity by adding nearly 12,000 square feet of office and lab space to the University. This space will allow the Department of Medicine to increase the number of new investigators who will bring new grants and new discoveries to the university.

- Title: Characterization of CXCR4 Function in Breast Cancer Metastasis
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The chemokine receptor CXCR4 has been implicated in a number of diseases including WHIM syndrome, HIV, and cancer. CXCR4 is overexpressed in breast, colon, and prostate cancer and contributes to the ability of these cancers to metastasize to tissues such as the bone, lung, and liver. The mechanisms involved in CXCR4 overexpression and its role in metastasis are poorly understood. In this project, molecular, biochemical, and cellular strategies will be used to better characterize the mechanisms that regulate CXCR4 expression and function in normal and cancer cells. It is hypothesized that this project will be able to reduce CXCR4 expression by manipulating the known regulatory pathways. The long-term objective of this work is to provide novel therapeutic strategies for preventing breast cancer metastasis.
- Title: Tumor Specific Alternatively Spliced Forms of Angiogenic Molecules as the Basis of Peptide Cancer Vaccines
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Using a vaccine is a potentially effective means to prevent or treat cancer. To be maximally effective, the vaccine should use proteins that are unique to cancer and not found in normal tissue. It is believed that tumor specific versions of proteins involved in cancer blood vessel formation will make ideal vaccines. To test this idea, a mouse model of prostate cancer called the TRAMP mouse will be used. The unique proteins involved in cancer blood vessel formation in these tumors will be identified, then chemically synthesize peptide replicas that will be used as the vaccines. These peptides will be used to vaccinate the TRAMP mice to see if this will prevent or alter the incidence of tumor formation.
- Title: Fused MR-Based Imaging Datasets Improving Surgical Outcomes and Providing Superior Response Classification System for Malignant Gliomas
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: To develop a clinically applicable methodology that fuses diffusion tensor imaging (DTI) and conventional structural MRI for the purpose of (1) quantitative assessment of white matter abnormalities resulting from tumor infiltration, and tracking and mapping the white matter tracts of the brain, which will broaden the surgical indications and improve the surgical outcomes; and (2) refining an MR-based response classification scheme for malignant gliomas the researcher previously published, which will provide more accurate and objective clinical response data upon which to judge the clinical efficacy of all future glioma protocols.
- Title: Preventing Colorectal Cancer Metastasis by Targeting Guanylyl Cyclase C
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Of patients with colorectal cancer, >50% die of metastatic disease. Metastasis is promoted by matrix metalloproteinases (MMPs), most notably MMP-9, which allows cancer cells to invade tissues. Guanylyl cyclase C (GCC), the receptor for bacterial diarrhea-producing toxins expressed by colorectal cancer cells, inhibits MMP-9-dependent metastasis. Thus, regulation of tumor cell MMP-9 by targeting GC-C may be a specific approach to inhibit metastatisis, without damaging normal tissues, in patients with colorectal cancer. The present studies will examine the impact of GCC on metastasis of colorectal tumor cells in mice. They will establish the

potential of targeting GCC to inhibit metastatic progression of colorectal cancer in patients.

- Title: Proteasomal Inhibition to Improve Therapeutic Outcomes in Hematologic Malignancies
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: Cancers of the blood are commonly treated with chemotherapeutic agents or blood stem cell transplantation (HSCT) from a donor. Unfortunately, graft-versus-host disease (GVHD) remains a single most problem that limits the application of HSCT. GVHD is caused by T-cells where the protein, NF-kappa B (NF-kB) is highly active. VELCADE decreases NF-kB activity. Based on our preclinical data, a clinical trial to determine the efficacy of VELCADE in patients with acute GVHD will be conducted. Effect of VELCADE on other T cell function will also be studied. Since NF-kB prevents cancer cells from succumbing to chemotherapy, enhancement of chemotherapy effect with VELCADE on blood cancer cells will also be tested.
- Title: Increasing Colon Cancer Screening in Primary Care
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: In an IRB-approved study, we are testing colorectal cancer (CRC) screening among average-risk adults randomly assigned to one of four study groups: a usual care Control Group (N=387), a Standard Intervention (SI) Group (N=387), a Tailored Print Intervention (TPI) Group (N=386), or a Tailored Print plus Call Intervention (TPCI) Group (N=386). The SI Group receives a standard CRC screening invitation letter, mailed screening kit, and a standard reminder letter. The TPI Group is sent a tailored screening invitation letter, a screening kit, and a tailored reminder letter. The TPCI Group is sent the same materials as the TPI Group and also receives a tailored telephone call from a nurse educator. In the proposed study, intervention impact among subgroups defined by gender and race/ethnicity will be assessed.
- Title: GI Stem Cell-Based Mechanisms in Tumor Initiation
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Since scientific evidence indicates that colonic stem cells are the cells of origin of colorectal cancer and that cancer stem cells drive tumor growth, finding drugs that target tumor stem cells should be more effective in preventing and treating colon cancer. This project will use a mouse model for colon cancer and study whether treating mice with the chemopreventive agent Sulindac leads to reduced number of tumor stem cells associated with a reduced number of tumors. These studies would support the view that if one is to effectively prevent or treat colon cancer, it is necessary to control or eliminate tumor stem cell populations.
- Title: Studies of Human Stem Cell Transplants in Non-Human Primate Models of Parkinson's Disease
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Over the last several decades, over 300 patients worldwide have received human fetal cell grafts to replace those neurons lost to Parkinson's Disease. Most individuals have experienced some, and many good, improvement in motor control and activities of daily living and with a surprisingly low complication rate. However, there are many practical and ethical concerns that limit this approach. If cell replacement therapy is to become a clinical reality, it is imperative that alternative sources are identified, like human stem cells, for transplantation. Therefore, the goal

of the present proposal is to test the utility of a number of newly available human stem cell lines in a non-human primate model of Parkinson's Disease.

- Title: Designing a New Generation of Implants: Tethering Bioactive Molecules to Prosthetic Devices
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Periprosthetic infection is a serious complication of orthopaedic surgery. The collaborative Jefferson research team, consisting of investigators in the Departments of Orthopaedic Surgery and Biochemistry & Molecular Pharmacology, as well as the Rothman Institute, proposes to develop a new generation of implants to combat this problem. Briefly, adhesion peptides and antibiotics will be tethered directly to the implant surface. The durably-tethered antibiotics will serve to prevent establishment of both early and late infections, while the grafted peptides will stimulate integration of the implant. Development of this technology, while directed at orthopaedics, is applicable to many other areas of clinical medicine and surgery.
- Title: Buprenorphine Treatment of Neonatal Abstinence Syndrome (NAS)
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: The purpose of this research project is to test a novel treatment of neonatal abstinence syndrome, a condition which now necessitates prolonged hospitalization (average of two months) and separation of infants from their mothers. The project proposes to apply basic principles opioid pharmacology to characterize the safety and pharmacokinetics of sublingually administered buprenorphine in neonates and to examine therapeutic efficacy in ameliorating the symptoms of NAS in these infants. Buprenorphine is a partial opioid agonist/antagonist that has a higher safety profile and allows for more rapid withdrawal than morphine. The project should be able to achieve desired blood levels with sublingual administration of buprenorphine, and that ultimately, infants with NAS treated with buprenorphine will be shown to have significantly shorter hospitalization times.
- Title: Prognostic Value of SNP Genotyping Using Tag-Arrays and Nanotechnology-Based Detection Strategies
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Many factors impede progress in understanding how tumor-specific genetic alterations influence cancer progression. Development of a rapid, sensitive method to characterize regions of DNA loss or gain would improve the diagnostic and prognostic abilities. The purpose is to develop a novel approach for monitoring changes in genomic DNA using gold nanoparticles, which will facilitate definition of cancer molecular signatures, and will be applied to detection of DNA gain or loss in patients with neuroblastoma (NB). Successful completion of this project will lay the foundation for realizing the relationship between genotype and disease presentation in a variety of cancers and lead to applications of this technology to other human diseases.
- Title: Impact of Chromatin Occupancy and Remodeling on Human Globin Gene Regulation
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: Disorders of the red blood cell (RBC) protein hemoglobin, including thalassemia and sickle cell disease (SCD), constitute the most common class of human genetic disorders, with ~180 million and 60 million carriers of beta thalassemia and SCD worldwide. Upregulation of fetal hemoglobin (Hb F) in adult life

offers a cure for these disorders and currently, a class of drugs called histone deacetylase inhibitors (HDI) are being examined for this purpose. HDI are known to have global effects on the transcriptome in other cell types, but their effects on the developing RBC are unknown. This project uses functional genomics including mRNA expression profiling and microarray-based protein:DNA interaction studies (ChIP:chips) to address regulation of the RBC transcriptome.

- Title: Functional and Anatomical Connectivity MRI Study of Brain Tumor Infiltration: Application to Neurosurgery
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of the project is to visualize, quantitatively assess, and characterize the effect of brain tumors on the involved brain functioning structures, aiming at establishing a readily applicable MRI methodology to assist neuro-surgeons to achieve the main goal of maximal tumor removal while minimizing postoperative neurological deficits.
- Title: Adiponectin: Cardioprotective Effects and Signaling Mechanisms
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Cardiovascular disease accounts for an overwhelming proportion of the morbidity and mortality in patients with obesity and type 2 diabetes mellitus. However, the pathogenic relationships among obesity/diabetes and its cardiovascular complications remain poorly understood. Adiponectin is a newly identified protein specifically secreted from adipocytes. It's plasma level has been found to be inversely related to the risk of ischemic heart disease. The proposed research will determine whether adiponectin can ameliorate cardiomyocyte death and cardiac dysfunction in an animal model of cardiac ischemia and reperfusion injury, and determine the intracellular signaling mechanisms by which adiponectin exerts its cardioprotective effects.
- Title: Modulation of T-cell Phenotype to Improve Clinical Outcome During Allogeneic Hematopoietic Stem Cell Transplantation
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Bone marrow transplant performed after chemotherapy in patients with cancer of blood can be curative, but side effects may prevent its success. This project is to determine whether donor T cells producing distinct sets of soluble proteins may be used to decrease these complications while maintaining the beneficial anti-tumor effects. For this, it will be determined whether different T cells can cure without causing side effects in mice with leukemia that undergo bone marrow transplant. Also, the possibility will be tested of generating T cells with similar functions from human transplant donors. This information would help design therapies to improve the success of blood stem cell transplantation.
- Title: Oncogenic Inflammation: Therapeutic Implications for Cancer and Autoimmunity
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this preclinical project is to determine the efficacy of farnesyl transferase inhibitors (FTIs) for treatment of thyroid autoimmune disease and thyroid cancer via inhibition of the fusion oncoprotein RET/PTC. Research has shown that the earliest stages of thyroid cancer and autoimmune disease feature the expression of RET/PTC that mediates its function through RAS and NFkB. In mouse models the researchers find that this activation causes both thyroid inflammation and cancer. Although cell signaling inhibitors have generally failed to cure advanced

cancers, they have shown clear efficacy in shutting off inflammatory pathways. The researchers anticipate a similar effect and, given the linkage to transformation, considerable impact on thyroid disease.

- Title: Detection and Targeting of Infected Cells with TCR-Like Antibodies
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Virus-infected cells express proteins that are distinct from normal host proteins. These proteins are chopped up inside the cell and their peptides, are picked up by specialized molecules, called MHC, which deliver the peptides to the cell surface and display them as peptide-MHC (pMHC) complexes recognizable by receptor (TCR) on T cells, a subset of normal lymphocytes. Thus, presence of `abnormal` pMHC complexes marks virus-infected cells as targets for T cells. The project will develop a soluble analog of TCR specific for abnormal pMHC to detect the infected cells. Being fused with a toxin, solube TCR analog will be used as a "poison pill" to target the infected cells helping to win the battle against the virus. The project also proposes to develop a general principal for designing pMHC-specific reagents.
- Title: The Role of Arrestin-2 in Platelet Signaling and Thrombosis
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: The project centers on understanding mechanisms of platelet activation. Blood platelets are critical mediators of thrombus formation, a process that is required to stop bleeding, but also leads to heart attacks and strokes. The purpose of the project is to determine whether arrestins, key regulators of G protein-coupled receptors, regulate platelet activity and thrombosis. All soluble platelet agonists bind to G protein-coupled receptors, yet the function of arrestins in platelets remains unexplored. The effect of the loss of arrestin activity on platelet signaling will be studied after virally expressing dominant negative arrestins in platelet precursors and the effect of arrestins on platelet function and thrombosis will be studied using arrestin-2 knock-out mice.
- Title: Diabetic Complications of Vein Graft Remodeling
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: This project seeks to elucidate the role of TNF in the process of diabetes associated vein–graft failure in a mouse model of vein graft disease that was recently developed in the applicant's laboratory. In Specific Aim 1, normal or diabetic mice will serve as recipients of normal vein grafts or grafts that lack expression of one of the two TNF receptors. Graft remodeling will be assessed four weeks post operation. In Aim 2 the usefulness of selective activation of the p75 TNF receptor-2 for treating vein graft disease will be evaluated in diabetic mice, either alone or in combination with a TNF-Inhibitor.
- Title: Accurate Measurement of Protein Expression and Phosphorylation Levels in Diabetic Organisms
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Protein molecules are responsible for the majority of activities that take place in a living cell at any given time. As such, there is great interest in increasing our understanding of how protein expression levels change as a function of disease state, age, therapeutic treatment, etc. Additionally, protein phosphorylation is known to be involved in many cell signaling and protein regulatory mechanisms, but is difficult to monitor on a large scale. The goals of these studies are to develop a

method to measure the absolute abundance of many proteins in a given sample simultaneously, as well as a method for measuring the phosphorylation states of proteins on a global scale. These new methodologies will be used to characterize differences in protein expression and phosphorylation between normal and diabetic mice.

Treatment Research Institute ($78,251) - 1 Project
Grant Period: 1/1/05 – 6/30/06
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Research Project:

- Title: Empirically-Supported Treatments among Pennsylvania Outpatient Substance Abuse Treatment Administrators
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to (a) provide descriptive information regarding the knowledge base and attitudes of administrators at licensed adult outpatient substance abuse treatment programs in Pennsylvania toward empirically-supported treatments (ESTs) vs. treatments with little empirical support, (b) investigate the impact of educational material on their knowledge, attitudes, and willingness to implement ESTs, (c) investigate the extent to which administrators' characteristics are associated with changes in their attitudes and willingness to implement ESTs, and (d) to understand perceived barriers to and methods for integrating ESTs into existing outpatient treatment programs.

University of Pennsylvania ($9,677,220) - 20 Projects
Grant Period: 1/1/05 - 12/31/08
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Research Projects:

- Title: Genomic Characterization of Human Papillomavirus (HPV)-Associated Squamous Cell Carcinomas of the Head and Neck
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The goal of this study is to determine how infection with HPV affects genome stability in squamous cell carcinoma of the head and neck (HNSCC), a cancer which is increasing in young individuals who lack exposure to tobacco and alcohol, possibly due to increased rates of HPV transmission. Genome-wide analysis of genetic changes that drive tumor development in HNSCC will identify molecular

targets necessary for novel therapeutic development and molecular data necessary to develop new classification schemes predictive of response to those treatments.

- Title: Cardiovascular Risk in Testicular Cancer Survivors
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this exploratory research is to examine cardiovascular risk factors in Testicular Cancer (TC) survivors. We will seek to identify the presence of atherosclerosis in TC survivors and examining the role of behavior in cardiovascular risk. The overall goal is to better understand cardiovascular risks in testicular cancer survivors and the value of behavioral risk reduction strategies for those TC survivors who have received chemotherapy that has the risk of causing cardiovascular problems.
- Title: Characterizing Nicotine Withdrawal: The Biobehavioral Effects of Bupropion
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This research will increase our understanding of nicotine withdrawal symptoms and develop treatments to reduce tobacco use. Specifically, the goal of this study is to examine effects of nicotine abstinence on laboratory measures of mood and to determine if there are genetic associations. By increasing our understanding of how nicotine abstinence affects mood, we can develop better treatments to help smokers quit.
- Title: Discovery and Testing of New Treatments for Leukemia
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this research project is to use modern molecular, cellular and chemical approaches to develop new drugs for the treatment of leukemia. This project will involve the use of leukemia-selected targeted therapies, which may also prove useful in the treatment of other cancers.
- Title: Statistical Methods for Measuring Cost-Effectiveness of Cancer Treatments
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Many cancer treatments offer limited benefit at considerable cost. The determination of the best therapies for insurers to cover involves a balancing of costs and effectiveness. It is straightforward to measure cost-effectiveness from randomized clinical trials, but less so from large observational studies and administrative databases. This project will develop statistical methods for handling this problem.
- Title: Construction of Life Sciences Building (Phase I Year 4) Research Infrastructure
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: The purpose of this infrastructure project is to provide state-of-the-art laboratory space for investigators in the Department of Biology in the School of Arts and Sciences, as well as space for the University-wide Penn Genomics Institute. This badly needed space will help Penn to attract the high-quality faculty, students, and postdoctoral researchers who are the essential critical success factor in modern research in the life sciences.
- Title: Vivarium – Research Infrastructure (Bid Award and Construction Phase I)
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: The purpose of vivarium construction is to breed and study specialized mice and other rodent models which have specific genes deleted, added or altered. Mouse models are our most important tool to study 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: Pilot Study of the Effectiveness of Process Standardization and Implementation of a Web-Based Study Operations Management Software Package (SiteMinder) in the Oversight and Management of Clinical Research
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The operational management of the myriad tasks and numerous regulatory requirements involved in the conduct of human research is complex, costly and generally burdened with inefficient practices. Many researchers tend to focus on specific elements of research regulations rather taking a systems approach to study management operations. This study will assess the effectiveness of a process improvement initiative aimed at instituting uniform process standards that are also automated to a degree with a study management software tool. The goal of the project is to introduce a working environment constructed to reduce administrative burden, allow easy access to key study tracking data, enhance study oversight, and permit easier cross coverage in the management of clinical research studies.
- Title: Stress and the Development of Obesity
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: This research project aims to identify the involvement of stress impact in central and peripheral pathways important for regulating food intake, metabolism, and adiposity, all key components in obesity development. We will develop genetic mouse models as valuable tools to allow the evaluation of the specific neurotransmitters involved in stress effects on the organism. Examination of stress systems in adipocytes in a cell culture model will provide a system easy to manipulate for determination of cell signals vital to fat storage, release, and development. Confirmation of these findings in vivo will be done using adipocyte targeted viral infection.
- Title: Calcium Signaling and Homeostasis in Healthy and Diseased Skeletal Muscle
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: An increase in calcium concentration is the key intracellular signal controlling the contraction of skeletal, cardiac, and smooth muscles. Abnormal calcium handling likely contributes to a number of skeletal muscle diseases including Duchenne Muscular Dystrophy (DMD). This project involves a multi-disciplinary study of the proteins and metabolites involved in calcium regulation in skeletal muscle, with the goal of obtaining a quantitative understanding of this biological system. A key aim is to discover which components of the calcium regulatory system are adapted to support the high speed of extra-ocular eye muscles (EOMs) and whether these adaptations are the reason that EOMs are spared in DMD.
- Title: System-Level Proteomic Characterization of Senescence Due to Telomere Shortening in S. Cerevisiae
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Genes are protected from damage by telomeres, which are structures that form the ends of chromosomes. Telomeres shorten and lose function with age, and this may contribute to cancer and several diseases of aging. To learn more about how telomeres guard against disease we will measure changes in proteins caused by

telomere dysfunction. Because we do not yet know which proteins are most important to measure, we will use new techniques that allow simultaneous examination of thousands of different proteins. We will also design and validate new computer methods for guiding the selection of proteins to be measured so that they provide the best representation of changes caused by telomere dysfunction in all proteins.

- Title: Measuring and Modeling the Complexity of Neuronal Synaptic Activity in Neurological Diseases
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The neuronal synapse is a basic building block of communication in the nervous system. Acting to either propagate or inhibit the transmission of an action potential, the synapse functions as a central modulator of electrical activity in neuronal networks. This project will develop a much more precise understanding of how individual 'synaptic units' – i.e., synaptoneurosomes isolated from neural tissue – respond and remodel after stimulations intended to mimic the activity that occurs in vivo. We will use a new imaging platform to measure the response in individual synaptic units, and will develop stochastic based models of the intracellular pathways that occur in the synaptic unit that will drive changes in the synaptic activity.
- Title: Genomic-Scale Analysis of Human Variation and Disease
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The overall goal of this project is to develop and expand new technologies for genomic-scale analysis, and to leverage these technologies to address important problems in human biology. This project will (1) build infrastructure for proteomics research, taking advantage of recent advances in mass spectrometry that enable more efficient analysis of protein sequences; (2) leverage computational resources for applied genomics, including the analysis of proteomics datasets for new gene discovery and quantitation, and the analysis of HIV interaction with the human genome; and (3) exploit technologies for gene expression analysis to explore the role of genetic variation in responses to toxic insults from the environment.
- Title: Optimization of Ex Vivo Expansion of Tumor-Infiltrating T Cells for Adoptive Therapy in Ovarian Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Effective immunotherapy for ovarian carcinoma can be developed using tumor-infiltrating lymphocytes. A new molecule has been discovered in my lab and is being used to devise a novel cell based culture system that permits, for the first time, the culture and expansion of activated tumor-killing lymphocytes. This novel culture system will allow the achievement of clinically relevant ex vivo expansion of tumor-specific T cells for adoptive therapy. This project proposes to identify subsets of patients with ovarian cancer that are eligible for adoptive T cell therapy. This investigation is highly translational and promises to develop a powerful therapeutic tool for the immunotherapy of ovarian cancer.
- Title: E3 Ubiquitin Ligase That Controls Phosphorylation-Dependent Ubiquitination of Cyclin D1
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Cyclin D1 is thought to contribute to the genesis of cancers of the breast, esophageous and head and neck wherein overexpression of cyclin D1 is documented

at a frequency approaching 50%. Identification of the enzymatic complexes (such as E3 ubiquitin ligases) that control the levels of cyclin D1 in normal and cancer cells should provide a framework necessary for the design of therapeutics that target the ensuing cyclin D1-dependent kinase. This project aims at identification and characterization of the unique SCF protein complex as a regulator of cyclin D1 stability, abundance and oncogenic activity.

- Title: Risk Barriers to Accrual of Patients to Breast Cancer Treatment Trials at the University of Pennsylvania Cancer Center
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This study will identify barriers to enrollment onto breast cancer treatment clinical trials at the Abramson Cancer Center. Using a survey design, 200 consecutive patients with breast cancer seeking treatment at the Rena Rowan Breast Clinic of the Abramson Cancer Center will be studied. The survey will evaluate clinical trial knowledge, beliefs, attitudes and willingness to participate in a clinical trial. Simultaneously, this study will determine the number of open breast cancer treatment trials open to each woman, their eligibility in these trials, and reasons for ineligibility. In addition, this study will allow us to explore how the barriers differ by race and ethnicity.
- Title: Real-Time Diffuse Optical Measurements for Dosimetry During Photofrin Pleural Photodynamic Therapy
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Photodynamic therapy (PDT) is a cancer treatment that uses laser light and a drug called a photosensitizer. The efficacy of PDT depends on sufficient concentrations of photons, photosensitizer and oxygen in cancer tissues. The purpose of this study is to develop a new way to simultaneously measure light intensity, photosensitizer concentration, blood oxygen, and blood flow in cancer tissues during PDT in order to improve treatment effect. These measurements will be related with treatment efficacy in patients with lung cancer with pleural spread to obtain PDT dose estimates.
- Title: Histone H3 Phosphorylation in Transcriptional Activation
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Our hereditary material, DNA, is wrapped around proteins called histones to form chromosomes. Specific chemical groups, or modifications, can be attached to histones to alter the function of the genes contained in the chromosomes. Modifications act to recruit other proteins that carry out the work that alters the cell's activity, specifically controlling whether genes are turned on or off. Histone phosphorylation plays a role in turning on genes and allowing cells to divide properly. Circumstances that lead to inappropriate control of these events are hallmarks of cancer cells. We propose to identify proteins that bind to phosphorylated histones to perform these functions. Characterization of the normal process will provide insight into how alterations lead to cancerous growth and will ultimately open new avenues for anti-cancer therapies.
- Title: Unravelling the Genomic Changes in Lung Cancer
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Lung cancer is a devastating disease that is difficult to manage with current surgical and medical approaches. In order to improve the treatment of patients with these cancers, we need a better understanding of the molecular

mechanisms that lead to these cancers in the first place. Array Comparative Genomic Hybridization (aCGH) and expression array analysis are state-of-the-art techniques to study the changes that accumulate in the DNA of cells that lead to changes in growth. By applying these techniques to the tissues obtained from cancer patients, we hope to determine what makes the normal cells become cancerous and what we can do to reverse or halt the process, once a patient has developed cancer.

- Title: Photodynamic Therapy Generated Anti-Tumor Vaccines in a Murine NSCLC Model
  Type of Research: Clinical
  Focus: Immunology
  Purpose: Surgery remains the cornerstone for treating early stage Non-Small Cell Lung Cancer (NSCLC) and provides a source for patient specific tumor antigens. Advances in the treatment of lung cancer, both early and late stage disease, must take the form of systemic adjuvant therapy. An autologous tumor derived immunotherapy could play a role in treating NSCLC. Photodynamic therapy (PDT), a light based cancer treatment, has been shown in animal models to induce tumor-specific systemic immune responses. Our group has published a phase II trial combining surgery and PDT for locally advanced NSCLC. This combination resulted in an increase in the median survival that was potentially due to PDT-induced immunostimulation. This project will test a PDT derived vaccine in an immunocompetent murine NSCLC model.

University of Pittsburgh ($9,677,220) - 6 Projects
Grant Period: 1/1/05 - 12/31/08
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Research Projects:

- Title: Small Molecule Protein-Protein Disruption Targeting Orphan Diseases
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Proteins are fundamentally important regulators of cellular and human functionality. They can interact with other proteins in a highly selective manner. Abnormal interactions can lead to diseases, including those often ignored by the commercial sector, namely the neglected and orphan diseases of which there are more than 6,000. This project seeks to develop and implement new biochemical and cellular techniques that will enable the discovery of useful small molecules or drugs that are capable of selectively disrupting protein-protein interactions that have an essential role in the development of neglected and orphan diseases.
- Title: Structural Biology of Neurodegeneration
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics

Purpose: The goal of this research is to elucidate pathways and structural features common to protein amyloidosis, a hallmark of neurodegenerative diseases, like Alzheimer's and Parkinson's diseases. Multiple biophysical techniques will be applied to characterize the dynamics, three-dimensional structures of intermediates, and architecture of fibrils for several amyloid forming proteins. These studies will provide the basis for understanding these pathological processes and interfering with them in a rational manner, with the ultimate goal of developing therapeutic interventions.

- Title: Viruses and Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Examination of the processes that viruses use to infect and transform cells has historically been one of the most fruitful means to understand the molecular biology of cancer. This study will expand upon existing results by developing molecular genetic approaches to screen for viruses associated with cancer, identifying host cell proteins involved in human papilloma virus-mediated chromosomal abnormalities, and characterizing a novel method of overcoming viral resistance to determine its potential use as a therapy for chronic viral infection.
- Title: Psychosocial Approaches in Cancer
  Type of Research: Biomedical and Clinical
  Focus: Oncological Sciences
  Purpose: The cancer diagnosis and ensuing treatments are highly threatening events that can change a person's life. The cancer patient is at risk not just for physical illness but also for the effects that psychological trauma brings to both interpersonal relationships and immune function. The purpose of this project is to continue to develop an understanding of the effect of psychological stress on physiological function and disease outcome. These studies will identify physiological and psychological approaches for measuring stress effects and will identify interventions helpful for mitigating some of these effects. This approach should be help define strategies to identify at-risk patients and their caregivers when early interventions are likely to have the most impact.
- Title: Regulatory Molecules and Cancer
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project involves basic research that focuses on understanding the differences between cancer cells and normal cells for improved cancer prevention and therapy development. In many cases, cancer results from the accumulation of changes that, at the cellular level, result in DNA, RNA, and protein abnormalities. This study includes an interdisciplinary project from the newly created University of Pittsburgh Cancer Institute Center for Environmental Oncology that will begin to identify and characterize toxic ingredients in personal care products used by young African-American women, who are at increased risk for breast cancer.
- Title: Research Infrastructure: Plum Borough Research Center Renovations
  Type of Research: Biomedical
  Focus: Research Infrastructure
  Purpose: The Plum Borough Research Center (PBRC) is a major University of Pittsburgh site for research using nonhuman primates. The PBRC consists of three separate research buildings located on a site 20 miles east of Pittsburgh: the Primate Research Laboratory, the Primate Rearing Facility, and the Animal Holding Facility. The major occupants of these buildings are the Center for Research in Reproductive Physiology, the Center for Neuroscience of Mental Disorders, and the research program on the neuro-endocrine basis for the manifestations of social stress in familial groups. The existing PBRC heating, ventilation, air conditioning, electrical,

and plumbing systems are inadequate to meet current needs. The goal of this project is to modernize the PBRC to meet current and future research needs.

Wills Eye Hospital ($9,146) - 1 Project
Grant Period: 1/1/05 - 12/31/05
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Research Project:

- Title: The Genotype-Phenotype Correlation of Retinoblastoma
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Retinoblastoma (RB) is the most common childhood cancer of the eye. Untreated it can be fatal, and it occurs, in both hereditary and nonhereditary forms. The purpose of this study is to identify associations between disease related manifestations (phenotype) and mutations in the gene (genotype) responsible for the eye tumor. Such phenotype profiling in relation to the gene mutation characteristics will useful in treatment and surveillance programs for RB.

Wistar Institute ($1,531,984) - 6 Projects
Grant Period: 1/1/05 - 6/30/06
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Research Projects:

- Title: The Role of Notch in Neoplastic Transformation
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to study the biochemical signaling mechanism of Notch and how it affects cancer growth, leading to identification of novel target genes important for diagnosis and/or treatment of human cancer.
- Title: Identification of Metastasis Promoting Genes by a Functional Genomics Approach
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this study is to establish in vivo cancer metastasis models and use a functional genomics approach to identify genes that are involved in metastasis process.
- Title: In Vivo Analysis of Histone Exchange and Genome Packaging Mechanisms
  Type of Research: Biomedical

Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The purpose of this study is to use a live cell imaging system to identify and study factors involved in histone exchange and genome packaging. Insight into the regulation of normal cellular growth by these processes will provide an understanding of how their deregulation results in disease progression, ultimately aiding in the development of diagnostic tools and therapeutics.

- Title: Evolutionary Strategies for Cancer Prevention
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Cells in tumors evolve by natural selection with different mutant cells competing for resources and spreading in the tumor. Current cancer therapy generally fails because some mutant cells in the tumor are resistant to the therapy. Thus, cancer therapy selects for resistance. However, almost all drug discovery is based on screening for drugs that kill cancer cells, rather than looking for drugs that prevent resistance. The purpose of this project is to demonstrate three strategies for testing drugs that alter the competition of cells in and around a tumor so as to delay or prevent the evolution of malignant cells that are resistant to chemotherapy. The long term goal is to introduce new drug screening strategies that may lead to entirely new classes of cancer drugs.
- Title: CD4 T Cell Responses to Influenza Infection
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Influenza virus infection (the "flu") is a potentially fatal respiratory disease. Despite the importance of the flu in both the industrialized world and in developing countries, the immune response against this infection is still incompletely understood. In particular, the role of CD4+ memory T cells (which constitute an important component of the immune system) has remained understudied. We will employ a newly developed mouse model to explore the activities and function of CD4+ memory T cells in immune responses against influenza virus. We also will study the mechanisms how CD4+ memory T cells develop during the course of infection. We expect that our experiments will increase the understanding of anti-influenza immunity, which may help to optimize vaccine strategies.
- Title: Molecular Mechanisms of CD8 T Cell Dysfunction During Chronic Infections and Cancer
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: T cells of the immune system have the capacity to recognize and eliminate viruses and tumors. Unfortunately, during many chronic viral infections, cancer T cells often lose their antiviral and antitumor functions. The purpose of this proposal is to investigate the mechanisms of this functional inactivation and to test strategies to restore antiviral and antitumor T cell immunity through rational immunotherapy.