Health Research Formula Grants – State Fiscal year 2012-13

Twenty-eight organizations received health research formula grants totaling $41,896,467 for the state fiscal year 2012-13. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2013 and have 1-48 months to complete the proposed research. The following list of grants provides the name of the grantee, amount of the grant award and a list of the research project(s) supported by the grant including the title of the research project, type of research (biomedical, clinical or health services research), focus of the project and purpose.

Albert Einstein Healthcare Network ($61,734)

Research Projects:
- **Title**: Electrophysiologic and Behavioral Evidence of Consciousness: a Longitudinal Analysis
  - **Type of Research**: Clinical
  - **Focus**: Neurosciences
  - **Purpose**: This project will collect preliminary longitudinal data from patients with Disorders of Consciousness (DoC) to investigate the reliability and sensitivity of electrophysiologic versus behavioral evidence of consciousness. The goal is to determine if evidence of covert command following exists in the absence of overt behavior and ultimately to generate sufficient data to power a larger, externally funded project on this topic. As an exploratory step, we will develop hypotheses about differences in both data domains using patients’ physical exam findings and brain neuroimaging.

- **Title**: Home-Based Mirror Therapy for Lower-Limb Rehabilitation Post-Stroke: A Pilot Study
  - **Type of Research**: Clinical
  - **Focus**: Neurosciences
  - **Purpose**: Hemiparesis, or a weakness on one side of the body, is a frequent and disabling consequence of stroke. Lower limb hemiparesis can greatly limit the ability to walk and participate in activities of daily living. Mirror therapy (MT) is a relatively new therapeutic intervention that has been shown to improve the range of motion, speed, and accuracy of hemiparetic upper limb movements. MT uses a mirror to create an illusion where movements of the unimpaired limb appear as if they are being made by the impaired limb. The purpose of this study is to investigate whether a home-based form of MT is an effective treatment for lower limb hemiparesis.

Allegheny-Singer Research Institute ($79,614)

Research Project:
- **Title**: Outdoor Air Pollution, Airway Inflammation and Acute Exacerbations of Asthma
  - **Type of Research**: Clinical
  - **Focus**: Respiratory Sciences
  - **Purpose**: The specific aim of this project is to characterize the relationship between levels of indoor and outdoor air pollution (OAP) and lower airway inflammation in patients with acute asthma exacerbations.

American College of Radiology ($1,851,408)

Research Projects:
- **Title**: Exploration of the RTOG Clinical Trial Database – Beyond Protocol-Specified Endpoints
  - **Type of Research**: Clinical
  - **Focus**: Oncological Sciences
Purpose: For over 40 years, the Radiation Therapy Oncology Group (RTOG) has been funded by the National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. Drawing upon this vast resource of demographic, treatment, and outcome data, the researchers will test new hypotheses and explore associations that were not defined in the treatment protocols for patients with gynecologic, head and neck, lung, and prostate cancers. These analyses may inform and/or lead to future protocols.

- **Title:** Community Learning of a Prediction Model for Treatment Outcome in Head and Neck Cancer Patients for Radiation Therapy Decision Support  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences

  Purpose: Personalized medicine for head and neck cancer (HNC) is promising, but validated decision support systems are needed to make the promise a reality. A decision support system relies on a model to predict treatment outcome (e.g., survival, quality of life, toxicity). Such a model can be developed through a machine learning process using a well-organized database and query system that is designed for a community based rapid learning approach. This project aims to build such a model to guide head and neck radiotherapy treatment, and includes the development of an IT infrastructure for the Radiation Therapy Oncology Group (RTOG) to manage and deploy the clinical trial data needed for machine learning and building predictive models for radiotherapy treatment of HNC.

- **Title:** Discovery of Plasma Biomarkers of Doxorubicin and Trastuzumab Induced Cardiotoxicity in Breast Cancer  
  **Type of Research:** Clinical  
  **Focus:** Cardiovascular Sciences

  Purpose: The overall objective of this proposal is to discover novel circulating biomarkers using powerful proteomic profiling methods to identify patients at increased risk for doxorubicin and trastuzumab-induced cardiotoxicity, before conventional decreases in ejection fraction or heart failure are evident. The key deliverables from this study are: 1) we will identify specific protein biomarkers indicative of early, subclinical cardiotoxicity; 2) we will gain insight into the mechanisms of doxorubicin and trastuzumab-induced cardiotoxicity, leading to new targeted therapies to prevent and treat this disease; and 3) we will build a multidisciplinary collaboration for the study of cardiotoxicity biomarkers that we can expand to other cancer therapies.

- **Title:** Novel Statistical Analysis and Evaluation Methods for Multiple Endpoints in Cancer Clinical Trials  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences

  Purpose: Clinical trials provide critical evidence necessary to advance clinical development in cancer research. The increasing number of promising new interventions mandates the improvement in clinical trial design and analysis, such that we can a) better understand disease progression; b) address clinical interests more quickly and efficiently; and c) conserve and optimize resources by terminating unpromising trials early. To address these needs, we propose a series of methodological projects aimed at addressing current questions in multiple endpoints in cancer clinical trials. These projects encompass a range of needs and challenges that apply broadly to cancer clinical trials and clinical research in general.
Carnegie Mellon University ($1,028,926)
Research Projects:

- **Title**: Mechanisms of Action Binding in Behavioral and Neural Systems
  **Type of Research**: Biomedical
  **Focus**: Neurosciences
  **Purpose**: Many skills involve learning to bind independent actions into a unified sequence of responses. Yet we don’t know precisely how the brain performs this type of skill learning, despite ample evidence that certain patient populations (e.g., Parkinson’s Disease, Huntington’s Disease, etc.) show impairments in procedural skill learning. We propose a research project centered on finding the mechanisms that regulate sequential action binding and determining how this takes place across weeks of training. Understanding how these skills are acquired can provide critical insights into optimal rehabilitation strategies for patients with pathological impairments in skill learning.

- **Title**: Development of Inhibitory Circuits in Visual Cortex
  **Type of Research**: Biomedical
  **Focus**: Neurosciences
  **Purpose**: GABAergic inhibition is a key mediator of experience-dependent plasticity during postnatal development, and accumulating evidence identifies aberrant GABAergic function in schizophrenia and autism. Strikingly, there are a number of disease-associated genes that, when mutated specifically in inhibitory neurons, reproduce behavioral deficits that characterize neurodevelopmental disease. However, it is not well understood how dysfunction of signaling pathways in inhibitory neurons impacts cortical function in-vivo. Using in-vivo multi-photon microscopy imaging of mice harboring targeted gene mutations we will evaluate the impact of specific genetic disturbances on circuit function and learning.

Children’s Hospital of Philadelphia ($3,713,220)
Research Projects:

- **Title**: Functional Follow up of Genetic Commonalities to Diabetes and Cancer
  **Type of Research**: Biomedical
  **Focus**: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  **Purpose**: Diabetes affects 18 million adults in the United States, with approximately 90 to 95 percent of those affected having type 2 diabetes (T2D). It is clear from recent genomic study observations that there is a specific yin and yang between cancer and T2D at the genetic level, including for the most strongly associated T2D gene, TCF7L2, which was discovered by the principal investigator. This has motivated us to systematically investigate the relationship between loci uncovered by genome wide association studies (GWAS) for cancer, leading us to ultimately carry out islet proliferation studies in mice, a mechanism which still largely eludes the diabetes research community but could revolutionize the way diabetes is treated if successful.

- **Title**: Comparative Effectiveness of Developmental-Behavioral Screening Instruments in Children
  **Type of Research**: Clinical
  **Focus**: Health of Populations, Behavioral and BioBehavioral Processes
  **Purpose**: Evidence of the advantages of using the Survey of Wellbeing of Young Children (SWYC) to screen for childhood behavioral-developmental disorders is accumulating. Findings are limited to English speaking, well-educated, predominantly U.S.-born families. Whether the findings are generalizable to other children from two groups rapidly growing in size in Pennsylvania-- Hispanic families lacking English language proficiency and African-born Black women-- is unclear. Consequently we
propose to recruit a sample of Hispanic children and a sample of children of African-born Black women and conduct a systematic comparison study of the SWYC to other instruments widely used to identify behavioral-developmental disorders in children.

**Drexel University ($1,401,259)**

**Research Projects:**

- **Title:** Role of MeCP2 in Pain and its Regulation by microRNAs  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** The goal of this research is to understand the role of methyl CpG binding protein 2 (MeCP2) in both normal and aberrant nociception. We hypothesize that the reduced pain sensitivity observed in Rett syndrome (RTT) patients results from a decrease in MeCP2 protein, and that a decrease in microRNAs (miRNAs) that bind and repress translation of MeCP2 will cause an increase in MeCP2 levels and thus contribute to pain. By integrating the two epigenetic mechanisms of DNA methylation and miRNAs, studies described here will render insight on how MeCP2 can bring about global gene regulation in a pain state. Our studies can lead to the identification of novel targets, a better understanding and thus innovative approaches for treating pain.

- **Title:** Making a Mouse to Study Hereditary Spastic Paraplegia  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** The purpose of this project is to generate and characterize a new transgenic mouse that expresses a human pathogenic mutant form of the SPG4 gene, which encodes for a protein called spastin. Mutations of this gene are the chief cause of Hereditary Spastic Paraplegia. The new mouse will be a key tool for studies on the etiology of the disease and the development of therapies for treating it.

- **Title:** Irreversible HIV-1 Inactivation for AIDS Intervention and Prevention  
  **Type of Research:** Biomedical  
  **Focus:** AIDS and Related Research  
  **Purpose:** Agents have been discovered at Drexel University that can irreversibly inactivate HIV-1 before host cell encounter. These virucidal agents have the potential to prevent HIV-1 infection and spread by treatment at early stages of human exposure to the virus. In addition, viruses from already-infected individuals can be isolated, inactivated by these agents and then used as therapeutic vaccines in the infected donors. This project will examine the breadth of virucide action on different virus tropisms and subtypes, determine inactivation potency in cellular environments, determine the immunoreactivity of the inactivated virus and test the neutralization activity following inactivated virus immunization.

- **Title:** Phenotypic Diversity of Neurons Modulating Executive Function in ADHD  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** The purpose of this project is to examine the phenotypic relationship between the mammalian prefrontal cortex (PFC), the area of the brain responsible for executive function, and the locus coeruleus (LC), one of the major brainstem modulatory centers that regulate functional operations in the PFC, in both normal and ADHD rats. This research will inform the development of drugs that are potential treatments for attention disorders.

- **Title:** Investigating Nervous System Structure and Function by 2 Photon Laser Scanning Microscopy  
  **Type of Research:** Biomedical
**Focus**: Neurosciences  
**Purpose**: A fundamental goal in neuroscience is to understand how neural circuits are formed and maintained in development, and throughout the life of the animal. Proper connectivity is critical to learning and memory processes in the healthy brain, and to functional recovery following injury or disease. Understanding the mechanisms regulating neural circuitry and connectivity is critical to developing therapies for treating neurological dysfunction as a result of injury or disease. This project aims to investigate the cell-cell interactions between astrocytes and dendritic spines, or synapses, in vivo. The results from this project will provide novel and important insight into the cellular and molecular mechanisms underlying astrocyte regulation of synaptic connectivity.

- **Title**: Tumor Characterization in Breast Carcinoma Using Computerized Image Analysis  
  **Type of Research**: Biomedical  
  **Focus**: Bioengineering, Surgical Sciences and Technology  
  **Purpose**: We have developed a computational method by which we can characterize lymph node metastasis status from histological images of primary breast tumor specimens. We propose to investigate the relationship between lymph node metastasis status and surrogate tumor markers, and to develop a novel machine learning technique designed to use histological images to predict tumor subtype, previously only possible with expensive molecular testing.

- **Title**: Innate Immunity and Bacterial Pathogenesis  
  **Type of Research**: Biomedical  
  **Focus**: Infectious Diseases and Microbiology  
  **Purpose**: The project aims to understand how innate immunity during viral-bacterial co-infections regulates susceptibility and pathogenicity and to establish models that allow the determination of important innate pathways that control infection. The studies proposed in this project will investigate important aspects of innate immunity in the context of bacterial infections. These studies will establish important models to understand the complex interaction between *N. gonorrhoeae* and HIV, and elucidate host factors that contribute to resistance to *L. pneumophila*.

- **Title**: Interaction of Interstitial Flow and ErbB2 Signaling in Breast Cancer Invasion  
  **Type of Research**: Biomedical  
  **Focus**: Oncological Sciences  
  **Purpose**: Interstitial fluid flow, which is the movement of fluid through tissues, increases in tumors and has been shown to promote tumor invasion, differentiation of stromal fibroblasts into myofibroblasts, increased cell motility, and activation of lymphatic endothelial cells. It is clearly evident that interstitial flow can have significant effects on tumor cells and their local microenvironment. However, there is a significant dearth of knowledge regarding how interstitial flow-induced cell signaling interacts with oncogenic signaling pathways to promote tumor invasion. Here, we propose a novel concept—that interstitial fluid flow mechanotransduction and ErbB2-activated signaling pathways cooperate to drive progression from premalignant to invasive cancer.

- **Title**: An Analysis of Mitochondrial Mutation and HIV Antiretroviral Therapy  
  **Type of Research**: Biomedical  
  **Focus**: AIDS and Related Research  
  **Purpose**: This project will examine the potential for mitochondrial changes to be used to predict clinical outcomes in HIV positive patients.
Duquesne University ($100,224)
Research Projects:

- **Title**: Regulators of Biofilm Formation in the Pathogenic Fungus, *Candida albicans*
  **Type of Research**: Biomedical
  **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  **Purpose**: The fungal pathogen, *Candida albicans*, is one of the most common hospital acquired infections worldwide. Critically ill patients, including those with various forms of cancer, are particularly susceptible to this infection. The pathogenicity of *C. albicans* is enhanced by its ability to grow on the surface of medical devices in the form of biofilms. Biofilms are complex networks of ovoid and filamentous cells that communicate with one another through secreted molecules. The purpose is to identify extracellular signaling molecules produced by *C. albicans* that regulate biofilm formation and thereby contribute to the pathogenicity of the organism.

- **Title**: Impact of N-Acetyl Cysteine on Heat Shock Protein 70
  **Type of Research**: Biomedical
  **Focus**: Neurosciences
  **Purpose**: The goal of our study is to understand the mechanism of action of N-acetyl cysteine (NAC). NAC has long been used to raise the critical antioxidant glutathione. However, our recent data suggest that it also increases heat shock protein 70, a chaperone that helps reduce the cellular burden of misfolded proteins. This may better explain why NAC has benefited patients with Alzheimer’s disease in clinical trials, because Alzheimer’s is primarily a disorder of protein misfolding. If we can show that NAC protects cells by raising heat shock protein 70, this would yield novel insight into its proven efficacy. Such a finding would usher in a new field of research on its impact on the heat shock family of proteins, all of which are protective chaperones.

Geisinger Clinic ($110,249)
Research Project:

- **Title**: Role of PP2A Antisense RNA in Human Glioblastoma
  **Type of Research**: Biomedical
  **Focus**: Oncological Sciences
  **Purpose**: Global transcriptome analysis provides evidence that a large proportion of the genome can produce transcripts from both strands. Antisense transcription (transcription from the opposite strand to a protein- coding or sense strand) has been ascribed roles in gene regulation involving degradation of the corresponding sense transcripts (RNA interference from small and long non-coding RNAs), as well as gene silencing at the chromatin level. The role of antisense transcription in human glioblastoma (GBM) has not been studied so far. The purpose of this proposal is to study the role and regulation of protein phosphatase-2A (PP2A) long antisense RNA in human GBM and how we can exploit the PP2A antisense RNA for therapeutic purposes.

Haverford College ($18,238)
Research Project:

- **Title**: Pathoadaptivity of Cell Detaching *Escherichia coli*
  **Type of Research**: Biomedical
  **Focus**: Infectious Diseases and Microbiology
  **Purpose**: We have accumulated preliminary evidence pointing to cell detaching *Escherichia coli* (CDEC) as diarrheal pathogens. We hypothesize that *E. coli* strains
that fit this description evolved greater virulence through loss of a common gene encoding the lactose repressor. We will determine whether CDEC represent a distinct diarrheagenic *E. coli* lineage and will identify potential virulence targets that could be repressed by *lacI*.

**Hepatitis B Foundation ($720)**

**Research Project:**

- **Title:** Perceptions of Hepatitis B Vaccine Status Among High Risk Foreign-Born Individuals in Philadelphia
- **Type of Research:** Health Services
- **Focus:** Health of Populations, Behavioral and Biobehavioral Processes
- **Purpose:** The purpose of this study is to assess the self-reported vaccination status and vaccine perceptions among high-risk Asian and Pacific Islander (API) and African immigrant communities in Southeastern Pennsylvania. These communities have disproportionately high rates of chronic HBV infection. Using anonymous data collected from 935 individuals, we will assess the agreement between people’s perception of having ever been vaccinated against HBV, and their actual hepatitis B immune status. Results from this study will allow us to better understand the health literacy and cultural barriers faced by these communities, and will be important in developing population-based interventions to reduce HBV in this region.

**Institute for Cancer Research (formerly Fox Chase Cancer Center) ($2,176,686)**

**Research Projects:**

- **Title:** ABCC10 Mediated Drug Resistance in Breast Cancer
  - **Type of Research:** Biomedical
  - **Focus:** Oncological Sciences
  - **Purpose:** A structurally distinct group of ATP Binding Cassette (ABC) drug efflux pumps, known as the Multidrug Resistance Proteins (MRPs), have been gaining increasing attention as sources of resistance. Our in vitro studies show that MRP7 (ABCC10) overexpression confers resistance to taxanes and vinca alkaloids. Excitingly, our recently developed *Abcc10*−/− knockout mice are highly sensitized to paclitaxel treatment, supporting the idea that changes in Abcc10 expression are sufficient to influence drug resistance. The purpose of this research is to evaluate the role of ABCC10 as a determinant of the efficacy of clinically relevant breast cancer therapies.

- **Title:** Quaternary Structure Dynamics in Protein Function, Disease, and Therapy
  - **Type of Research:** Biomedical
  - **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  - **Purpose:** Protein structure dynamics are essential for protein function. Factors that modulate protein structure dynamics can contribute to disease pathology and therapeutic mechanisms. Our laboratory is focused on the role of quaternary structure dynamics in the control of protein function, the etiology of disease, and the discovery of small molecule therapeutics. This project uses disease-associated human proteins to correlate quaternary structure dynamics with protein function.

- **Title:** Interactions of EGFR with the Scaffolding Protein NHERF1 and their Role in Cancer
  - **Type of Research:** Biomedical
  - **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
**Purpose:** The epidermal growth factor receptor (EGFR) plays a central role in controlling cell growth and differentiation of normal and malignant cells, and is an important target for cancer therapy. Efforts to develop improved cancer drugs depend critically on understanding how EGFR activity is controlled at the molecular level. This project is aimed at elucidating the role of a signaling adaptor protein, Na\(^+\)/H\(^+\) exchanger regulatory factor 1 (NHERF), in controlling the activity and subcellular distribution of EGFR. Biophysical and cell-biological techniques will provide insight into the structural basis of NHERF-EGFR interactions and their impact on internalization and turnover of the cell-surface receptor.

- **Title:** Epigenetic Reprogramming of Breast Cancer Metastasis  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The incidence and mortality of triple negative breast cancer (TNBC) are increasing in women younger than 40 years old, who are more likely to be African American or Latina and who develop metastases in response to the conversion of epithelial to mesenchymal cancer cells (EMT). The purpose of this project is to use breast epithelial stem cells that are undergoing EMT for understanding first the epigenomic processes and second for developing preclinical studies targeting DNA methylation and histone deacetylation, processes that ensure transcriptional suppression, for implementing in this way a novel strategy for the treatment of TNBC.

- **Title:** New Approach to Identifying Poly(ADP-ribose)Polymerase 1 Inhibitors  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The purpose of this research project is to develop and test a new class of Poly(ADP-ribose) Polymerase 1 (PARP-1) inhibitors for targeting and eliminating cancer cells. Our new assay is based on the protein-dependent pathway of PARP-1 activation. It will be used to screen for inhibitors, as well as to determine their mechanism of action. This method allows determining whether the inhibitors impair PARP-1 by targeting gene transcription or DNA repair pathway, thus aiding the in discovery of new drugs of superior specificity to be used in future treatment protocols. Our method will identify novel classes of PARP-1 inhibitors that disrupt PARP-1 activation by targeting its interaction with specific proteins.

- **Title:** Cell Culture Facility Research Infrastructure Renovation  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this project is to renovate existing space that will accommodate laboratory and office space for the Cell Culture Facility (CCF). The CCF supports the culture of mammalian cells by research laboratories at The Institute for Cancer Research (ICR), Fox Chase Cancer Center (FCCC) by providing culture media, supplies, technical expertise, and specialized equipment. Currently, the CCF research space, equipment, and offices are decentralized across four distant rooms and two hallways on three floors of two adjoining buildings. The renovation will modernize the central laboratory and adjacent laboratory space to consolidate all components of the facility into a centralized location and greatly improve the capacity of the facility to provide state-of-the-art cell culture services.

**Lankenau Institute for Medical Research ($115,879)**  
**Research Project:**  
- **Title:** Fluorodeoxyglucose and HEDS to Improve Human Colon Cancer Cells Response to Radiation
Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: There is a great interest in the inhibitors of glucose metabolism since glycolysis and oxidative pentose phosphate cycle (OPPC), which require glucose, play a major role in the survival and radiation response of tumor. Fluorodeoxyglucose (FDG), believed to be an inhibitor of glucose metabolism, is used for the positron emission tomography (PET) of tumors. Although FDG has been used for PET, it is not known whether FDG is a potent inhibitor of OPPC and thiol redox homeostasis, and improves the radiation response of tumor cells. We will determine the combinatorial therapy of FDG and hydroxyethyl disulfide, which is known to induce oxidative stress in OPPC deficient cells, in improving the radiation response of human colon cancer cells.

- Title: Preclinical Evaluation of a Novel Experimental Therapy for Multiple Myeloma
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This study will employ an established preclinical model of multiple myeloma (MM), an aggressive blood cancer composed of B immune cells, to evaluate the safety, pharmacology and efficacy of a novel experimental therapy developed by scientists at the Lankenau Institute. The therapy is a monoclonal antibody that blocks a signaling molecule abundantly produced by MM cells and hypothesized to be required for their uncontrolled growth on the basis of genetic studies of its role in cancer and immune disease. Positive results from the work would provide needed justification for its clinical evaluation in MM patients.

Lehigh University ($75,533)
Research Projects:

- Title: Long-Term Consequences of Controlled Forgetting for Remote and Complex Memories
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of the proposed research project is to define the scope and limitations of intentional forgetting, which will inform the mental health sector as to whether intentional forgetting could become a therapeutic tool helping patients to regain control over unwanted memories and intrusive thoughts that are characteristic of anxiety disorders. It has been shown that the intention to forget individual items in memory can impair their subsequent retrieval, but only short-term effects have been demonstrated. With the project, I seek to specify the conditions under which controlled forgetting can affect the retrieval of remote and complex memories in a long-lasting manner.

- Title: Mental Health Issues in the Bethlehem Community
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Despite the high prevalence, psychological problems are overlooked and undertreated in adolescents from low-income and ethnically diverse populations. School based mental health clinics (SBMHC) are one way to provide mental health services by increasing health care utilization for these hard to reach communities. Based within the Community Voices Clinic (CVC), an SBMHC, this research study will build knowledge about the issues that impact low-income children and families in Southside Bethlehem, in order to develop culturally sensitive prevention and treatment interventions. Focus groups with five stakeholders will provide multiple perspectives on mental health needs of this community.
Lincoln University ($44,916)
Research Project:

- **Title**: Association of GST Deletions with ITC Metabolism and ROS in African American Students  
  **Type of Research**: Biomedical  
  **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose**: The main purpose of this preliminary study is to investigate the relationship among glutathione-S-transferase genotype, isothiocyanate metabolism and urinary reactive oxygen species in African American college students. The results will illuminate health disparities in the areas of gene-nutrient interaction and will contribute new knowledge to a field in which the African American population is understudied and therefore likely underserved. Other purposes are to foster collaboration between biology faculty members with expertise in genetics and neuroscience and to establish genotyping and oxidative stress protocols at Lincoln University. In addition, this study will generate preliminary data for publications and for future grant applications.

Magee-Womens Research Institute and Foundation ($1,017,609)
Research Projects:

- **Title**: Maternal Lipids and Placental Function  
  **Type of Research**: Clinical  
  **Focus**: Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  **Purpose**: Women with preterm births (PTB) have excess cardiovascular disease later in life, but mechanisms linking these conditions are not understood. Placental underperfusion may account for some PTBs, and perhaps mark women at risk for later life vascular disease. Incorporating placental vascular findings into studies of PTB is difficult due to nonstandard classification of what are often subtle histologic findings. Syncytial knots are groups of syncytiotrophoblast nuclei thought to reflect normal aging of the placenta at term, but excess presence in preterm placentas may indicate underperfusion. We propose to identify evidence of placental underperfusion, including excess syncytial knots in term and preterm placenta, and relate these to evidence of maternal hyperlipidemia and hypertension.

- **Title**: Mouse Study of the Distribution of Placenta Originated miRNAs in the Maternal and Fetal Tissues  
  **Type of Research**: Biomedical  
  **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose**: We hypothesize that the chromosome 19 microRNA cluster (C19MC) can be transported from the placenta into the fetus, maternal blood, and even other maternal tissues, and that the methylation status of C19MC determines its tissue-specific expression. We will use sequencing technologies to examine the expression profiles of microRNAs in a mouse model transfected with the C19MC miRNAs, apply statistical tools to interrogate the distribution and transportation of the C19MC miRNAs in the transgenic mice during pregnancy, and use the reduced representation bisulfite sequencing to investigate the methylation pattern of the C19MC region. The study may help us understand the influence of the C19MC miRNAs on human embryonic development.

- **Title**: Preeclampsia and Post-partum Vascular Function  
  **Type of Research**: Biomedical
**Focus:** Cardiovascular Sciences  
**Purpose:** This project is designed to learn more about the relationship of the pregnancy complication preeclampsia (PE) and blood vessel function after pregnancy. PE affects about 5% of all pregnant women, and these women are more likely to get cardiovascular disease (CVD) years after pregnancy. We believe that measureable deficiencies in vascular function in young women after a PE pregnancy are surrogate markers of future CVD. This project to measure carotid-femoral pulse wave velocity (vessel stiffness) and brachial artery flow-mediated vasodilation, and their relationship to sublingual artery surface layer (glycocalyx) depth and circulating lipids, could help clarify why CVD risk is increased in women who have had PE.

- **Title:** Oxidative Stress, Hypoxia and Placental Cholesterol Metabolism  
  **Type of Research:** Biomedical  
  **Focus:** Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  **Purpose:** While oxidative stress and hypoxia are known to cause placental injury and to disrupt cholesterol homeostasis, their effect on placental cholesterol metabolism is not known. We posit that disruption of placental cholesterol homeostasis adversely affects placental function and fetal growth. Our focused interrogation of placental cholesterol metabolism and its effect on fetal growth will elucidate central pathways in placental metabolic function, and highlight therapeutic targets for the amelioration of placental injury.

- **Title:** Effects of Telomerase Inhibitors on Centrosomes and Centromeres in Cancer Cells  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Nearly all human cancers bypass replicative senescence and DNA damage signaling pathways by preventing the shortening of telomeres, the protective ‘caps’ at chromosomal ends, using the reverse transcriptase Telomerase. This cancer cell exclusive enzyme is an ideal biomarker and target for cancer diagnosis, prognosis and therapies. Genomic instabilities also correlate with centrosomal abnormalities and defects to the spindle assembly checkpoint (SAC) system, increasing spindle multipolarity and chromosome misalignment, a hallmark of many cancers. Here, fixed and dynamic confocal imaging with living markers for centrioles and microtubules are used to explore the telomerase inhibitors impact on centrosome and SAC constituents in normal somatic and cancerous cells.

- **Title:** Genetic Biomarkers of Inherited and Acquired Forms of Male and Female Germ-cell Infertility  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** We propose a novel pilot study to investigate genome-wide DNA coding mutations related to male and female infertility using novel oligonucleotide microarray Comparative Genome Hybridization (CGH) and Next Generation Sequencing. We expect to identify a significant number of genomic, genetic, inherited and de-novo germ-cell-specific defects characteristic for infertile male and female germ cells (sperm and oocyte). We hypothesize that these findings will highlight disruption(s) of specific molecular mechanisms of spermatogenesis and oogenesis and would serve as future infertility-associated diagnostic markers of pathological reproductive tissues.
Monell Chemical Senses Center ($234,200)
Research Projects:

- **Title:** Early Stage Recordings of Cognitive Odor Processing  
  **Type of Research:** Biomedical  
  **Focus:** Neurosciences  
  **Purpose:** The purpose of this project is to establish a novel measure of olfactory responses occurring at the first input to the human brain, the olfactory bulb (OB). This innovation would not only enable further explorations of the role fulfilled by the olfactory bulb in the cognitive and perceptual processing of odors but would also be easily implemented as an everyday clinical tool. A technique allowing measures of human OB signals will greatly aid future olfactory-related translational work and establish a new paradigm for studies of human olfactory processing.

- **Title:** Bitter Taste-Induced Nausea  
  **Type of Research:** Biomedical  
  **Focus:** Digestive Sciences  
  **Purpose:** Bitter taste stimuli can directly elicit nausea. Usually nausea is the negative experience that accompanies toxin-induced illness. The problem lies in that some toxins are also medicines and their induced nausea is a disincentive to medical compliance, especially among children who cannot ingest encapsulated drugs. Moreover, a wide variety of gastrointestinal disorders are frequently accompanied by bitter taste reflux from gastric contents and by chronic nausea. The proposed work will determine the extent to which bitter taste evokes nausea in healthy people. This knowledge in a normative state might lead to new preventions for patients suffering from nausea due to gastric reflux or direct stimulation of bitter taste.

National Disease Research Interchange ($56,394)
Research Project:

- **Title:** Susceptibility Genes for Microvascular Complications in Patients with Type 1 Diabetes  
  **Type of Research:** Health Services  
  **Focus:** Endocrine, Metabolism, Nutrition and Reproductive Sciences  
  **Purpose:** Genetic factors likely influence susceptibility to microvascular complications of diabetes, including retinopathy, nephropathy and neuropathy. A linkage analysis of chromosome 6 identified three loci that contributed to Type 1 Diabetes (T1D) complications; the human leukocyte antigen (HLA) locus, which is the main locus for susceptibility to T1D itself, and 2 novel loci. One of the novel loci appears to relate to susceptibility to retinopathy and the other, possibly, to neuropathy. The fact that they could be identified by linkage analysis indicates that they are major contributors to complications susceptibility. We propose using dense single nucleotide polymorphism (SNP) typing in this area of chromosome 6 to identify the genes at these novel loci.

National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation ($967,037)
Research Project:

- **Title:** Evaluation and Mechanistic Studies of Molecularly Targeted Agents in Colon Cancer  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** The purpose of this project is to evaluate the efficacy of molecularly targeted agents, alone and in combination, on cell viability. Signaling pathway
studies will be conducted to understand mechanisms of resistance and sensitivity to specific agents. Molecular profiling studies will be conducted with the purpose of identifying molecular subtypes in colon cancer cell lines that have been shown to be particularly resistant to therapy and identifying potential combinations of targeted therapies that may overcome this resistance. Identification of these agents and the mechanisms responsible for their success and failure in our studies will lead to new and improved approaches to colon cancer treatment.

Pennsylvania State University ($6,589,749)

Research Projects:

- **Title:** Targeting Pancreatic Cancer with Aptamers to the CCK-B Receptor  
  **Type of Research:** Biomedical  
  **Focus:** Bioengineering, Surgical Sciences and Technology  
  **Purpose:** The purpose of this research project is to select and develop aptamers which will be useful for specifically targeting pancreatic cancer; the aptamers will be selected to specifically recognize the CCK-B receptor, a growth-stimulatory receptor whose ligand is gastrin. Here we will explore targeting nanoliposomes to pancreatic cancer cells using high affinity aptamers; aptamer-targeted nanoliposomes will be developed containing reagents for imaging, or containing therapeutic reagents (chemotherapeutics, siRNAs, etc.).

- **Title:** Perioperative Circulating Tumor Cell Detection in Stage IV Colorectal Cancer  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** Circulating tumor cell (CTC) isolation during colorectal cancer (CRC) liver and lung metastasectomy will increase understanding of CTC shedding during surgery, discover targets for guided therapy and identify high-risk patients for recurrence. This study will also evaluate a novel filtration-based technology that allows isolation of viable cells. By analyzing biomarker expression in CTCs, therapeutic molecular targets can potentially be identified. The studies to sample CTCs intraoperatively apply innovative approaches to unsolved problems in patients with metastases from CRC. The results can be fundamentally important to understanding cancer spread, and further personalize therapy in patients undergoing cancer-related surgery.

- **Title:** Analysis of the Role of YAP1 in the Self Renewal of Leukemia Stem Cells  
  **Type of Research:** Biomedical  
  **Focus:** Hematology  
  **Purpose:** Leukemia is a hierarchical disease with Leukemia stem cells occupying the apex. Conventional therapies for leukemia are designed to kill leukemia cells, but leukemia stem cells have active mechanisms to evade these drugs. Leukemia stem cells that survive treatment can then cause relapse of disease. Thus, a greater understanding of the mechanisms that regulate the self-renewal of leukemia stem cells will identify new targets for therapeutic intervention. The purpose of this project is to test the hypothesis that Yap1 promotes the self-renewal of leukemia stem cells and will test whether inhibiting Yap1 can eliminate leukemia stem cells and effectively treat disease. These studies are initial basic studies using mouse models of leukemia that if successful could be translated into the clinic.

- **Title:** Reprogramming HBV-specific CTL from Stem Cells for Cell-based Therapies  
  **Type of Research:** Biomedical  
  **Focus:** Immunology  
  **Purpose:** Virus-specific T cells capable of controlling hepatitis B virus (HBV) and eliminating hepatocellular carcinoma (HCC) expressing HBV antigens are deleted or
dysfunctional in patients with chronic HBV infection. Adoptive cell transfer (ACT) of highly reactive HBV-specific CD8+ cytotoxic T lymphocytes (CTL) is a highly promising treatment for chronic HBV infection and HBV-related HCC. However, such ACT is often not feasible due to difficulties in obtaining these cells from patients. The studies in this project will define the unique properties of HBV-specific CTL derived from induced pluripotent stem cells (iPSC-CTL) and determine anti-HBV activity of iPSC-CTL.

- **Title**: Investigating the Mechanisms of Esophageal Squamous Cell Carcinoma Invasion
  **Type of Research**: Biomedical
  **Focus**: Oncological Sciences
  **Purpose**: Esophageal squamous cell carcinoma (ESCC) is the most prevalent form of esophageal cancer throughout the world and carries a dire prognosis, primarily due to presentation at an advanced stage and the invasiveness of the disease. The Epidermal growth factor receptor (EGFR) gene is commonly overexpressed in almost 90% of ESCC tumors. Another gene, p120ctn, is frequently down-regulated in approximately 60% of ESCC tumors. Esophageal cells that have been altered to have decreased p120ctn expression and overexpression of EGFR invade the extracellular matrix in a 3D-culture system. Our project proposes to define the mechanisms by which p120ctn and EGFR cooperate to synergistically influence esophageal squamous cell carcinoma invasion.

- **Title**: Immunological and Anti-tumor Mechanisms of LipC6 Treatment in a Murine Model of HCC
  **Type of Research**: Biomedical
  **Focus**: Oncological Sciences
  **Purpose**: We have established a novel murine model which uniquely approximates hepatocellular carcinoma (HCC) tumor progression, tumor morphology, microenvironment with liver fibrosis. Using this model, we will initially determine the role of LipC6 in modulating a variety of subset T cells and preventing tumor antigen-specific CD8 T-cell tolerance in vivo; then we will determine the role of LipC6 alone and in combination with adoptively transferred TCR-I T cells in HCC treatment. The results will be used to further apply for an R01 grant sponsored by NIH. The knowledge gained will lay the foundation for translational approaches in human HCC that combine LipC6 with new or existing immunotherapies.

- **Title**: Enhancing Smokers’ Control over Brain Reward Circuitry Using fMRI Neurofeedback
  **Type of Research**: Biomedical
  **Focus**: Health of Populations, Behavioral and Biobehavioral Processes
  **Purpose**: Non-drug rewards (e.g., money) are used frequently to enhance the motivation of individuals trying to quit smoking cigarettes. Although this approach is grounded in well-established behavioral principles, converging evidence indicates that non-drug rewards may be least effective at promoting smoking abstinence in the very situations that they are needed most – i.e., when cigarettes are available and cravings are high. The goal of this project is to test the utility of a novel approach for increasing the motivational impact of non-drug rewards in smokers. The project will be used to support a program of research with the potential to significantly improve incentive-based strategies for treating cigarette addiction.

- **Title**: Mechanism and Inhibition of the Antibiotic Resistance Protein, Cfr
  **Type of Research**: Biomedical
  **Focus**: Infectious Diseases and Microbiology
Purpose: Cfr is a metalloprotein that employs an unusual reaction mechanism to methylate carbon 8 of adenosine 2503 (A2503) of bacterial rRNA, which leads to resistance to over five classes of antibiotics that target the ribosome. The cfr gene was first identified in 2000 on a plasmid extracted from *Staphylococcus sciuri*, an animal pathogen. Since then it has crossed over into staphylococci that infect humans, including methicillin-resistant *Staphylococcus aureus* (MRSA), resulting in a number of fatal infections. More recently, it has been found in *Enterococcus faecalis* and is widespread in the order Bacillales. Approximately 40% of all clinically used antibiotics target the ribosome. This study aims to generate compounds that will block this reaction as a means of preserving our current arsenal of antibiotics.

- **Title**: Research Infrastructure: Zebrafish Functional Genomics Core  
  **Type of Research**: Biomedical  
  **Focus**: Research Infrastructure Project  
  **Purpose**: The project will renovate existing animal facilities to build a new Zebrafish Functional Genomics Core for Penn State scientists and collaborators to develop zebrafish as a vertebrate model for human disease. The research resource can be used by scientists interested in using a powerful vertebrate model system, the zebrafish, to study human biology and disease.

Philadelphia College of Osteopathic Medicine ($14,266)  
Research Project:
- **Title**: Functional Roles of IMP Isoforms in Axon Regeneration by Localizing Specific mRNAs  
  **Type of Research**: Biomedical  
  **Focus**: Neurosciences  
  **Purpose**: Axon degeneration is a common pathway leading to neurological deficits after spinal cord and nerve injuries. However, therapeutic approaches to enhance axon regeneration are very limited. Our recent studies point to the functional importance of localizing mRNAs into neuronal axons and subsequently translating them into proteins. The purpose of this project is to investigate molecular mechanisms underlying axon regeneration. We will focus on insulin-like growth factor-II mRNA-binding protein (IMP) isoforms which are known to localize specific mRNAs into regenerating axon. This study will advance our knowledge of the regenerative process and lead to effective therapeutic strategies for axon regeneration.

Salus University ($40,030)  
Research Project:
- **Title**: Interaction of Guanylyl Cyclase GUCY2D with its Regulatory Proteins: Effects of Mutations Causing Inherited Blindness  
  **Type of Research**: Biomedical  
  **Focus**: Neurosciences  
  **Purpose**: GUCY2D guanylyl cyclase is essential for retinal responses to light stimuli. Mutations in GUCY2D gene and in its regulatory proteins cause various forms of congenital blindness found in the North American population. Molecular mechanisms leading to GUCY2D malfunction are multiple and vary for different types of mutations. The purpose of this short-term pilot project is to obtain new knowledge of how principle mechanisms of GUCY2D interactions with its regulatory proteins become altered by the disease-causing mutations. This knowledge should be valuable for planning future studies on approaches to gene therapy of the GUCY2D-related blindness.
Temple University ($2,220,937)
Research Projects:

- **Title**: Grand-Aides in Reducing Re-admission of Heart Failure Patients  
  **Type of Research**: Clinical  
  **Focus**: Cardiovascular Sciences  
  **Purpose**: Nationally, patients admitted to the hospital for exacerbation of heart failure symptoms have a 38% chance of readmission to the hospital within 60 days of discharge. At Temple, the rate of readmission for heart failure is as high as 34.7% within 30 days of discharge. Grand-Aides program combines trained community-based workforce and iPAD technology to provide improved access to care, optimal follow-up, and at a lower cost. We propose a randomized controlled trial to compare 30-day hospital readmission rates of heart failure patients assigned to conventional discharge care and follow-up, with those assigned to the Grand-Aides program. Our hypothesis is that 30-day readmission rates will be lowered by 30% with Grand-Aides.

- **Title**: Protein Kinase A Inhibition and Heart Failure  
  **Type of Research**: Clinical  
  **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose**: Heart failure (HF) is a lethal syndrome characterized with progressive cardiac function depression, reduced exercise capacity, decreased cardiac reserve and blunted adrenergic responsiveness. Myocardial infarction (MI) is a major cause of HF. The mechanisms responsible for the development of HF after MI are not entirely clear. The purpose of this project is to evaluate the roles of endogenous protein kinase A inhibitor peptide (PKI) in cardiac physiology and pathophysiology and the potential of using PKI as a novel way to prevent adverse cardiac remodeling after myocardial infarction (MI).

- **Title**: Therapeutic Potential of Myocyte Caveolae NO-cGMP Signaling in Cardiac Diastolic Dysfunction and Diastolic Heart Failure  
  **Type of Research**: Clinical  
  **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose**: Diastolic dysfunction--- abnormal left ventricular (LV) diastolic relaxation, filling, and/or distensibility--- characterizes one of the great challenges in cardiovascular medicine, heart failure with preserved ejection fraction (HFP EF). HFP EF accounts for more than half of chronic heart failure cases, yet evidence-based therapy for HFP EF is lacking. Our primary objective is to study the changes in myocyte caveolae NO-cGMP signaling with diastolic dysfunction, focusing on regulatory mechanisms of sGC activity and the functional implications of caveolae-localized NO-cGMP signaling.

- **Title**: Vasopressin 1A Receptor and Heart Failure  
  **Type of Research**: Clinical  
  **Focus**: Cardiovascular Sciences  
  **Purpose**: The progression of heart failure (HF), a disease that affects over 5 million individuals in the U.S. alone, is mediated in part by the release of neurohormonal signals and subsequent activation of G protein-coupled receptors. Arginine vasopressin (AVP) is a neurohormone that modulates cardiovascular function through activation of AVP type 2 receptors in the kidney and AVP type 1A receptors (V1AR) in the heart and vasculature. AVP levels are elevated in patients with HF and increased AVP levels are associated with increased morbidity and mortality. Little is known about AVP signaling in the heart. Our studies will elucidate the role of V1AR in HF
progression and form the foundation for novel and rational HF therapy targeted at biased V1AR signaling.

- **Title**: Transient Receptor Potential-Melastatin 2 (TRPM2) and Ischemic Heart Injury  
  **Type of Research**: Clinical  
  **Focus**: Cardiovascular Sciences  
  **Purpose**: TRPM2 channels are non-selective cation channels that are involved in cell proliferation and are emerging to be drug discovery targets for cancer therapy. In addition, TRPM2 channels are activated by ischemia. The physiological function of TRPM2 in the heart is unknown. We have generated a TRPM2-knock out mouse and observed that after ischemia-reperfusion injury or doxorubicin (chemotherapeutic agent) treatment, cardiac function is significantly worse in TRPM2KO compared to wild-type hearts. The proposed studies are to elucidate cellular mechanisms by which TRPM2 channels protect hearts from ischemic and anthracycline injury. The results have significant impact on both ischemic heart disease and cancer chemotherapy.

- **Title**: Polydrug Use: Interactions between Cannabinoids, Opioids, and Nicotine  
  **Type of Research**: Clinical  
  **Focus**: Neurosciences  
  **Purpose**: The purpose of this project is to study drug interactions among the systems that mediate addiction to nicotine, opioids and cannabinoids. All three classes of drugs are of major public health interest because their use can lead to abuse and dependence. Substance abuse is a major public health problem in Pennsylvania and worldwide. Most people use more than one drug. This project will investigate polydrug interactions in preclinical rodent models to determine the effect of nicotine or cannabinoid exposure on cognitive parameters and pain responses to opioids. In addition, the role of the two major cannabinoid receptors, CB1 and CB2, will be evaluated to determine how each affects the polydrug interactions.

**Thomas Jefferson University ($2,776,880)**  
**Research Projects:**

- **Title**: The BRM (brahma) Atpase as a Gatekeeper for Prostate Cancer Development and Progression  
  **Type of Research**: Biomedical  
  **Focus**: Oncological Sciences  
  **Purpose**: There is a critical need to discern the mechanisms that govern prostate cancer development and progression. Based on our published and preliminary data, it is evident that the Brm ATPase plays a significant role in both processes. Our findings strongly support a model wherein loss of Brm functions as a tumor suppressor by modulating cell cycle progression and checkpoints. Moreover, “weakened” BRM activity cooperates with loss of the p27 tumor suppressor to induce hyperplastic phenotypes and castrate-resistance. Studies will determine the molecular mechanisms by which p27kip1 is induced by Brm loss (Aim 1), the impact of p27kip1 as a barrier to Brm-loss induced tumorigenesis and ADT-resistance in vivo (Aim 2), and the impact of coordinate p27kip1 and Brm loss in human disease (Aim 3).

- **Title**: Modulation of Human Breast Cancer Growth *In Vivo* by Activated Human Breast Fibroblasts  
  **Type of Research**: Biomedical  
  **Focus**: Oncological Sciences  
  **Purpose**: The work is part of a long-term objective of providing new experimental models for more accurate drug response testing of human breast cancer in mice. Many drugs work well when tested on human breast cancer xenotransplant lines in
mice, but fail in patients. The focus of this proposal is to characterize growth and drug-responsiveness of human breast cancer xenotransplants in mice with or without humanized tumor stroma. We hypothesize that novel human mammary fibroblast lines will humanize the stromal microenvironment and modulate tumor growth and drug responsiveness more accurately.

- **Title:** Creating and Phenotyping New Mouse Models of Cancer Cachexia  
  **Type of Research:** Biomedical  
  **Focus:** Musculoskeletal, Oral, and Skin Sciences  
  **Purpose:** Cachexia, or dysmetabolism leading to muscle and fat wasting, diminishes quality of life and response to therapy in cancer patients. Cachexia afflicts most patients with tobacco-related cancers, including up to 80% of those with lung cancer. Cachexia itself, distinct from other tumor effects, causes ~1/3 of cancer deaths. Despite this, few animal models of cancer cachexia have been well characterized and ~4 are commonly used. The purpose of this project is to create and phenotype new mouse models of cancer cachexia. Mice with tumors of mouse and human origin will be subjected to clinical, pathological, histological, and molecular profiling in order to expand the models available to the research community.

- **Title:** Liganded Glucocorticoid Receptor Functionally Interacts with Transcription Factor Stat5 in Human Prostate Cancer Cells  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Glucocorticoids are the standard treatment of advanced prostate cancer. Recent preclinical and clinical studies have challenged the benefits of glucocorticoids because of potential induction of therapy resistance in malignant solid tumors. Stat5a/b is highly critical for the viability of human prostate cancer cells in vitro and for prostate tumor growth in vivo, and active Stat5a/b predicts poor clinical outcome of prostate cancer. We hypothesize here that the glucocorticoid receptor (GR) functionally interacts with transcription factor Stat5a/b in prostate cancer cells. The purpose of this work is to establish whether Stat5a/b interacts with GR signaling in human prostate cancer cells, and if this functional co-action promotes prostate cancer cell survival.

- **Title:** Increasing Patient-Centered Care for Patients with Early Prostate Cancer  
  **Type of Research:** Health Services  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** More than 90% of patients with newly diagnosed prostate cancer have localized disease, and therefore face the difficult decision of whether to initiate active surveillance (AS) or active treatment (AT). Given that AT may have serious side effects, and mortality rates are comparable for men who have AS and those who have AT, it is important for men to make an informed decision about treatment. We propose to conduct a pilot study to test the impact of a novel patient decision support intervention, on AS versus AT uptake. The study will involve early-stage prostate cancer patients who have a scheduled visit for consultation at the Jefferson Prostate Cancer Multidisciplinary Clinic (JMDC) in Philadelphia.

- **Title:** Cell Fate Factor Protein DACH1 Modification in Signaling and Cancer  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The DACH1 protein has features of a tumor suppressor, however very little is known of its modification by phosphorylation or acetylation, which may in turn govern signaling by this protein. DACH1 was cloned as a Drosophila homologue (Dac) that blocks Epidermal Growth Factor Receptor (EGFR) signaling. Hyperactive growth factor signaling is a common feature of terminal cancer. Identifying new
mechanisms to attenuate hyperactive growth signaling in cancer may provide important new therapeutic options. Identifying the functional modifications of DACH1 may allow us to target the DACH1 protein and its activity in tumors.

- **Title**: Molecular Aberrations in Adenocarcinoma and Neuroendocrine Prostate Cancer
  **Type of Research**: Biomedical
  **Focus**: Oncological Sciences
  **Purpose**: We hypothesize that Adenocarcinoma (AdCa) and Neuroendocrine (NE) Prostate Cancer carry different molecular aberrations that may explain the aggressive phenotype of NE Prostate Cancer (NEPC). Using two mouse models of prostate cancer, we plan to delineate the signaling aberrations by which neuroendocrine prostate cancer (NEPC) differ from AdCa. In both in vivo mouse models, we will profile all samples for aberrant expression and activities of signaling molecules and identify the molecules which contribute to an aggressive cancer cell phenotype. This study presents an unmet clinical need for NEPC patients with advanced disease.

- **Title**: Anoikis-Resistance in Metastatic Breast Cancer Cells and the Role of the Focal Adhesion Kinase (FAK1)
  **Type of Research**: Biomedical
  **Focus**: Oncological Sciences
  **Purpose**: Many breast cancer patients die after the removal of primary tumors because of metastasis. A very aggressive type called inflammatory breast cancer (IBC) is responsible for a disproportionate number of deaths due to its propensity to rapidly metastasize. IBC primarily affects younger women under the age of 50 at diagnosis, and is difficult to detect as it does not present as a lump, but rather occurs as tumor emboli. Anchorage-independent growth (anoikis-resistance) is a crucial step in metastases. The focal adhesion kinase (FAK1) is an important regulator of anoikis-resistance. In this project, we propose to study the mechanism responsible of anoikis-resistance in IBC to determine if FAK1 inhibition suppresses the metastatic potential of these cells.

- **Title**: Long Non-coding RNAs Regulate Protein-coding Transcripts in Colon Cancer with the Help of a Specific Family of MicroRNAs
  **Type of Research**: Biomedical
  **Focus**: Oncological Sciences
  **Purpose**: Decades of research have been invested towards understanding genetic defects in colon cancer. Until recently, the lack of available tools and of critical insights resulted in the community having paid only limited attention to the mechanisms of post-transcriptional regulation of the colon cancer cell. The work we propose will explore unexpected facets of microRNA-mediated regulation of colon cancer-related genes by long non-coding RNAs. Our goal is two-fold: a) provide evidence for a novel paradigm of microRNA targeting in colon cancer cells; and b) demonstrate that non-coding RNAs can regulate important protein-coding genes through interactions that obviate direct molecular contact ("decoying").

- **Title**: Mechanisms of Presynaptic Dysfunction of Dopaminergic Neurotransmission in Human LRRK2 (R1441G) Transgenic Mouse Model
  **Type of Research**: Biomedical
  **Focus**: Neurosciences
  **Purpose**: The major goal of this project is to understand the role of synaptic mitochondria in dopamine (DA) release and DAergic axon degeneration in LRRK2 transgenic mouse. We hypothesize that mutant LRRK2 impairs mitochondrial function at the pre-synaptic terminals, which in turn diminishes local ATP synthesis or calcium buffering required for normal DA release. We will utilize a combination of fast cyclic
voltammetry recording and two-photon imaging in living brain slices, and mouse genetics to uncover mechanisms underlying DAergic transmission deficits in Parkinson’s (PD). These findings will likely provide new insights into pathogenesis of PD and open new avenues for therapeutic intervention.

- **Title**: Using Transfer RNA Fragments to Identify Race-Specific Molecular Events in Triple Negative Breast Cancer
  - **Type of Research**: Biomedical
  - **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  - **Purpose**: In this project we will study transfer RNA fragments (tRFs) to discern race-specific therapeutic targets in Triple Negative Breast Cancer. Transfer RNAs (tRNAs) are non-coding RNAs (ncRNAs). Each tRNA genomic locus produces a precursor transcript whose mature product, the tRNA, is integral to the process of translation of codons to amino acids. Traditionally, the tRNA loci have been thought to give rise to a single product but recent studies have shown that tRNA fragments (tRFs) also arise from these loci and represent a potentially important group of ncRNAs. Our analyses of breast cancer (BRCA) datasets from The Cancer Genome Atlas (TCGA) repository suggest that tRNA fragments are relevant to BRCA biology and their expression depends on BRCA subtype and on race.

**Treatment Research Institute ($174,793)**

**Research Project:**

- **Title**: Screening, Treating, and Advising Aging-out Teens (STAAT)
  - **Type of Research**: Clinical
  - **Focus**: Health of Populations, Behavioral and Biobehavioral Processes
  - **Purpose**: The purpose of this project is to develop an intervention that can address health-compromising behaviors, in particular substance abuse, for adolescents who are between the ages of 15-18 years old and are in the process of aging-out of the foster care system. The intervention will: 1) identify substance abuse and target it for intervention; and 2) pair youth with a recovery mentor to provide overall social support, support for abstinence, and linkages with pro-social activities. Once developed, the intervention will be pilot tested to assess the degree to which it is implemented with fidelity. We will examine its feasibility with the staff and participant population, and collect preliminary data on substance use, social support, self-efficacy, and overall well-being in aging-out adolescents.

**University of Pennsylvania ($7,752,646)**

**Research Projects:**

- **Title**: HLTF Silencing: A Novel Determinant of Sensitivity to Autophagy Inhibition
  - **Type of Research**: Clinical
  - **Focus**: Oncological Sciences
  - **Purpose**: Autophagy is a new therapeutic target in cancer, and we have identified HLTF as a potential marker of sensitivity to autophagy inhibitors. The overall goal of this proposal is to understand the mechanistic underpinnings that link HLTF and autophagy, and develop a new predictive assay for HLTF gene silencing that will potentially have a major impact on the development of clinical trials and the treatment of diseases such as colon cancer, lung cancer, gastric cancer, melanoma, and pancreas cancer, for which HLTF is known to be or is likely to be silenced in a high proportion of patients.

- **Title**: Molecular Pathways of T Lineage Lymphomas
  - **Type of Research**: Biomedical
  - **Focus**: Oncological Sciences
**Purpose:** The proposed research project will provide novel insights and greater understanding of molecular mechanisms through which tumor suppressor proteins cooperate to prevent development of T cell acute lymphoblastic leukemia (T-ALL). Elucidating mechanisms of T-ALL initiation and progression is critical to the development of treatments for patients with therapy-resistant or relapsed disease. The knowledge and mouse models gained through our studies could lead to more effective clinical management of an aggressive subset of lymphoid malignancies.

- **Title:** Tumor Antigen-specific T-cells and Hepatocellular Carcinoma  
  **Type of Research:** Clinical  
  **Focus:** Immunology  
  **Purpose:** This proposal encompasses work designed to demonstrate that a cell-based tumor vaccine can induce potentially protective immunity in cirrhotic patients against tumor-associated antigens relevant to hepatocellular carcinoma (HCC). We propose to define the mechanism for tumor-induced suppression of these T-cells in patients with HCC, to prove that highly functional effector tumor-specific T-cells can be expanded from cirrhotic patients, and to investigate a cell-based vaccine platform for immunizing cirrhotic patients against tumor-associated antigens. If ultimately successful, a preventive vaccine could have a major impact on survival and reduction of the need for liver transplantation in well-compensated cirrhotic patients.

- **Title:** Repurposing Cholinesterase Inhibitors for Smoking Cessation  
  **Type of Research:** Clinical  
  **Focus:** Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose:** The purpose of this project is to evaluate cognitive enhancing interventions for smoking cessation. The focus will be on the cholinesterase inhibitor, galantamine.

- **Title:** Clinical-pathologic Correlates in Neuroendocrine Tumors  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** Gastrointestinal neuroendocrine tumors (GI NETs) are rare tumors of the alimentary tract or pancreas that commonly metastasize to the liver and beyond. They arise from neuroendocrine cells distributed throughout the body and have a low incidence, but high prevalence because their clinical behavior is generally indolent. It has been estimated that there are about 100,000 people in the United States with GI NETs including in the State of Pennsylvania. How these tumors develop is not well understood. We are interested in understanding more about the patients who develop these tumors and the biology of the tumors themselves in order to ultimately improve the diagnosis, treatment, and clinical outcome of individuals who develop GI NETs.

- **Title:** Notch Signaling and Esophageal Carcinogenesis  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Little is known about the role of Notch signaling in esophageal squamous cell carcinoma (ESCC), one of the most deadly cancers. In particular, there is a fundamental gap in understanding how Notch signaling regulates a subset of ESCC cells that are more capable of forming tumors, prone to metastasize and foster resistance to conventional chemotherapy. This research aims at elucidating how Notch signaling contributes to the pathogenesis of esophageal squamous cell carcinoma (ESCC).

- **Title:** Calcineurin-NFAT Signaling in Megakaryocytic Leukemia of Down Syndrome  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences
**Purpose:** Down syndrome is the most common genetic disorder and causes many clinical effects including an increased incidence in the blood cancer, acute megakaryoblastic leukemia (AMKL). This project is based on preliminary data showing that the DSCR1 and DYRK1A genes located on chromosome 21 play a role in leukemia in Down syndrome patients. These genes block the calcineurin-NAT signaling pathway. Thus, the goal of this project is to determine whether this pathway is important in megakaryocyte development and whether increased expression of these 2 genes are necessary for AMKL in Down syndrome patients. This project may lead to new treatments for Down syndrome AMKL and other diseases with defects in megakaryocytes.

- **Title:** p53 and Tumor Cell Metabolism  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** The tumor suppressor p53 is most frequently mutated gene in human tumors, and recent evidence indicated a critical role for p53-mediated metabolic regulation and senescence in tumor suppression. However, it is still poorly understood how p53 regulates metabolism and senescence, and how p53 may connect these two processes. Our preliminary studies suggest reciprocal regulation between p53 and two tricarboxylic acid (TCA) cycle-associated enzymes that modulates both metabolism and senescence. We plan to elucidate this reciprocal regulation and its deregulation in tumor cells. This project will lead to better understanding of p53 biology and the molecular mechanisms of tumor suppression.

- **Title:** Single Cell Transcriptomics for High Resolution Cell Characterization  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** The purpose of this project is to develop new technologies for assessing the transcriptome at the high resolution level of individual cells and use the characterization to understand the role of hidden molecular subtypes in modulating cell phenotype, including those involved in development and response to therapeutics.

- **Title:** Research Infrastructure: Construction of the Neuro-Behavioral Sciences  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this research infrastructure project is to contribute to the creation of a 45,000 gross square foot research facility that facilitates basic science research at the boundaries of Psychology and Biology. This research facility will occupy the contiguous upper 3 floors of a larger 75,000 GSF building dedicated to (1) research at the boundaries of Psychology and Biology to (2) undergraduate instruction in both Biology and Psychology and to (3) creation of a shared home for four of the undergraduate life science programs in the School of Arts and Sciences. Health research grant funds shall be used for construction of a facility that shall be used solely for the purpose of biomedical, clinical or health research as defined by Act 2001-77.

- **Title:** VEGF Receptor Inhibition in Lung and Liver Metastases  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Therapies that target vascular endothelial growth factor (VEGF) pathways are being increasingly utilized in the treatment of metastatic cancers. This project focuses on tissue-specific differences in the tumor microenvironment that may affect the efficacy of anti-angiogenic therapies. This project specifically explores the
effectiveness of VEGF receptor 1 and 2 inhibition in preventing the establishment or
growth of lung and liver metastases and may lead to the identification of the optimal
combination for site specific anti-angiogenic strategies. Thus, this work could have
substantial impact in treatment approaches for metastatic disease.

- **Title:** Understanding Wnt5a Regulation of Protein Depalmitoylation During Cell Migration  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Most cancer deaths are caused by dissemination of cancer cells away from the primary tumor to distant sites in the body. However, little is known about what causes cancer cells to metastasize. Highly motile cells require cell polarity to establish the front and rear of the cell for efficient directional migration and chemotaxis, but the mechanisms that regulate cell polarity are poorly understood. Since starting my own lab I have found that Wnt5a induces protein depalmitoylation that causes polarized protein localization and increased invasion in melanoma cells. We will continue these studies to understand how Wnt5a regulates this process to promote metastasis.

- **Title:** Long Noncoding RNAs Required for Human Female Preimplantation Development  
  **Type of Research:** Biomedical  
  **Focus:** Biology of Development and Aging  
  **Purpose:** This project will focus on recently discovered epigenetic regulators of expression called long noncoding RNAs (lncRNAs). We will utilize human cell culture models to identify lncRNAs important for early human female preimplantation development, in particular X-linked transcripts involved in X-chromosome silencing, a critical event required for normal female development. Our goal is to develop markers that can identify abnormal placental development, predict poor implantation, and signal problems with embryonic differentiation, a powerful tool for preimplantation genetic diagnosis screens.

- **Title:** John Morgan Building – Research Infrastructure Project for the Department of Radiology  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this research infrastructure project is to renovate space in the John Morgan Building in support of the University of Pennsylvania Perelman School of Medicine's Department of Radiology. The project will provide approximately 8,400 square feet of renovated space and infrastructural improvements in order to consolidate Radiology labs currently located in disparate locations across campus. This will greatly enhance scientific synergies within the department and increase economies of scale for equipment and other resources, as well as create research bridges with other programs which address critical needs common to Penn, the NIH road map, and the Commonwealth of Pennsylvania.

- **Title:** Cellular Transdifferentiation for Regenerative Therapies  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** The purpose of this work is to make substantial advancements toward the direct conversion of endogenous cell types into cells that provide therapeutic benefit for cardiovascular or neurodegenerative disease.

- **Title:** Isolation, Biogenesis and Cargo of Microvesicles from Brain and Pancreatic Tumor Cells  
  **Type of Research:** Clinical
Focus: Oncological Sciences
Purpose: The purpose of this project is to develop new techniques and knowledge about brain and pancreatic tumor microvesicles (MV) that will allow their use for detection, prognosis and identification of treatment targets in patients. We will develop a handheld device that will reduce the collection and measurement time and increase the sensitivity of detection compared to currently available methods. We will interrogate the biogenesis of MV under tumor-like microenvironmental conditions and determine the nature of the material (cargo) within them using RNA isolation techniques and deep sequencing.

University of Pittsburgh ($7,752,646)
Research Projects:

- **Title:** Understanding the Role of Inflammation in Chronic Obstructive Pulmonary Disease
  Type of Research: Clinical
  Focus: Respiratory Sciences
  Purpose: Chronic Obstructive Pulmonary Disease (COPD) exhibits significant variability in disease pattern and rate of progression. At this time, no clinical attribute or biomarker can determine disease prognosis in an individual patient. This project will offer the most robust analysis to date defining the natural progression of tobacco-related lung disease, which should lead to a reclassification of COPD into more meaningful biological phenotypes. We further aim to discover biomarkers that identify patients at greatest risk for disease progression. Discovery of new markers associated with unique subclasses of disease will lead to more effective personalized treatment algorithms and monitoring of a therapeutic response.

- **Title:** Dissecting the Molecular Mechanisms of Stress-Response Proteins in Cancer
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This project leverages modern biocomputation and experiments to study the molecular mechanisms of stress-response proteins in cancer. We have selected two key stress response proteins, Y box binding protein 1 (YB-1) and heat shock protein 27 (Hsp-27), that are not only highly conserved but also involved in cancer drug resistance. Our approach will: (i) define, establish, and further study the YB-1 and Hsp27 interaction networks by understanding these networks’ composition and evolution and by determining the phenotypic consequences of their perturbations (Aim 1); and (ii) determine the physical principles of protein-protein and protein-ligand interactions in the Hsp27 and YB-1 networks (Aim 2).

- **Title:** Mitochondrial Biology in Cancer: A New Therapeutic Target for Killing Tumor Cell
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this study is to develop novel strategies that target mitochondrial biology to kill tumor cells. Two complementary approaches will be examined. We have recently discovered that inhibition of mitochondrial fatty acid oxidation (FAO) causes diminished oxidative phosphorylation, loss of adenosine triphosphate (ATP), and cell growth inhibition. FAO inhibitors alone and in combination will be examined for tumor cell growth inhibition, and novel in vivo imaging will be used to monitor fatty acid uptake into tumors. The second aim of this project is to inhibit mitochondrial dynamics in combination with cisplatin to initiate apoptotic cell death. Both in vitro and in vivo models will be examined.
• **Title:** A Pilot Study Evaluation of Sulforaphane in Atypical Nevi  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** This pilot trial is designed to determine the tolerance and pharmacokinetics of broccoli sprout extract-derived sulforaphane as a melanoma preventive agent in patients with multiple atypical nevi and a history of prior melanoma.

• **Title:** A Phase III Study of Adjuvant Ipilimumab vs. High-Dose Interferon α-2b for Resected High-Risk Melanoma  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** In this clinical trial, patients with stage III or stage IV melanoma that has been completely resected and who are at high risk for recurrence and death after surgery will be randomly assigned to receive adjuvant (post-surgical) treatment with either ipilimumab (investigational agent) or high-dose interferon α-2b (HDI, the current standard of care). This study has the potential to change the management of patients with high-risk resected melanoma, if ipilimumab is shown to be superior to HDI as hypothesized.

• **Title:** Phase II Study of Azacitidine and Entinostat (SNDX-275) in Patients with Advanced Breast Cancer  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** The purpose of this trial is to determine the objective response rate, safety, tolerability, progression-free survival, overall survival, and clinical benefit rate of the combination of the DNA methyltransferase inhibitor azacitidine (5-AZA) and the histone deacetylase inhibitor entinostat in women with advanced breast cancer (triple-negative and hormone-refractory). In addition, an optional continuation stage will evaluate whether the addition of hormonal therapy to 5-AZA and entinostat provides benefit after progression while receiving 5-AZA and entinostat.

• **Title:** Antigen-Engineered Dendritic Cell Vaccine +/- IFNα-2b Boost for Melanoma  
  **Type of Research:** Clinical  
  **Focus:** Oncological Sciences  
  **Purpose:** This project tests an improved dendritic cell (DC) vaccine for melanoma that is designed to promote in vivo cross-presentation and determinant spreading. We are engineering the DC with three full-length, defined, tumor antigens to activate multiple CD8+ and CD4+ T cell clones; providing antigen presentation for the life of the DC; providing CD4+ T cell help to the CD8+ T cells; using a matured DC; activating innate immunity via natural killer (NK) cell migration and activation; and boosting with systemic interferon alpha (IFNo). Together, this vaccine strategy should more potently activate a polyclonal anti-tumor response, which we predict will lead to more patients who develop determinant spreading and a significant clinical response.

• **Title:** Research Infrastructure: Biomedical Science Tower 10th Floor East Laboratory Renovation  
  **Type of Research:** Biomedical  
  **Focus:** Research Infrastructure Project  
  **Purpose:** The purpose of this project is to renovate approximately 25,000 square feet of laboratory space on the 10th floor of the Thomas E. Starzl Biomedical Science Tower (BST). The BST, a biomedical research facility providing nine floors of dedicated laboratory space, is located in the heart of the University of Pittsburgh campus. The proposed design will renovate the eastern half of the 10th floor. The
renovated space will be used to create and expand critical research facilities for the Department of Immunology. The proposed design will create a consolidated, modern, flexible, open laboratory space with associated support spaces.

- **Title**: Identification and Characterization of Regulators and Therapeutics of Cancer Signaling Networks  
  **Type of Research**: Biomedical  
  **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose**: This project leverages modern biocomputation and experimentation to study the molecular mechanisms, networks, and therapeutic targets of signaling pathways and molecules important for cancer progression. Our multifaceted approach will (1) identify novel apoptosis signaling pathway regulators and dissect the regulation mechanisms of the stress-response protein, Hsp27, which plays an important role in this process and (2) identify novel cancer therapeutic targets using computational analyses at the molecular and network levels.

**University of the Sciences in Philadelphia ($29,488)**

**Research Project:**

- **Title**: Health Literacy Interventions to Improve Medication Adherence  
  **Type of Research**: Health Services  
  **Focus**: Health of Populations, Behavioral and Biobehavioral Processes  
  **Purpose**: Our goal is to collect preliminary data leading to an efficacy trial of whether public health center patients with limited literacy (LL) or limited English proficiency (LEP) report (1) better comprehension of their illness and their medication regime (i.e. have better health literacy/HL), and (2) have better medication adherence (MA), following receipt of medication instructions written at a reduced reading level and/or in a foreign language of their choosing. Our purpose is to assess the effectiveness of this intervention in a busy, urban public health care setting.

**Wistar Institute ($1,491,186)**

**Research Projects:**

- **Title**: Informatics Solutions for NextGen Sequence Data Analysis  
  **Type of Research**: Biomedical  
  **Focus**: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose**: Recent genome-wide studies suggest that at least half of the human genes, including many therapeutic target genes, produce multiple protein isoforms through alternative transcription. Many of the isoforms produced in this manner are tightly regulated during normal development but are mis-regulated in cancer cells. We propose to develop novel algorithms and build an informatics platform for understanding gene regulation at isoform-level (alternative promoter or alternative transcript-level) by developing statistically rigorous bioinformatics resources for processing Next-Generation Sequencing (NGS) data to better understand gene regulatory mechanisms in mammalian cells, and more importantly, how dis-regulation of these mechanisms leads to cancer. The informatics platform will be tested by analyzing The Cancer Genome Atlas data.

- **Title**: Regulation of Immune Responses in Multiple Myeloma Bone Marrow Microenvironment  
  **Type of Research**: Biomedical  
  **Focus**: Immunology
Purpose: The purpose of this project is to evaluate the contribution of bone marrow immature myeloid cells in insufficient immune responses observed in multiple myeloma and validate strategy aimed to improve anti-tumor immune responses based on targeting these cells.

- **Title:** Molecular Basis of BRCA1 and PALB2 Tumor Suppression  
  **Type of Research:** Biomedical  
  **Focus:** Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics  
  **Purpose:** Our long-term goal is to detail the molecular basis of tumor suppressor activity of breast and ovarian cancer susceptibility genes (BRCA1 and PALB2) in order to develop a more rational and effective therapy following inactivation of these genes in breast and ovarian cancers. We postulate that BRCA1 and PALB2 are transducers of multiple signaling pathways and their functional inactivation in breast and ovarian epithelial cells lead to a loss of responsiveness to extracellular signals. Our working hypothesis is that the tumor suppressor activity of BRCA1 and PALB2 is due to their function as co-activators of transcription for growth inhibitory signals.

- **Title:** Analysis of Markers of Progression and Therapy Resistance in Melanoma  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Melanoma is an aggressive disease for which there is a universally poor prognosis. We have discovered that a dynamic transition of melanoma cells to a mesenchymal phenotype results in a highly invasive and therapy-resistant subpopulation of cells, marked by expression of the protein Wnt5A. This may hold significant implications for novel therapies currently being used to treat melanoma patients, specifically, BRAF inhibitors that are meeting with great success in the clinic, but to which, unfortunately, patients quickly develop resistance. We will test whether inhibiting the Wnt5A signaling pathway can overcome this observed resistance, and elucidate the mechanisms by which Wnt5A contributes to therapy resistance.

- **Title:** Developing Rational Strategies for Therapeutic Targeting of NRAS-Mutant Melanomas  
  **Type of Research:** Biomedical  
  **Focus:** Oncological Sciences  
  **Purpose:** Mutations in NRAS are found in approximately 25% of melanomas. These tumors are extremely aggressive and are among the most difficult tumors to treat. Unfortunately, there are no effective therapies to treat patients with NRAS mutant melanomas. Targeting NRAS itself has thus far not been successful; therefore, alternative strategies are necessary. The goal of this project is to identify key molecules that promote survival of NRAS mutant melanomas. These essential molecules could be potential targets for the treatment of NRAS mutant melanomas. We postulate that blocking critical molecules that are essential for survival of NRAS mutant tumors can kill these neoplasms.

*Updated 6/10/2015*