Health Research Formula Grants – State Fiscal Year 2018-19

Twenty-three organizations received health research formula grants totaling $33,426,300 for the state fiscal year 2018-19. Grants may support one or more research projects and research infrastructure projects. The grants started on 6/1/2019 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 ($48,955) – 1 Project

Research Projects:

- **Project 01**
  Title: *Positive Personality Attributes in Traumatic Brain Injury*
  Type of Research: Clinical Research
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of the present study is to examine engagement in inpatient rehabilitation (IR) as a mechanism that intervenes in the relationship between pre-injury positive personality attributes (PP) and post-injury outcomes. Traumatic Brain Injury (TBI) patients will be recruited from IR after patients' emergence from post-traumatic amnesia and within 60 days of injury, to complete retrospective ratings of patients' pre-injury PP. For the remaining duration of their IR stay, speech, physical, and occupational therapists will rate patients' engagement in therapy at each session. At 6 months post-injury, patients will be contacted by telephone for a follow-up assessment, including measures of post-injury PP and functional and psychosocial outcomes.

Allegheny Singer Research Institute ($55,390) – 1 Project

Research Projects:

- **Project 01**
  Title: *Novel Extracardiac Adhesive Strain Sensor to Measure Post-cardiotomy Cardiac Function*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: As many as 20% of patients undergoing open heart surgery can have immediate or delayed postoperative cardiovascular compromise. Patients at risk of right ventricular (RV) dysfunction are at higher risk and mortality. Cardiac function is monitored using a pulmonary artery catheter (PAC) to detect early problems via changes from the information gathered from the catheter. Additionally, in the setting of patients at risk of right sided heart failure, particularly those undergoing left ventricular assist device placement, heart transplant, or those with preoperative RV concerns, information regarding right ventricular function can be monitored to a degree. However, the PAC presents significant risks to patients including fatal arrhythmias, perforation of blood vessels or the heart, airway bleeding, entanglement and thrombus formation, bloodstream infection and sepsis. Additionally, the measurement of cardiac output from this catheter is often unreliable and inconsistent. Our objective is to show that application of an adhesive transient strain sensor can be applied to the surface of the pulmonary artery, right ventricular free wall and right atrial free wall and will measure the

same cardiac parameters as the PAC, as well as RV strain. The envisioned device application will: 1) be easily and effectively deployed; 2) avoid risk of bloodstream infection; and 3) provide accurate and precise measurements of cardiac function.

American College of Radiology ($477,587) – 1 Project

Research Projects:

- **Project 01**
  Title: *Improving Utilization of Lung Cancer Screening in Underserved PA Populations*
  Type of Research: Health Services Research
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to test a strategy for increasing lung cancer screening for Pennsylvania residents living in zip codes with high lung cancer mortality and low screening utilization, with focus on African Americans, Hispanics and rural residents served by two primary care networks - Lehigh Valley Health Network and Thomas Jefferson University Health System.

Baruch S. Blumberg Institute ($60,279) – 1 Project

Research Projects:

- **Project 01**
  Title: *The Mechanism of Immune Control of Hepatitis B Virus Infection*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The outcomes of Hepatitis B Virus (HBV) infection are determined by the strength and nature of host immune response. Studies in the last three decades indicate that in addition to the killing of infected hepatocytes by HBV antigen specific cytolytic T lymphocytes (CTL), noncytolytic cure of infected hepatocytes by proinflammatory cytokines plays an essential role in resolving HBV infection. In this project, we will focus our efforts to understand how interferons (IFNs), the key antiviral cytokines of innate and adaptive immune responses against HBV infection, silence the transcription of covalently closed circular (ccc) DNA minichromosomes and achieve a durable control of HBV replication.

Carnegie Mellon University ($516,169) – 2 Projects

Research Projects:

- **Project 01**
  Title: *Research Infrastructure for Shared Testing Labs for Health Psychology*
  Type of Research: Health Services
  Focus: Research Infrastructure Project
  Purpose: The Psychology Department intends to construct new shared testing areas for the health psychology research area. Faculty and students in this area specialize on assessing the interactions between human behavior and health outcomes, as well as how to improve outcomes through new interventions. The purpose of these new labs is to enable more effective, state-of-the-art studies within health psychology, as well as the efficacy of potential interventions.

- **Project 02**

Title: *The Integration of Object Identity with Object Use Knowledge in Parietal Cortex*
Type of Research: Biomedical
Focus: Biology of Development and Aging
Purpose: Everyday behavior depends on recognizing objects and manipulating them according to their function. An established finding with functional Magnetic Resonance Imaging (fMRI) is that viewing manipulable objects (i.e., 'tools') elicits differential blood oxygen level dependent (BOLD) responses in left parietal cortex. This program tests hypotheses about the roles of parietal sub-regions in object recognition and use. The results have implications for neurocognitive models of object processing and for rehabilitation strategies in brain-damaged patients.

The Children's Hospital of Philadelphia ($4,824,238) – 2 Projects

Research Projects:

- **Project 01**
  Title: *Single-cell Analysis to Study Mechanisms of Pediatric Cancer and Developmental Disorders*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The increasing awareness of molecular heterogeneity across a population of cells is driving a fundamental rethink as to how research questions related to normal development and diseases of childhood should be tackled. Single-cell technology has made its greatest impact in the fields of oncology, neuroscience and immunology. The overarching goal of this project is to harness the power of single-cell technology to better understand the transcriptomic, epigenomic, and tissue-microenvironmental heterogeneity in pediatric sarcoma, childhood epilepsy, and premature birth. Novel gene markers and therapeutic targets derived from the single-cell studies will be tested using cell line and animal models.

- **Project 02**
  Title: *Unbiased Identification of Gene Modifiers for Protein Aggregation Diseases*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The presence of protein aggregates is a hallmark of almost all neurodegenerative diseases including Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS) and other similar diseases. Despite the strong association between the formation of protein aggregates to disease, our understanding of the molecular mechanisms controlling it remains poor. The goal of this project is to systematically map and validate genes that affect the propensity of different disease-causing proteins to aggregate and to delineate how cells counter protein aggregation and whether this information can be used to devise new therapeutic approaches.

Drexel University ($1,012,965) – 11 Projects

Research Projects:

- **Project 01**
  Title: *Assessment of Brain Function During Social Interaction Among Children with Autism Spectrum Disorder*
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: Deficits in social communication and engagement represent a core symptom of autism spectrum disorder (ASD). In this project, we will investigate brain function, using functional near-infrared spectroscopy (fNIRS), in response to social stimuli in toddlers with and without ASD. This will be the first study to measure fNIRS brain response to social stimuli and brain to brain coupling in toddlers with ASD. Results will pave the way for additional studies to examine changes in brain function in response to interventions.

- **Project 02**
  Title: *Intra- versus Intermolecular Protein-Protein Interactions in Natural Product Biosynthesis*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Engineering of biosynthetic pathways to produce 'unnatural natural products' is necessary for the discovery of new therapeutics. Thus far, engineering efforts have been largely unsuccessful due to a lack in understanding of the protein dynamics and protein-protein interactions within these natural product synthases. Using one of the smallest multi-domain synthases, Ebony from *Drosophila melanogaster*, as a model system, we will elucidate the contributions of intra- and intermolecular protein-protein interactions to biosynthesis of a natural product. Engineering of the synthase will lead to an optimized synthase with enhanced productivity and novel activity.

- **Project 03**
  Title: *Characterization of the Conformational Change Properties of the HIV-1 Envelope Protein*
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: Antiretroviral therapy (ART) has dramatically prolonged and improved the lives of those infected with HIV. Nonetheless, HIV/AIDS continues to persist in PA (close to 36,000 people as of 2017) as well as globally. No cure exists for infected patients, and no vaccines or microbicides have been developed to protect the human population against HIV-1 infection. HIV-1 Env is the sole viral protein on the surface of virions and infected cells, is required for infection, and as such remains a critical target for prevention, treatment and eradication. These studies will examine the fundamental conformational change properties of the Env protein in order to inactivate the virus and stop infection and transmission by employing basic research approaches.

- **Project 04**
  Title: *Involvement of Hypocretin/Orexin in Opioid Withdrawal and Relapse*
  Type of Research: Biomedical

Focus: Neurosciences
Purpose: Physical withdrawal is the main reason that patients with opioid use disorder are unable to stop using opioids. Managing acute withdrawal (i.e., detoxification) is the first step in the continuum of care. Although buprenorphine, methadone and clonidine are widely used for acute withdrawal, they are not appropriate in certain clinical settings and have not been associated with long-term sobriety. Thus, there is a need for developing novel treatments that are effective for treating acute withdrawal symptoms and can lead to long-term abstinence. These studies will examine the role of the hypocretinergic/orexinergic system in opioid withdrawal by employing basic research approaches.

- **Project 05**
  Title: *Cardio-Electric Alterations and Cell-Based Therapies after Spinal Cord Injury*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this study is to examine cardio-electric disorders after high-level spinal cord injury (SCI) and to test the possibility of transplanting embryonic neural stem cells (NSCs) into the injured spinal cord for cardiac recovery. Although disrupting supraspinal vasomotor pathways causes abnormal basal hemodynamics and incidence of autonomic dysreflexia, it is unknown what cardiac conduction system changes occur following SCI. In this project, we will establish a rat SCI model and employ electrocardiography (ECG) and blood pressure records to disclose disordered cardiac electrophysiology; we will also examine the effect of transplanting embryonic brainstem derived NSCs on cardiac functional improvement.

- **Project 06**
  Title: *Targeting Cyclic-Dependent Kinase 5/Acyl-CoA Synthetase Short Chain 2 (CDK5/ACSS2) Axis in Glioblastoma*
  Type of Research: Oncological Sciences
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to perform basic research using brain cancer cells (T98G and U87-MG cells obtained from commercial sources ATCC, CRL-1690 and HTB-14 respectively) to uncover new pathways and treatments for patients with brain cancer. This study will further our understanding of how metabolism is reprogrammed in brain cancer cells to further drive cell growth and survival and to elucidate the connection between cyclic-dependent kinase 5 (CDK5) and acetate metabolism in glioblastomas. We aim to determine the molecular mechanism by which CDK5 regulates ACSS2, an essential metabolic enzyme, and the impact of this regulation on glioblastoma multiforme (GBM) growth and survival in vitro and using a novel glioblastoma tumor-host brain organotypic *ex vivo* slice system.

- **Project 07**
  Title: *Macrophage-derived Exosomes as Pain Therapeutic for Spinal Cord Injury*
  Type of Research: Neurosciences
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The identification and development of new and improved analgesics has

come to a virtual halt in recent years and a contributing factor to the growing opioid epidemic. Chronic neuropathic pain resulting from injury or malfunction of the nervous system is difficult to treat. The goal of this project is to harness the body's own analgesic mechanisms to provide more complete and long-lasting relief of pain. Exosomes are 30-150 nm vesicles playing a key role in intercellular communication. Our studies using exosomes from antigen presenting cells showed an attenuation of mechanical and thermal hypersensitivity in inflammatory pain model. Here we will test the efficacy of these exosomes in reversing pain using a spinal cord injury model.

- **Project 08**

  Title: *Control of Actin Dynamics by Disease-Linked Septin Isoforms and Mutants*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Dynamic changes in the filamentous protein actin underlie many cellular behaviors, including metastatic cancer invasion and cellular response to pathogens. SEPT9 is spliced into multiple isoforms. Upregulation of isoforms 1 and 3 or down regulation of isoform 2 correlate with poor cancer prognosis, suggesting they have opposite effects. Cell motility experiments mirror this pattern, but the mechanism of action however is unknown. Here we identify SEPT9 isoform 1 as a novel regulator of actin filament polymerization, providing a direct link to the machinery of cell motility. In this project, we will study the other SEPT9 isoforms, testing the idea that SEPT9 isoform effects on cell motility are connected to changes in actin dynamics.

- **Project 09**
  Title: *Examine Tau-Based Mechanisms and Therapies for Organophosphate-toxicity Using Organoids*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Organophosphates (OPs) comprise a lot of common agricultural and commercial pesticides that are widely used in Pennsylvania, USA. These proposed studies will potentially shed light on research in neurological disorders, such as Alzheimer's Disease, Parkinson's Disease and Gulf War Illness (GWI). The mechanism of the acute toxicity of OPs is primarily caused by cholinesterase inhibition. However, the neurological deficits associated with repeated exposures of "low-level" OPs that produce no overt signs of acute toxicity remains elusive. The purpose of this project is to perform basic research using diisopropylfluorophosphate (DFP) and human induced pluripotent stem cell (hiPSC, (#ASE-9109, Applied StemCell, CA)) derived forebrain organoids to determine whether tau pathology is the underlying mechanism of "low-level" OP exposure which induces neurological defects, such as reactive astrogliosis and synaptic hyperactivity.

- **Project 10**
  Title: *Targeting the Glucocorticoid System to Reduce Behavioral Deficits Following Pediatric TBI*

Type of Research: Biomedical
Focus: Neurosciences
Purpose: Pediatric traumatic brain injury (TBI) impacts an estimated 250,000 children under the age of 4 each year. As children with a history of TBI age into adolescence, they become susceptible to negative psychological outcomes following exposure to stress, suggesting that TBI may impair functional and behavioral mechanisms of the stress response and lead to deficits in stress coping behavior. Downregulation or suppression of the glucocorticoid receptor (GR) in the hippocampus of rats and mice leads to decreases in adaptive coping responses. The experiments in this project will investigate whether regulating the glucocorticoid system offers a viable therapeutic treatment to improve coping behaviors in children with TBI.

- **Project 11**
  Title: *Mitophagy and Senescence in the Pathogenesis and Therapeutics of Bronchopulmonary Dysplasia (BPD)*
  Type of Research: Biology of Development and Aging
  Focus: Oncological Sciences
  Purpose: The project is based on recent developments from our laboratory on the role of impaired mitophagy (mitochondrial quality control) in the induction of senescence in Type II alveolar epithelial cells (AECs) in the Bronchopulmonary Dysplasia (BPD) lungs leading to decreased epithelial cell proliferation and differentiation, a required process for normal lung development. This project will explore mitophagy and cellular senescence network in the developing lung as a therapeutic target for BPD. We aim to test novel strategies that prevent or reverse the impaired lung development in BPD caused by senescent Type II AECs in the developing lungs.

Duquesne University of the Holy Spirit ($85,398) – 1 Project

Research Projects:

- **Project 01**
  Title: *Prediction of Ipilimumab Response by Analysis of Circulating Melanoma Cells*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: This project tests the hypothesis that enumeration of circulating melanoma cells will predict response of ipilimumab in Stage III melanoma patients to prevent advancement to metastatic disease. We will complete a pilot study that will be used to develop a statistical model that relates CMC number to the prevention of metastatic disease in early stage melanoma patients undergoing ipilimumab treatment. This information can be used to design therapy for melanoma patients. Furthermore, we can use the same paradigm to determine the effectiveness of other chemotherapies that can be correlated with CMCs.

Franklin and Marshall College ($12,306) – 1 Project

- **Project 01**
  Title: *Nervous System Arousal and Social Learning in Autistic and Typically*

Developing Children
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Autism spectrum disorder (ASD), characterized primarily by impaired social abilities and abnormal reactions to sensory stimuli, now affects one in every 59 children. However, little is known about the connection between autonomous nervous system activity and socio-cognitive abilities in this population. The purpose of this study is to explore differences in autonomic nervous system (ANS) activation between children diagnosed with ASD and a matched typically-developing population. We will use infrared corneal eye-tracking technology to examine differences in attention and pupil dilation (controlled by the ANS) to social stimuli, examining how this reactivity changes across populations and influences social learning.

Geisinger Clinic ($225,671) – 1 Project

Research Projects:

- **Project 01**
  Title: *Genetic Contributions to Post-treatment Lyme Disease Syndrome*
  Type of Research: Biomedical Research
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This project addresses an important public health problem – Lyme disease – and one of its long-term consequences, post-treatment Lyme disease syndrome (PTLDS). Pennsylvania has more cases of Lyme disease than any other state. PTLDS, defined by persistent symptoms of fatigue, musculoskeletal pain, and cognitive complaints lasting at least six months (but often lasting many years) occurs in 15-20% of Lyme disease cases. Understanding the causes of and risk factors for PTLDS is a critical first step in its prevention. This research will provide greater understanding of the etiology of this condition by using electronic health record (EHR) and existing single nucleotide polymorphism (SNP) data to complete the first genome-wide association study (GWAS) of PTLDS.

The Institute for Cancer Research ($1,121,111) – 4 Projects

Research Projects:

- **Project 01**
  Title: *New Modes of Recognizing Histone Acetylation*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to explore the function of histone binding proteins in regulating the post-translational modification (PTM) of histone proteins. Histone PTMs have been shown to change with respect to aging and disease. Understanding this regulation may help us discover new therapeutic targets.

- **Project 02**
  Title: *Innate Immune Cell Responses to Early Stage Pancreatic Cancer*
  Type of Research: Biomedical
  Focus: Immunology

Purpose: Pancreatic cancer is one of the most deadly neoplastic diseases with a critical need for improved therapies. In a mouse model of pancreatic cancer, we have observed the infiltration of innate immune cells into early stage pancreatic lesions. In the studies for this project, we will better characterize these immune cells, test how they are recruited to pancreatic tissue, and whether they prevent or promote progression to cancer. Results from this project could lead to the development of effective immune-based therapies to prevent or treat this deadly disease.

- **Project 03**
  Title: *A New Pro-Pancreatic Cancer Desmoplastic Signaling Axis*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: It is predicted that the number of cancer deaths due to pancreatic cancer will increase to make it the second deadliest cancer (trailing lung cancer) in the U.S.A. by the year 2030. No effective therapies are available to treat this cancer. This project will establish if it is possible to inhibit pro-tumor while harnessing selected anti-tumor aspects of non-cancerous tumor neighboring cells. For this, we will employ a three-dimensional culturing system, used in the laboratory setting with human cells harvested from surgical samples, which models the cancer-associated neighborhood cells and their secreted fibrous substrate matrices, known as desmoplasia. We expect to learn new means to effectively stimulate anti-tumor neighborhoods.

- **Project 04**
  Title: *Influenza A Virus Infection of Neurons: Replication and Pathogenesis*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The identification of new influenza A virus (IAV) strains that can infect the central nervous system demands a thorough understanding of how these viruses can spread to and within the brain, as well as to define how IAV infection causes neuropathology. This project takes an integrated and comprehensive approach to address these issues, focused on the IAV reproductive cycle in neurons, innate immunity within permissive resident brain cells, and the basis of neuropathogenesis.

Lankenau Institute for Medical Research ($133,892) – 1 Project

Research Projects:

- **Project 01**
  Title: *Generation and Characterization of a TDO2 Specific Antibody*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project will develop a novel reagent that can be used in preclinical animal models and on human tissue samples to characterize the expression patterns of tryptophan 2,3-dioxygenase (TDO2). We will use an approach that relies on the availability of TDO2 genetically deficient mice and an antigen design using in silica analyses. With this strategy we will produce validated antibodies that will be TDO2 specific and recognize murine and human TDO2 when used in

immunostaining and western blotting analyses.

Lehigh University ($116,029) – 2 Projects

Research Projects:

- **Project 01**
  Title: *Validity of Multi-System Developmental Screening for Low-Income Infants and Toddlers*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to examine the psychometric quality of routine developmental screening with the Ages and Stages Questionnaire, Third Edition (ASQ-3) as conducted concurrently by primary healthcare providers and home visitors for low-income infants and toddlers. The consistency of administration integrity, scores, and subsequent recommendations across primary healthcare providers and home visitors will be statistically evaluated. Additionally, parents' understanding of the ASQ-3 content and processes for developmental screening, as conducted in both settings will be evaluated.

- **Project 02**
  Title: *Integration of Liquid Biopsy in Clinical Monitoring of Metastatic Cancer Therapy*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Liquid biopsy is a low-cost method to detect and analyze circulating cancer biomarker such as circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) in blood samples. However, liquid biopsy has not been adopted in clinical practice, due to the lack of benchmark tests and validation with traditional monitoring tools. In this project, we will correlate liquid biopsy quantification of CTCs, ctDNA, and next generation sequencing (NGS) results with regular clinical data, such as CT/MRI imaging, thus to provide a benchmark case for integration of liquid biopsy in clinical monitoring of metastatic cancer therapy.

Magee-Womens Research Institute and Foundation ($1,306,087) – 5 Projects

Research Projects:

- **Project 01**
  Title: *Impact of Contraceptives on Mediators of Immunity in the Female Reproductive Tract*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The project will expand our knowledge of how contraceptives used by Pennsylvanian women affect immune factors in the female reproductive tract. These markers of immunity have relevance to these women's susceptibility to reproductive infections, including HIV, and are of particular relevance to minority populations in Pennsylvania who more frequently use injectable forms of contraception, which have been linked to increased susceptibility to HIV.

- **Project 02**

Title: *Endothelial Dysfunction in Preeclampsia: Role of Extracellular Vesicles*
Type of Research: Biomedical
Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: The etiology and pathogenesis of preeclampsia, a pregnancy disorder that remains a major cause of maternal and fetal morbidity and mortality, remains poorly understood. The purpose of this project is to test whether extracellular vesicles (EVs) from maternal plasma affect vascular endothelial function differentially by EV source (normal pregnancy vs. preeclampsia). Data from this investigation should provide insight into the physiology of normal pregnancy adaptation and the pathophysiology of preeclampsia.

- **Project 03**
  Title: *Macrophage Senescence in the Pathogenesis of Mesh Complications in Diabetic Women*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The purpose of this project is to elucidate the mechanism of diabetes-associated risks in the pathogenesis of mesh-related complications (mesh exposure through vaginal epithelium and pain), which constitutes a significant clinical problem that occurs in diabetic women who undergo synthetic mesh augmented procedures in the surgical repair of stress urinary incontinence and pelvic organ prolapse. This study will test the hypothesis that premature macrophage senescence induced by diabetes through epigenetic modulations is the underlying mechanism by which diabetic women are at increased risk for mesh complications.

- **Project 04**
  Title: *The Gut Microbiome and Treatment in Ovarian Conditions*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to investigate the relationship between the gut microbiome and ovarian cancer response to therapy. We will compare differences in gut microbiome diversity and composition between women with ovarian cancer who do and do not respond to platinum-based chemotherapy in order to determine whether differences in gut microbiome diversity and composition correspond to differences in response to chemotherapy. We expect to identify differences in gut microbiome diversity and composition that are associated with improved therapy response. We further expect to identify specific gut bacteria that could serve as biomarkers of response to therapy.

- **Project 05**
  Title: *Analysis of Cell-Free Nucleic Acids in Pregnancy*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: In this project we hope to advance understanding of fetoplacental DNA methylation in early gestation via maternal plasma analysis by characterizing temporal changes in cell-free DNA (cfDNA) methylation signatures in maternal

plasma across the early gestational age span and profile changes in DNA methylation in maternal leukocytes through early gestation. In addition, we will undertake preliminary identification of non-invasive biomarkers for the future prediction of Spontaneous Preterm Birth (sPTB) and identify associations between an eventual outcome of sPTB and early gestational DNA methylation signatures in maternal plasma.

Monell Chemical Senses Center ($103,668) – 1 Project

Research Projects:

- **Project 01**
  Title: *Single-Cell RNA-Seq to Track Taste Cell Trajectories*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We will use single-cell RNA-Seq (scRNA-Seq) of taste cells to better understand taste cell turnover – the biological process responsible for maintaining structural and functional homeostasis in taste buds. Taste bud homeostasis is essential to protect against the taste loss and taste distortion that accompany certain disease states and promote poor nutrition. We will perform scRNA-Seq of ~30,000 taste cells: 10,000 each from the circumvallate and fungiform papillae of wild type mice and the circumvallate papillae of *Gli3* conditional knockout mice – mice that have dysregulated sweet taste receptor cell turnover. Powerful algorithms will be used to identify known and novel taste cell types and their marker genes and to track gene expression related to taste cell turnover. This study will improve our understanding of taste cell turnover and how turnover is affected by factors such as diet, aging, and cancer treatments.

Penn State University ($5,103,791) – 21 Projects

Research Projects:

- **Project 01**
  Title: *Angiotensin-(1-7) and Energy Expenditure in Human Obesity*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The purpose of this project is to better define the potential for targeting the beneficial hormone angiotensin-(1-7) to improve energy balance in obesity. We will test the overall hypothesis that angiotensin-(1-7) increases energy expenditure by promoting fat tissue heat production (adipose thermogenesis) in human obesity. To test this, we will determine if acute intravenous angiotensin-(1-7) infusion increases energy expenditure and gene expression for markers of adipose thermogenesis in obese human subjects in a randomized, double-blind, placebo-controlled, two-arm parallel group study. We will also examine for potential hemodynamic and hormonal mechanisms underlying any effects of angiotensin-(1-7) on energy expenditure.

- **Project 02**
  Title: *Novel Implant for Total Wrist Arthroplasty*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology

Purpose: Outcomes for arthritic patients following total wrist arthroplasty (TWA) are currently poor. Unfortunately, arthritis arises most commonly in elderly population, shows a female predilection, and is estimated to currently afflict over 50 million adults in the United States. The outcomes for patients with wrist arthritis need to be improved. We propose development of a novel TWA technology which can overcome some limitations of previous designs. Such a device could address shortcomings of state-of-the-art designs. However, cadaver testing including dislocation biomechanics and range of motion (ROM) analysis as well as metallic prototyping are required to demonstrate expected improvements in patient outcomes following TWA.

- **Project 03**
  Title: *Molecular and Cellular Dissection of AUTS2-regulated Neural Program Using Mini Brain*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Recent genetic and genomic efforts have identified hundreds of risk genes for neurological disorders. However, the functional impact of most of these disease-associated alleles remains unclear due to the remarkable complexity of the nervous system. There is a tremendous need to define cell type-specific effects and underlying mechanisms in order to better understand disease pathogenesis, improve diagnoses, and ultimately to develop treatments for neurodevelopmental disorders. Our research seeks to address these challenges for a key risk gene, Autism Susceptibility Candidate 2 (AUTS2), and define its role in neural differentiation.

- **Project 04**
  Title: *Opioid-Induced Hyperalgesia (OIH) Effects on Neuronal Output in the Periaqueductal Gray*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: OIH is characterized as enhanced or aggravated pain with decreases in the pain threshold from baseline. The pain is often diffuse and unassociated with previous tissue damage. These clinical symptoms illustrate opioid-induced side effects that are deleterious to their intended pain-relieving purpose. Additionally, because of its overlapping symptoms with opioid tolerance and opioid withdrawal, OIH is often hard to diagnose. Therefore, it is necessary to understand the neurocircuits and cellular mechanisms mediating OIH in order to design more effective opioid treatments and diagnostic strategies.

- **Project 05**
  Title: *Epinephrine as an Antidote against Lethal H2S Intoxication*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The aim of our project is to demonstrate the efficacy of epinephrine during the period of post-sulfide exposure, to treat H_2S-induced depression in cardiac contractility; i.e., during life-threatening sulfide intoxication. Our objective is

to prevent pulseless electrical activity (PEA). The known and expected effects of *epinephrine* on cardiac contractility and intra-cellular calcium should restore circulation in severely intoxicated victims presenting with persistent cardiogenic shock. Finally, *epinephrine* is readily available in many ambulances in large quantities and can be administered by pre-hospital providers without delay via intravenous, intramuscular, or intra-osseous routes.

- **Project 06**
  Title: *Role of Red Blood Cell Released ATP in Vascular Inflammation and Atherosclerosis*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: While the systemic risk factors such as hyperlipidemia are exposed to entire vasculature under pathological conditions, the atherosclerotic plaques often preferentially develop at vascular sites with disturbed flow, indicating a role of hemodynamic forces in atherogenesis. For decades, the flow dynamics related studies only focused on the effect of fluid-generated wall shear stress on endothelial cells, and overlooked the impact of mechanical force-activated blood cells on the vascular walls. The proposed research will fill this gap and investigate how disturbed blood flow-activated red blood cells affect endothelial cell function and promote inflammation and atherosclerosis.

- **Project 07**

  Title: *Cellular and Molecular Roles for Autoimmune Regulator in Early Skin Tumorigenesis*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Human skin is continuously exposed to ultraviolet irradiation, the leading cause of non-melanoma skin cancers (NMSC). The incidence rate of NMSC continues to rise, particularly in aging and immunocompromised patients. Current drug therapies are often unsuccessful with high rates of recurrence and often severe side effects owing to the lack of specificity for cancer cells. This project will address the role(s) of autoimmune regulator (Aire) as a key contributor to NMSC development. In particular, this project will define the impact of Aire expression and function on cellular growth and death, inflammation, and deoxyribonucleic acid (DNA) damage – all of which are critical enablers of tumor initiation and progression. Altogether, this project will lay the groundwork for future studies targeting Aire and Aire-dependent molecular pathways to delay or reverse skin tumorigenesis.

- **Project 08**
  Title: *Voltage-gated Sodium Channel Remodeling of Vagal Afferents in an Animal Model of Spinal Cord Injury*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: While the investigation of Na_V channels are well-established in the focused research area of nociceptive processing and pain, the investigation of

sensory remodeling is not established in the field of spinal cord injury (SCI). The remodeling of Na_V1s in other vagally-innervated organ systems (e.g., cardiac baroreflex and tracheal/pulmonary function) have provided tantalizing models and insights, but they do not inherently reflect gastrointestinal dysfunction. Our focus on the remodeling of gastrointestinal-projecting vagal afferents in gastrointestinal dysfunction following SCI is completely unexplored and opens new ground in what is a profoundly altered physiology that is unlike any other neurological deficit.

- **Project 09**
  Title: *Development of an Optimized Merkel Cell Polyomavirus Infection System*
  Type of Research: Infectious Diseases and Microbiology
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Merkel cell polyomavirus (MCV) is a recently discovered polyomavirus causing a rare but aggressive form of skin cancer, Merkel cell carcinoma (MCC). Studies on the lifecycle of this cancer virus have been difficult because it is detectable only by polymerase chain reaction (PCR) in healthy humans and no cell culture systems are available to efficiently propagate the virus and study cell-to-cell transmission. Developing new experimental model systems to resolve cell host factors that regulate the latent and lytic infection of MCV would facilitate preventative and diagnostic methods to reduce the spread of MCV, as well as other human polyomaviruses that cause severe human diseases.

- **Project 10**
  Title: *CCK Receptor Antagonist Proglumide as a Novel Anti-fibrotic Agent for Pancreatic Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Cholecystokinin (CCK) receptor signaling influences pancreatic tumor fibrosis, and pharmacologic blockade of the CCK receptors decreases but does not eliminate pancreatic ductal adenocarcinoma (PDAC) tumor fibrosis – a mechanism that is different from that of other anti-fibrotic agents. In this project, we will further investigate the mechanism of action of proglumide using cell lines in vitro and tumor samples previously generated by our lab, generate a profile of fibrosis development in a genetically-engineered, fully penetrant murine model of metastatic pancreatic ductal adenocarcinoma: the KPC mouse, which expresses mutated Kras and p53 genes in a pancreas-specific manner (Pdx1-**C**re/LSL-**K**ras$^{G12D/+}$/ LSL-Tr**p**53$^{R172H/+}$). We will directly compare the efficacy of proglumide to another clinically relevant anti-fibrotic agent, all-trans retinoic acid (ATRA), in an orthotopic murine PDAC model.

- **Project 11**
  Title: *Efficacy and Safety of Novel Naltrexone Formulations for Diabetic Wound Treatment*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The purpose of this research study is to prepare novel Good Manufacturing Practices (GMP) formulations with naltrexone as the active ingredient and test the efficacy to close full-thickness cutaneous wounds and the

safety of this novel formulation using diabetic rats.

- **Project 12**
  Title: *Novel Approaches to Improve Precision Oncology by Targeting the Replication Stress Response*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Genome instability is a hallmark and driver of cancer, but also an Achilles heel to be exploited for cancer therapy. The objectives of our multidisciplinary collaboration are to understand how the genetic background of tumor cells impacts genome instability-targeted therapies, and to discover new inhibitors of this process that can be used as primary or adjuvant chemotherapy reagents and positively impact the clinical management of cancer patients. The premise of this project is that additional genetic backgrounds will confer improved responses to drugs targeting DNA repair/replication stress pathways. Because tumor cells become therapy resistant, new targets in this pathway are urgently needed to obtain sustained clinical responses.

- **Project 13**
  Title: *The Role of IFN-λ in Anti-pathogen Responses at Barrier Surfaces*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this project is to study the role of interferon lambda in immune responses to examine viral, parasite and bacterial pathogens to identify common and specific traits in the immune response to each. Because Interferon lambda, but not other interferons, is produced only at barrier surfaces, it is a strong candidate for therapeutic intervention without significant systemic side effects. The information gained in this project will be used to apply for subsequent funding, and information from those studies can then potentially be applied in the design of therapeutics.

- **Project 14**
  Title: *Systemic Lupus Erythematosus: Genes to Mechanisms*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Our multidisciplinary team project is focused on studying the mechanisms of disease contributing to the pathogenesis of systemic lupus erythematosus (SLE). Many advances in understanding lupus autoimmunity have made use of animal models, but biomarker and therapeutic target validation for translation to patient care will require human studies. The current project includes investigations using samples from patients, in vitro experiments and limited murine studies to probe the idea that early changes leading to full-blown disease might be identified and targeted for therapeutic interventions.

- **Project 15**
  Title: *Precision Mapping of Metabolites and Micronutrients through Mass Spectrometry*
  Type of Research: Biomedical

Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
Purpose: Understanding changes in metabolite concentrations has yielded important insights into numerous diseases including obesity, diabetes, and cancer. Additionally, along with macromolecules, micronutrients (e.g., iron, zinc, magnesium) have been demonstrated to play critical regulatory roles. Using combinations of mass spectrometry-based imaging (time-of-flight secondary ion mass spectrometry [TOF-SIMS]) and inductively coupled plasma mass spectrometry (ICP-MS) we will explore the spatial distribution of metabolites along with the regulatory roles of micronutrients in cells and tissues in models of obesity and cancer. These novel approaches will provide unprecedented insight in cellular metabolism.

- **Project 16**
  Title: *Establishing the Authenticity of Epstein-Barr Virus Infection in the Rabbit*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Animal models are critical to a full understanding of infectious diseases in humans. The purpose of this study is to determine whether rabbits serve as an authentic model of Epstein-Barr virus infection in humans. An animal model allows the study of infection in the context of an immune system and a full exploration of the lifecycle of the virus and its passage between different tissues and is essential for the future development of vaccines or therapeutics.

- **Project 17**
  Title: *A Novel Mouse Model of Post-Traumatic Stress Disorder: Development and Validation*
  Type of Research: Biomedical/Clinical
  Focus: Neurosciences
  Purpose: Post-traumatic stress disorder (PTSD) is a debilitating mental health condition with limited treatments. To find novel treatments, better mouse models of PTSD are needed that can utilize cutting edge research tools not currently available in other species. This project aims to establish and validate a novel, reliable, and reproducible model of PTSD in C57Bl6/J mice, a strain of mice typically used as a background strain in many transgenic lines. Once this novel mouse model of PTSD is established, further testing will utilize cutting edge neuroscience techniques to test the hypothesis that PTSD exposure enhances excitability of stress-related neurons in the amygdala. Overall, these studies will provide new tools to examine PTSD and aid discovery of novel treatments.

- **Project 18**
  Title: *Nonalcoholic Steatohepatitis Fitness Intervention for Thrombosis (NASHFit) Trial*
  Type of Research: Biomedical/Clinical
  Focus: Digestive Sciences
  Purpose: This project presents a two-year research career development program focused on the study of physical activity in nonalcoholic fatty liver disease (NAFLD) to improve patient-oriented outcomes. NAFLD is the leading cause of chronic liver disease in the United States. The *central hypothesis* of this project is

that gains in fitness and changes in body composition can mitigate clotting risk in nonalcoholic steatohepatitis (NASH) as measured by adipose tissue produced plasminogen activator inhibitor one (PAI-1), an established biomarker for clotting risk. The foundation for this project is based on our *preliminary studies* showing patients with NASH are predisposed to venous thromboembolism and the mechanistic work of others showing defects in clot breakdown, which is mediated by PAI-1. We found that NAFLD patients are at 250% increased risk for venous thromboembolism.

- **Project 19**
  Title: *Gender and Stress: Effect on the Brain-gut Axis*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The project will provide a deeper understanding of the cellular and neural mechanisms by which estrogen influences the etiology of functional gastrointestinal disorders and, by consequence, help identify potential targets for more effective therapeutic interventions directed specifically towards women, in addition to providing novel insights into changes in GI functions that occur in the peri-menopausal period.

- **Project 20**
  Title: *Integration of Differentially Regulated Pathways of Selective Targeting of Leukemia Stem Cells in Models of Human Acute Myeloid Leukemia*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Acute myelogenous leukemia (AML) is a devastating blood cancer. Persistent leukemia stem cells (LSCs) represents a major cause of chemotherapy resistance and leukemia relapse. Recent studies from our group have shown that a cyclopentenone prostaglandin (CyPG) metabolite □^{12}-PGJ$_3$) successfully targets AML stem cells for apoptosis. The purpose of this collaborative study is to understand how LSCs isolated from either the humanized AML model as well as the murine model of AML differ from hematopoietic stem cells (HSCs) and identify the basis for the increased sensitivity of LSCs to □^{12}-PGJ$_3$. The outcome of this investigation could lead to a clinical trial targeting LSCs by □^{12}-PGJ$_3$ for AML treatment. In addition, the data collected here will provide novel targets to be tested as part of future grant proposals.

- **Project 21**
  Title: *Innate Immune Responses to Intracellular Parasites*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Pathogenic parasitic infectious diseases such as Toxoplasmosis, Chagas disease, Trichomoniasis and Toxocara, which infect humans through cat and dog feces or tick bites, cause several life-threatening diseases including seizures, schizophrenia, blindness, pregnancy complications, heart failure, severe lung and kidney pathology, and even deaths. Although proinflammatory responses produced upon parasitic infections have been shown to contribute to several organ-specific pathologies, the mechanisms that underlie adverse immune

responses leading to disease pathogenesis still remain unclear. Here, we plan to study the modulation of dendritic cells (DCs) and T cell function by B1 cells using a parasite-infection model. The knowledge gained is likely to help in developing strategies to manage and treat infectious parasitic diseases.

Salus University ($37,725) – 1 Project

Research Projects:

- **Project 01**
  Title: *Protein Inhibitor to Suppress Dominant GUCY2D Retinopathy in a Mouse Model*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Autosomal dominant retinopathy CORD6 is a form of hereditary blindness caused by rod and cone photoreceptor degeneration due to abnormally high stimulation of a mutated retinal guanylyl cyclase, GUCY2D, by its regulator protein, GCAP1. We will develop a protein inhibitor of the cyclase (GCAP-In), by modifying GCAP1 such that it binds to but does not activate GUCY2D and, furthermore, prevents the cyclase activation by the normal GCAP1. Transgenic expression of GCAP-In in a mouse model will then be used to test its ability to rescue or delay the dominant GUCY2D retinopathy in mice. We expect that the knowledge obtained from this pilot project could lead to a new approach to a potential treatment of GUCY2D dominant retinopathy in humans.

Temple University-of the Commonwealth System of Higher Education ($2,366,163) – 6 Projects

Research Projects:

- **Project 01**
  Title: *The Role of Non-coding RNAs in Neurodegenerative Dementias*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Tauopathies are neurodegenerative disorders characterized by accumulation of abnormal tau protein which results in memory loss and dementia. The mechanisms responsible for them are unknown and no effective treatment is available. We hypothesize that specific small noncoding RNAs play a functional role in the onset and progression of these diseases. This research, by characterizing the biological link between noncoding RNAs, tau metabolism, brain activity and synaptic function and the pathogenesis of these neurodegenerative diseases with dementia, will provide new insights on the neurobiology of these small molecules, and most importantly has the potential to establish them as new therapeutic targets for the diseases.

- **Project 02**
  Title: *Wells and Enteric Disease Transmission (WET) - A randomized controlled trial (WET-Trial)*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: We estimate that up to 80,000 cases of acute gastrointestinal illnesses (AGI) per year could be attributed to the consumption of untreated private

well water in Pennsylvania (PA). These cases of AGI can cause a significant burden in terms of health care costs and lost work/school days. The purpose of this research is to understand the extent that child AGI can be attributable to consuming untreated private well water, which viral, bacterial and protozoan pathogens are the most likely contributors of AGI in these water supplies, and whether ultraviolet water treatment is an effective intervention. The results will help inform AGI burden estimates and policy decisions regarding the management of private well water supplies in PA and across the US.

- **Project 03**
  Title: *Individualized Concussion Risk Assessment and Cellular Implications*
  Type of Research: Health Services
  Focus: Neurosciences
  Purpose: Studies have been conducted to identify signs and symptoms of concussions; however, well-controlled studies exploring why some athletes require a longer time to recover than others do not exist. This is important since athletes that are prone to prolonged recovery are at risk for sustaining long-term dysfunction such as depression, memory problems, and deficits in judgment. Thus, it is imperative that athletes receive counsel about their risk prior to participating in sports and sustaining a concussion. Our project will add significant knowledge regarding potential genetic associations with concussion by utilizing a large cohort and performing genetic analyses that focus on an individualized approach to providing medical care. We will also conduct experiments to increase understanding of the cellular dysfunctions that contribute to long term cognitive, sensorimotor, and functional impairment.

- **Project 04**
  Title: *Epigenetic Reprogramming of Diabetic Stem Cells for Cardiac Repair*
  Type of Research: Health Services
  Focus: Cardiovascular Sciences
  Purpose: Heart disease is a leading cause of morbidity and mortality amongst Americans and patients with diabetes pose an additional risk for heart disease and failure. Adult stem cells from patients own bone marrow are currently used in the clinical trials to enhance the repair and regeneration of the diseased heart and have shown limited improvement in patients with ischemic heart disease in part due poor functional properties and survival of stem cells obtained from diabetic patients. Studies proposed in this project will test a novel approach to reprogram diabetic stem cells and improve their functional ability to repair injured heart using diabetic mice as a model system. Findings from this research may significantly improve upon existing regenerative cell therapy for diabetic patients with cardiovascular diseases.

- **Project 05**
  Title: *Understanding how the Heart and Secreted Factors can Regulate Fat Cells and Obesity*
  Type of Research: Health Services
  Focus: Cardiovascular Sciences
  Purpose: This project is designed to elucidate novel biological signals released

from the heart and its cells that can control adiposity. Discovering such signals could uncover innovative strategies to combat obesity, a key risk factor for cardiovascular disease as well as to identify undiscovered pathways that are linked to systemic metabolic dysfunction present in heart failure (HF) patients. The global prevalence of obesity has reached epidemic proportions and is a multi-organ disorder that over time, predisposes development of numerous comorbidities including type II diabetes, hypertension, stroke and HF. This project will uncover, for the first time, factors released from the heart that regulate fat, which may lead to new strategies to combat obesity.

- **Project 06**
  Title: *Research Infrastructure Project: Late Stage Research Gene Sequencing Core Facility*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to renovate a space within the Old Dental School (Old Dental School) facility that is presently vacant and not being utilized for any research purpose; and install a new Late Stage Research Gene Sequencing Core Facility (Sequencing Core Facility) in the Old Dental School, to include: a high throughput computing station and analysis area for sequencing data; a conference and service center for sequencing and computation; and additional lab area comprised of two lab benches and a hood for research.

Thomas Jefferson University ($2,014,710) – 5 Projects

Research Projects:

- **Project 01**
  Title: *Molecular and Functional Characterization of Human Prostate Cancer Stem Cells*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The goal of this project is to characterize prostate cancer stem cells by conducting multidimensional analyses of the molecular biology and genetics of human prostate cancer. The experimental design includes the development of two clinical tangibles to be delivered to the community of prostate cancer patients, namely the generation of a new predictive assay of tumor aggressiveness and metastatic potential, and the identification of novel therapeutic targets.

- **Project 02**
  Title: *Role of Inflammatory Cytokines in Pathogenesis of Peripheral Cutaneous T-cell Lymphoma*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Cancer development is an evolutionary process driven by the accumulation of molecular events across multistage carcinogenesis. The purpose of this project is to understand the process of cytokine-driven oncogenic events in cancer development and identify novel targets for treatment of peripheral

cutaneous T-cell lymphoma.

- **Project 03**
  Title: *Functional Screening for Oncogenic Dependencies*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: In this project we will address the major lack in understanding of the identities and the tumorigenic roles of genes impacted by epigenetic alterations in AML. To do this we will quantify global changes in gene expression in response to modulation of unnamed gene activity in AML, and perform a functional screen to knockdown these gene responses using CRISPR-Cas9 system to identify important genes necessary for AML maintenance with the goal of identifying therapeutically actionable targets. *(gene is considered confidential and not specified here)*

- **Project 04**
  Title: *Understanding the Biology of Very Early Onset -Inflammatory Bowel Disease (VEO-IBD)*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: VEO-IBD is a more aggressive and refractory form of IBD in children under 6 years old. Because of the early onset and noticeable family history it is believed that there is a strong underlying genetic contribution to the process. Recent whole genome studies, by our lab and others, have revealed an intimate association between mutations in Primary Immunodeficiency-related genes and VEO-IBD in these cohorts of patients. In this project, we aim to investigate the contributions of specific novel gene mutations on the pathophysiology of the disorder and shed light into novel defective pathways that could be used for diagnostic purposes and targeted for potential therapies for Hyper Inflammatory Disorders and Immunodeficiencies.

- **Project 05**
  Title: *Deficient T regulatory Cell (Treg) Function in Relapsing Remitting Multiple Sclerosis (RRMS)*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this research is to find out how the T regulatory (Treg) cells control autoimmune response in multiple sclerosis. We will identify Treg molecular markers and changes in function in patients with RRMS. The study results may provide new therapeutic targets.

The Trustees of the University of Pennsylvania ($6,004,460) – 13 Projects

Research Projects:

- **Project 01**
  Title: *Mitochondrial Mutation Dynamics in Degenerative Cellular Diseases*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes

and Genetics
Purpose: Mitochondria dysfunction has been associated with a wide range of degenerative human diseases as well as with general aging. The degenerative states are hypothesized to arise through an increase in frequency of defective mutant mitochondria during somatic expansion until a threshold level is reached. The goal of this project is to determine the dynamics of germline transmitted and somatic mutations of the mitochondria within an individual, especially transmitted as cryptic hetroplasmy (variant mitochondrial genomes in single cell) in a single mitochondrion. We will investigate the dynamics of changes in mutant allele frequency at single mitochondria resolution and develop a state-of-art model of mitochondrial disease risk.

- **Project 02**
  Title: *Transgenerational Effects of Parental Nicotine*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Children of parents who smoke are at high risk for developing nicotine dependence and cognitive impairments, which suggests that nicotine may reprogram the germline to produce trans-generational addiction-like behaviors. In order to model these heritable phenotypes, we recently established a novel rat model in which voluntary paternal nicotine taking confers increased vulnerability to nicotine reinforcement and elicits memory deficits in male and female progeny. In this project, we will use this behavioral paradigm to further characterize the heritable effects of paternal nicotine taking and identify novel neurobiological mechanisms that may be targeted to prevent increased nicotine taking and cognitive deficits in subsequent generations.

- **Project 03**
  Title: *Molecular Mechanisms of TRPA1 Modulation: Protein Involved in Cardiovascular Biology*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: In this project, we will utilize cryo electron microscopy as a tool to discover molecular mechanisms of TRPA1 ligand modulation. This approach will provide significant knowledge about this TRPA1 channel that plays a critical role in mediating vascular flow and blood pressure.

- **Project 04**
  Title: *Expand Hematopoietic Stem Cells to Improve the Treatment of Hematologic Disorders*
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: The purpose of this project is to identify regulators that control hematopoietic stem and progenitor cell (HSPC) expansion and to explore their therapeutic potential for the treatment of blood disorders, such as Fanconi Anemia (FA).

- **Project 05**
  Title: *Improving Cartilage Repair by Applying Selected Stem Cell Populations and Biomaterials*
  Type of Research: Biomedical
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Osteoarthritis (OA) is a crippling disease that limits mobility and decreases quality of life and ultimately directs patients towards total joint replacement with metal and plastic prosthetic devices. As the US population ages, joint degeneration and OA has become pandemic with upwards of 2 million joints expected to be replaced annually by the year 2030. To address this issue, this project uses biomaterial-based stem cell therapies to treat early stages of disease progression, and evaluates these stem cell therapies in a large animal model. The purpose of this experiment is to test the hypothesis that selected stem cell populations with superior chondrogenic capacity will result in improved tissue repair in vivo.

- **Project 06**
  Title: *Molecular and Cellular Mechanisms Underlying Glioblastoma Invasion and Pathogenesis*
  Type of Research: Biomedical
  Focus: Nurosciences
  Purpose: Glioblastoma (GBM) is the most prevalent malignant brain tumor in adults. Due to its aggressive and invasive nature, GBM remains invariably lethal with poor prognosis. One major contributor for GBM malignancy and its worse prognosis, is the highly infiltrative growth of GBM cells into the healthy brain that is difficult to remove by surgery. Current GBM models commonly utilized in the research laboratories do not recapitulate the complex tumor characteristics and lack infiltrative phenotypes. We have recently developed a novel tissue model by generating tumor organoids from resected GBM from patients. The purpose of the project is to develop in vitro and in vivo experimental models to model GBM migration and invasion using organoids and to identify key molecules that drive tumor cell motility. Our study may lead to the development of novel therapies to treat or prevent the recurrence of GBM.

- **Project 07**
  Title: *Anti-fibrotic Immunotherapy in Heart Tests Genome Stability and Cell Fate Regulation by Matrix*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Motivated by the fact that heart disease is the leading cause of death for women and men, and that both chronic and acute events increase extracellular matrix collagen, the purpose of this project is to discover mechanisms that link heart fibrosis and extracellular matrix collagen to genome integrity and to gene expression in heart. The latter nuclear features are key to a healthy cardiac cell phenotype. As part of validating discovered mechanisms, we will explore a cell immunotherapy approach for the treatment of heart disease.

- **Project 08**

Title: *Exploiting Stem Cell Plasticity to Enhance Skin Regeneration*
Type of Research: Biomedical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: The healing of skin wounds occurs ideally with full regeneration of all cell types and structures, but typically involves some level of replacement by fibrotic scars. The regeneration vs. scarring balance can be perturbed in pathologic wound healing including in keloids (a type of exaggerated scar), and in the elderly, who display slowed rates of healing. Telomere dysfunction is hypothesized to contribute to these types of pathologic wound healing. We will investigate how different stem cell populations contribute to healing and scar formation, how healing vs. scaring associated with cellular plasticity, and how these are impacted by telomere dysfunction. Our findings will help lead to novel therapeutic approaches to enhance wound healing.

- **Project 09**
  Title: *Development and Maturation of Male Germline Stem Cells*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Germ cells are the only cells that transmit genetic information from one generation to the next. If errors occur during germ cell development or if germ cells are destroyed by drugs such as chemotherapy during cancer treatment, the outcome is permanent infertility. In the post-natal mammal, male germ cells are called spermatogonial stem cells (SSC) which are the foundation of spermatogenesis and critical for fertility maintenance in males. The mechanisms underlying germ cell development and SSC differentiation and maturation are not fully understood. We will investigate the development and maturation of human male germline stem cells and SSCs in vitro. These studies may offer important insight into fertility preservation and infertility.

- **Project 10**
  Title: *Environmental Polycyclic Aromatic Hydrocarbons and Risk of Lung Cancer in Never Smokers*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Our long-term goal is to understand individual and population level environmental exposures to polycyclic aromatic hydrocarbons (PAHs) and to predict sub-populations of never smokers at high-risk of non-small cell lung cancer (NSCLC) using sophisticated metabolomics methodology. Our hypothesis is that PAHs are major modifiers of NSCLC risk in never-smokers. We will generate PAH-associated metabolic profiles in never smokers with NSCLC and matched controls. Levels of the dysregulated metabolomic biomarkers will be correlated with individual PAHs to determine if they confer excess risk to NSCLC. This will be the first study to look at PAH-metabolites in non-smoker population living in an urban area in the US.

- **Project 11**

Title: *Improving Outcome Assessment in Survivorship Care Planning*
Type of Research: Health Services
Focus: Health of Populations, Behavioral and Biobehavioral Processes
Purpose: Survivorship care plans have been mandated, but implementation has been modest, due, in part, to a lack of evidence for efficacy that would justify the expenses necessary in routine care. A primary reason for this appears to be a lack of reliable outcome measures that assess consensus-driven and relevant constructs across populations. This project will refine and psychometrically evaluate an existing, peer-vetted outcome measure that will serve as a basis for comparisons across disease sites in order to foster the evaluations of efficacy that are required to support efforts to implement appropriate survivorship/follow-up care for cancer survivors.

- **Project 12**
  Title: *Mechanisms of Immunotoxicology in Cancer Patients*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The administration of checkpoint blockade to patients with non-small cell lung cancer (NSCLC) has altered the therapeutic landscape. However, checkpoint inhibitors are associated with immune-mediated adverse events (irAE) that resemble spontaneous autoimmunity. The mechanisms underpinning irAE's remain poorly understood and there are no predictive algorithms to identify patients that may develop these complications. This project will utilize CURE funds to perform a prospective observational clinical trial of lung cancer patients with immune-related complications of checkpoint blockade. The goal of this project is to identify the clinical and biological markers to predict the development of irAE's.

- **Project 13**
  Title: *Improving Tobacco Treatment Rates for Cancer Patients Who Smoke*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project will evaluate a pragmatic method of enhancing tobacco use treatment rates within oncology, utilizing the behavioral economics of clinician decision-making.

University of Pittsburgh-of the Commonwealth System of Higher Education ($6,004,460) – 3 Projects

Research Projects:

- **Project 01**
  Title: *MRI Assessment of Regional Brain Variability with Gender and Age*
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: The overall goal of this research is to investigate, in a population of nonhuman primates, the anatomical variability in overall brain size with gender and age, as a way to understand how the prevalence, age of onset, and symptomatology of common neurological conditions differ between males and females. As the number of Americans over age 65 is projected to more than

double in the next 40 years, it is essential to understand how the brain changes with aging to help distinguish normal changes from those associated with diseases such as dementia and Alzheimer's disease. We have chosen marmosets as our nonhuman primate model because we can study, in great detail, the brains of a large number of individuals.

- **Project 02**
  Title: *Assessment of Decline in Functional Brain Connectivity with Age*
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: The goal of this research is to investigate the decline in functional brain connectivity with gender and age using a nonhuman primate model to understand how age-dependent cognitive decline in males and females may differ. Alzheimer's disease, the most common cause of dementia, afflicts over 5.5 million people aged 65 or older in the United States, two-thirds of whom are women. Since the population of those over 65 is projected to more than double in the next 40 years, it is essential to understand how brain function changes with aging to help us distinguish normal changes from those associated with disease. We have chosen marmosets because we can study the brains of a large number of individuals in detail.

- **Project 03**
  Title: *Optimizing ATR Inhibitor Therapy through Physiologically Based Modeling*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Ataxia telangiectasia- and Rad3-related (ATR) protein, a serine/threonine kinase, is one of the most important initiators and regulators of DNA damage repair and checkpoint signaling. As such, the potential of ATR inhibitors (ATRi) to enhance ionizing radiation (IR) and chemotherapy for cancer is under investigation in 33 clinical trials (www.clinicaltrials.gov). This project aims to characterize physiologically relevant tissue exposures of ATRi in mice and evaluate how these concentrations, and the differences between different ATRi drugs, predict toxicity, immune response, and efficacy read-outs when combined with IR. This knowledge will inform optimal drug choice and timing of radiation therapy relative to ATRi dosing.

University of the Sciences in Philadelphia ($43,799) – 1 Project

Research Projects:

- **Project 01**
  Title: *Repurposing of Anti-Psychotic Drugs for Treating Aggressive Triple Negative Breast Cancer: A Focus on African American Women*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Repurposing of FDA-approved drugs is an excellent strategy to accelerate drug discovery. Triple Negative Breast Cancer (TNBC) cells rely heavily on STAT3 signaling for growth and migration. Pimozide, an atypical antipsychotic, has shown activity in TNBC models through STAT3 inhibition. However, research with pimozide and related compounds focused on Caucasian women and efficacy

in African American (AA) TNBC models remains unknown. The current proposal will use relevant TNBC models from AA and Caucasian donors to test the effectiveness of pimozide, as well as related FDA-approved and novel compounds, for anticancer activity and investigate the associated mechanisms of action and structure activity relationships.

The Wistar Institute of Anatomy and Biology ($1,751,447) – 4 Projects

Research Projects:

- **Project 01**
  Title: *Dual-acting Immune Antibiotics to Combat Antibiotic Resistance*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Gram-negative bacteria are becoming resistant to antibiotic treatments faster than new therapies can be developed. Infection by drug-resistant ESKAPE bacteria makes any surgery impossible and can cause simple wounds to become life threatening, like in the pre-antibiotic days. We are developing a novel dual-action immune-antibiotic strategy that kills bacteria directly and activates rapid immune response against bacteria that survive the direct killing. Elimination of these resistant bacterial survivors by the induced and sustained immune response therefore prevents any resistant bacteria from persisting and developing an antibiotic resistant bacterial population.

- **Project 02**
  Title: *Computational Design of Multivalent Vaccine Antigens*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Nanoparticle-based immunogens can induce robust humoral and cellular immunity offering an exciting vaccine development platform. Our preliminary experiments demonstrated that synthetic DNA-electroporation technology can be used to launch one type of nanoparticle displaying an HIV immunogen *in vivo* and induce strong immune responses. Here, we seek to expand our platform by designing multiple classes of nanoparticles capable of decoration with diverse immunogens from Influenza and Nipah viruses. *The goal of our research will be to discover the design principles and immunological factors driving assembly and enhanced responses which will lead to next-generation therapies*.

- **Project 03**
  Title: *Development of Small-Molecule Protein Modulator for Ovarian Cancer Immunotherapy*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: This project seeks to develop a combination therapy with small-molecule modulator, AP-3-84, for the treatment of ovarian cancer that can act to induce apoptosis of tumor associated immunosuppressive myeloid cells to allow for T-cell proliferation and increase antitumor response.

- **Project 04**
  Title: *Role of S6K in Melanoma*

Type of Research: Biomedical
Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
Purpose: The serine/threonine kinase S6K plays an important role in cancer by regulating cell cycle, translational regulation, and cell metabolism. However, there is a knowledge gap regarding the role of S6K in melanomagenesis. Our working hypothesis is that S6K is essential for survival of melanoma cells. A corollary of this hypothesis is that blocking S6K will decrease melanoma cell viability and promote tumor cell death. We propose to establish the dependency of melanoma on S6K and mechanistically determine the role of S6K for melanoma cell survival. We expect that these data will be critically important to understand the role of S6K in melanoma and to delineate effective therapeutic strategies to target drug resistance melanoma.