Health Research Formula Grants – State Fiscal Year 2017-18

Twenty-eight organizations received health research formula grants totaling $30,308,000 for the state fiscal year 2017-18. Grants may support one or more research projects and research infrastructure projects. The grants started on 6/1/2018 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 ($59,512) – 1 Project

Research Projects:

- Title: *Evaluating Patient Reported Outcomes: Pre- and Post-Liver Transplant (PRO-LT)*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: In this project, we propose to assess patient reported outcomes (PROs) using PROMIS-29 for ESLD (end stage liver disease) patients who are evaluated for liver transplant (LT); and to evaluate if there is any predictive or prognostic role of PROs, which could possibly supplement clinical markers. In addition, we will utilize a disease specific quality of life instrument to supplement generic PRO measures. The overall purpose is:

1) To understand the trajectory of PROs through the pre- and post-transplant scenarios,
2) Evaluate if PROs correlate with disease severity or have additional clinical value, and
3) If specific domains in PROs had an impact on disease specific quality of life

Allegheny Singer Research Institute ($55,501) – 1 Project

Research Projects:

- Title: *Generation of Bioengineered "Hybrid" Thymi to Induce Islet Allo-specific Immune Tolerance*
  Type of Research: Clinical Research
  Focus: Immunology
  Purpose: Using our intra-thymic injection-based approach to generate "hybrid" thymi, it will be possible to induce immune central tolerance in transplant recipients and consequently to become able to protect any type of allotransplant without impairing self-tolerance or requiring conventional immunosuppression.

American College of Radiology ($244,014) – 1 Project

Research Projects:

- Title: *Opportunistic Osteoporosis Screening Using Computed Tomography and Artificial Intelligence*
  Type of Research: Clinical Research
  Focus: Musculoskeletal, Oral and Skin Sciences
  Purpose: Osteoporosis is underdiagnosed and undertreated with high morbidity and mortality, which can be reduced through fall prevention and drugs. Current screening relies mainly on dual x-ray absorptiometry (DXA) to measure bone mineral density (BMD). A previous single-center study has shown that computed tomography (CT) scans, obtained in the course of routine patient care, can be used to measure BMD, without additional radiation exposure or cost. This multicenter study will confirm the earlier

single center result and compare conventional radiologist-supervised approaches to BMD detection with automated artificial intelligence (AI) approaches. This study could lead to improved national screening strategies for osteoporosis.

Carnegie Mellon University ($467,894) – 2 Projects

Research Projects:

- Title: *Encoding of Familiarity in Visual Cortex*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Memory is among the cognitive abilities most susceptible to impairment in neurodegenerative and neurological disorders. One of the most basic forms of memory is the ability to recognize things as familiar. The detection of a visual image as familiar is thought to depend on a phenomenon in visual cortex known as repetition suppression. This project enhances understanding of the neural mechanisms of repetition suppression in visual cortex. The results will lead to better understanding of the brain mechanisms underlying the experience of familiarity and thereby will provide a framework for understanding and ameliorating the loss of this function in disease.

- Title: *The Neural Substrates of Brain Overactivation-Related Normal Cognitive Decline*
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Aged subjects show a paradoxical condition of increased brain activation with a decline in cognitive performance. Current methodology, such as fMRI and PET, are too spatially and temporally coarse to identify genetic or neural circuit mechanisms underlying this overactivation. Recent research has suggested that NMDA receptor mediated cellular stress can drive overactivation and age-related cognitive deficits. We plan to study the mechanism of this age related overactivation at the level of single genetically identified cells and neural ensembles across the brain during a task testing cognitive ability in different ages as well as in the presence of an NMDA antagonist leading to insight and potential therapies to such cognitive deficits.

The Children's Hospital of Philadelphia ($4,684,980) – 1 Project

Research Projects:

- Title: *Studying Mechanisms Related to Anemias and Novel Treatments*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Some of the most common forms of anemia are anemia of inflammation and the hemoglobinopathies. Our laboratory focuses on studying the regulation of inflammation, iron and globin related genes, which are involved in the pathophysiology of these disorders. To further understand the mechanisms leading to anemias, the studies in this project aim to identify the role of reactive oxygen species ROS in the fate of erythroid cells, to investigate if Il6 affects erythroid cells and to characterize inflammatory pathways in erythroid or other bone marrow-derived cells. In addition, this research will identify novel gene therapy vectors that express a high level of curative hemoglobin

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Drexel University ($984,334) – 10 Projects

Research Projects:

- Title: *Corticotropin-releasing Factor Mediates Behavioral Disturbances Following Adolescent Mild Traumatic Brain Injury*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Each year, about 2.8 million people experience a traumatic brain injury (TBI), with concussion or other mild TBI (mTBI) accounting for more than 75% of this number. Adolescents are far more likely than adults to sustain an mTBI and, for those playing contact sports, girls are twice as likely as boys to sustain an mTBI. Moreover, girls are more likely to suffer long-term emotional consequences, such as depression and apathy, and they take longer than their male counterparts to recover from an mTBI. The neurobiological changes that underlie these symptoms are vastly understudied in female pre-clinical models. Our proposal seeks to determine whether corticotropin releasing factor may be a viable treatment to reverse these behavioral changes.

- Title: *Role of miR34a in Senescence Associated with Bronchopulmonary Dysplasia*
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory disease in infants. It occurs due to an interaction between genetic and environmental factors in preterm babies and leads to disruption in alveolar formation and growth by modulating inflammatory mediators, impairing vascularization and accelerating apoptosis. We have recently shown that miR-34a has a causal role in severe BPD in both mice and humans resulting in increased cell death. This project will enhance our understanding of the pathogenesis of BPD by providing mechanistic information about a novel signaling pathway involving miR34a regulation of senescence in hyperoxia-exposed developing lungs.

- Title: *Infant T Cell Response to Respiratory Viruses*
  Type of Research: Clinical
  Focus: Immunology
  Purpose: This project seeks to determine the $CD8^+$ T cell repertoire of infants less than the age of 6 months infected with a respiratory virus. For this pilot study, we seek to enroll 30 infants in the two-year study period, with roughly 15 former preterm neonates and 15 former term neonates. We hypothesize that preterm infants are susceptible to infection because their naïve T cell repertoire is dominated by germline, public TCR clones. This has direct benefit for the development of neonatal vaccines. Neonates display a suboptimal response to many vaccines. Adjuvants that simulate the effect of acute infection in terms of inflammation may improve neonatal vaccine efficacy

- Title: *A Therapeutics Delivery Scaffold for In Situ Generation of Tolerogenic Dendritic Cells*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this research is to develop a novel injectable scaffold that

recruits dendritic cells (DCs) *in situ* and programs them via the delivery of biological therapeutics for generating antigen-specific tolerogenic DCs (tDCs). These cells are promising for the treatment of autoimmune diseases, which arise from a loss of immunological self-tolerance. Autoimmune diseases affect 23.5 million Americans and are currently incurable. Scaffolds can provide spatiotemporally controlled signals to modulate immune cells *in situ* at a level that cannot be reached by other approaches. Once established, our method can conveniently generate millions of tDCs *in situ* and may cure some autoimmune diseases by establishing immune tolerance.

- Title: *Implications of Unstable Cerebral Oxygenation on the Safety and Tolerability of Hemodialysis*
  Type of Research: Clinical
  Focus: Renal and Urological Sciences
  Purpose: Hemodialysis (HD) is life-saving for hundreds of thousands of patients with kidney failure, though current treatment strategies have failed to prevent patients from experiencing numerous side effects and health problems. This study will contribute knowledge on the clinical impacts of variation in oxygen supply to the brain during HD, and provide novel therapeutic targets for future trials to improve patient-centered outcomes in the vulnerable HD patient population

- Title: *Virtual Reality Inhibitory Control Training for Reducing Binge Eating*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Binge eating is a major public health problem, yet existing treatments leave great room for improvement in outcomes. Existing treatments do not target deficits in inhibitory control, which have been strongly linked with the maintenance of binge eating. State-of-the-art "serious games," such as computerized inhibitory control trainings, show promise for enhancing outcomes, but findings are mixed. The present study aims to develop and test the first-ever personalized, virtual reality inhibitory control training for binge eating to address the shortcomings of existing inhibitory control trainings

- Title: *A Nano Photonic Integrated Probe System to Enable Multi Wavelength Optogenetics*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The ability to accurately monitor and sometimes alter the electrical activity of the central nervous system (CNS) is important for diagnosing neurophysiological problems and is a crucial element of modern medicine. A means of interfacing with the CNS originates from the field of optogenetics, which uses pulses of light to control and monitor the activities of individual neurons within living tissue. This project leverages recent progress in nanophotonics to develop a means of delivery of light at different wavelengths, with proper temporal characteristics, to spatially modulated sites, with unprecedented precision thus leading to a revolutionary rescaling of optogenetic implants well beyond the current state of the art achievable with fibers or with microLEDs.

- Title: *Mechanisms of Eph-dependent Cell Death*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The goal of this project is to study the mechanisms induced by EphA4 and EphB3 receptors that lead to cell death when they function as dependence receptors. While many studies show these dependence receptors function as tumor suppressors, most of the research examining the role of Eph receptors in cancer development focuses on the dysregulation of the positive signaling elicited by these tyrosine kinase receptors. We aim at gaining a stronger knowledge of the Eph signaling leading to cell death in order to leverage their pro-apoptotic potential to limit tumor growth

- Title: *Investigating the Molecular Mechanism of lncRNA HOTAIR in Breast Cancer*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to investigate the role of long non-coding RNA HOTAIR (HOX transcript antisense RNA) in breast cancer progression. Recent studies showed that HOTAIR plays a crucial role in breast cancer invasion and metastasis. This study integrates techniques from RNA biochemistry and cell biology to advance our knowledge of HOTAIR function in breast cancer progression. The results will not only allow us to understand the structural basis of HOTAIR function but also provide potential new therapeutic targets.

- Title: *Role of Septin 9 in Breast Cancer Metastasis*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Metastatic breast cancer has no cure and is poorly understood. Identifying new therapeutic targets and understanding their role in metastasis is critical for the development of new treatments. The purpose of this research study is to determine how septin 9, which is abnormally expressed in invasive breast cancers, affects metastasis and the mechanism of tissue invasion. These studies will advance our basic knowledge of breast cancer metastasis and explore the potential of septin 9 as a prognostic biomarker and therapeutic target.

Duquesne University of the Holy Spirit ($112,997) – 1 Project

Research Projects:

- Title: *Small Molecule Microtubule Targeting Agents for Pancreatic Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to synthesize and evaluate 20 novel compounds against pancreatic cancer (PaC) cell lines in vitro. This will provide optimized compounds that target the colchicine site of tubulin and allow a selection of the most potent compounds against PaC to be used in the preclinical in vivo studies against PaC.

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Franklin and Marshall College ($12,920) – 1 Project

- Title: *A Rodent Model of Drug Abuse Liability following Prenatal Overnutrition*
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project will examine the consequences of the growing obesity epidemic both in the U.S. and abroad. Specifically, this project will determine the likelihood of drug abuse in offspring exposed to prenatal overnutrition (i.e., pregnant mothers eating foods high in sugar and/or fat) before, during, and after gestation. Importantly, the prenatal period represents a critical developmental timepoint in which the mother and fetus experience the same environmental events. A small number of studies suggest that maternal overnutrition leads to changes in brains structures containing dopamine neurons. Such changes in these brain structures may be reflected in increases in drug-taking behaviors as a consequence of maternal overnutrition.

Geisinger Clinic ($176,152) – 1 Project

Research Projects:

- Title: *Automated Echocardiography Image Analysis with Machine Learning*
  Type of Research: Clinical
  Focus: Cardiovascular Sciences
  Purpose: This project will develop a machine learning tool to analyze and interpret echocardiograms.

Hepatitis B Foundation ($195) – 1 Project

Research Projects:

- Title: *Evaluating Strategies for Student Engagement in Community Hepatitis B Programming*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project shall evaluate the effectiveness of the Multilevel Approach to Community Health (MATCH) model in engaging public health and medical students at local Philadelphia colleges and universities. Students were educated, trained and led through the five-phases of MATCH to develop community-based programming for addressing hepatitis B in high-risk local communities. This project shall evaluate the effectiveness of the model in engaging students to conduct successful community-based hepatitis B education. Study results could improve effectiveness and sustainability of future interventions to improve hepatitis B screening and linkage to care rates in highly impacted, hard to reach communities.

The Institute for Cancer Research ($1,091,646) – 4 Projects

Research Projects:

- Title: *Defining the Role of Cytoplasmic ThPOK in Leukemogenesis*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Acute Myeloid Leukemia (AML) is a genetically heterogeneous cancer that is thought to arise from myeloid progenitor cells. Both leukemic hematopoietic stem cells (L-HSC), multipotent progenitors (MPPs), common myeloid progenitors (CMPs) and

leukemic granulocyte-monocyte progenitors (L-GMP) have been defined, based on their resemblance to normal HSC and GMP populations. Our preliminary evidence indicates that ThPOK-deficient Lin- BM cells are substantially protected from leukemogenesis, while mice and zebrafish in which ThPOK is restricted to the cytoplasm develop leukemia with high penetrance, suggesting a critical role for ThPOK and particularly cytoplasmic ThPOK (cytoThPOK) in promoting pathological differentiation to leukemia.

- Title: *Impact of Cancer Mutations and Domain Mapping of the CCDC170 Breast Cancer Protein*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of the project is to assess the impact on protein structure of cancer-associated mutations in the *CCDC170* (Coiled Coil Domain Containing 170) breast cancer gene. The *CCDC170* gene was implicated in breast cancer risk through Genome-Wide Association Studies (GWAS) and mouse studies. The normal function of the CCDC170 protein was unknown, and we found that it has a critical role in the Golgi-microtubule network that controls cell migration. The project will investigate the impact and mechanism of cancer-associated amino acid changes on CCDC170-Golgi-microtubule association and further examine structure-function of the normal CCDC170 protein.

- Title: *Live Cell Imaging of Hepatitis B Virus Nuclear DNA*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: An estimated 300 million people are chronically infected with hepatitis B virus (HBV). Based on the Global Burden of Disease Study, over 700,000 patients die of HBV-induced diseases, with approximately half succumbing to hepatocellular carcinoma. The purpose of this project is to investigate HBV covalently closed circular deoxyribonucleic acid (cccDNA) that is synthesized during the life cycle of HBV and present in nuclei of infected hepatocytes. CccDNA is the cause for the persistence of the virus in infected hepatocytes, resulting in chronic hepatitis B (CHB). Using a novel imaging technology, we seek to investigate location and molecular interactions of cccDNA in live resting and dividing liver-derived cells.

- Title: *Identification of Tumor Suppressor Gene Targets in the Cancer Genome*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Epigenetic factors are enzymes that chemically modify the chromatin or the DNA to activate or silence gene expression and are critically important for tumorigenesis. Given the increasing interest in epigenetics therapy, identifying the genes that they regulate are critically important for understanding cancer biology and identifying biomarkers for future therapy. Transposon tagging is a relatively new method that was developed to enhance the identification of gene targets by regulatory factors. We will use

transposon tagging to identify gene targets of epigenetic factors that are critical in melanoma and pancreatic cancer.

Lankenau Institute for Medical Research ($111,517) – 1 Project

Research Projects:

- Title: *HuR Inhibition: A Novel Therapy to Combat Ovarian Cancer Drug Resistance*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project will develop a novel therapy for ovarian cancer that addresses the need to overcome multiple drug resistance that is characteristically acquired by ovarian tumors in patients treated with chemotherapeutic drugs. The new therapy uses a novel nanocarrier to target suppression of Human antigen R, aka ELAVL1 (HuR), an RNA-binding protein that regulates many genes known to function in multiple drug resistant pathways, specifically in tumor cells and not in healthy cells. In contrast to other approaches that have aimed to overcome drug resistance by targeting a single pathway/gene, the strategy in this project is likely to make the evolution of drug resistance by tumor cells much more difficult. Preclinical experiments in animals will generate data supportive of advancing this new therapy to the clinic.

Lehigh University ($111,441) – 1 Project

Research Projects:

- Title: *Synthetic Immune-Attractants Against Drug-Resistant Bacteria*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Drug resistance to our current stock of antibiotics is projected to increase to levels that threaten our ability to reduce and eliminate bacterial infections, which is now considered one of the primary healthcare crises of the 21st century. Traditional antibiotic agents (e.g., penicillin) paved the way for massive advances in human health but we need novel strategies to maintain the upper hand in the battle against pathogenic bacteria. The goal of this project is to establish the fundamental framework of a non-traditional antibiotic therapy based on the specific recruitment of antibodies and immune cells to the surface of pathogenic bacteria.

Magee-Womens Research Institute and Foundation ($1,201,505) – 8 Projects

Research Projects:

- Title: *Mechanisms and Physiological Significance of Adipocyte Death*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Although fat cells (adipocytes) are crucial contributors to metabolic health and disease, to date, very few studies have addressed the physiological control of adipocyte death. Our previous studies have shown that deletion of the nuclear receptor PPAR□ (peroxisome proliferator-activated receptor □) in adipocytes leads to their rapid death via CASP1- and/or -11-driven pyroptosis. Importantly, this appears to be the same death mechanism of adipocytes in animals and patients with chronic or diet-induced obesity. Here, we will investigate the roles of CASP1 and 11 in the death of both PPAR□-deprived and obese adipocytes, the molecular mechanisms that lead to their activation,

and the physiological roles of adipocyte death in the development and outcomes of dietary obesity.

- Title: *Severe Maternal Morbidity and Mortality: Precursors and Consequences*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to determine patterns of maternal health care utilization that increase the risks of maternal morbidity and mortality.

- Title: *The Function of lncRNAs that are Regulated during Human Trophoblasts Differentiation*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We seek to perform an in-depth analysis of the expression and function of long noncoding RNAs (lncRNAs) in term primary human trophoblasts (PHT cells) during their differentiation to syncytiotrophoblasts. Specifically, we will measure the expression of lncRNAs and microRNAs (miRNAs) in differentiated and undifferentiated PHT cells by RNA sequencing, analyze the interaction between miRNAs, mRNAs, and lncRNAs during PHT cell differentiation, determine the impact of lncRNA on mRNA expression, and compare the results with our previous analysis of PHT cells that were cultured in hypoxic conditions. These data will provide unique insights into the repertoire of RNAs that play an important role in trophoblast differentiation

- Title: Effects of Advanced Maternal Age on Genomic Imprinting in Oocytes and Embryos
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Advanced maternal age (≥35 years) is associated with increased risk of spontaneous abortion, stillbirth, preterm birth, and birth defects. These women often turn to assisted reproductive technologies (ARTs) to improve their chances of conceiving. Our published findings have demonstrated that ARTs lead to imprinted methylation errors in early embryos from young mothers. However, there has been little investigation on the effects of advanced maternal age, with or without ARTs, on genomic imprinting. The purpose of this project is to advance our scientific knowledge on whether advanced maternal age, alone or in combination with ARTs, leads to a greater burden of imprinted methylation errors in oocytes or preimplantation embryos.

- Title: *Mesh Biorepository Study: Insight into the Pathogenesis of Mesh Complications*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Polypropylene mesh is widely used in urogynecologic surgery to reduce the high failure rates of surgeries to repair pelvic organ prolapse (~40% by 2 years) and as a first line treatment for stress urinary incontinence. However, its use is limited by relatively high complication rates, most commonly pain and exposure. The known risk factors for mesh complications of aging and postmenopausal status are minimally useful in clinical

decision making as they apply to the majority of the treated population. The immune system plays a critical role in the body's response to biomaterials. This research aims to define demographic, clinical, and immunologic biomarkers that increase risk for mesh complications, allowing for more effective individualized treatment.

- Title: *Generation of Mouse Models for Studying the Roles of Ddx3 Subfamily of RNA Helicases in Spermatogenesis*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Deletions in the azoospermia factor regions of the Y chromosome (AZFa, AZFb, and AZFc) are the most common genetic cause of azoospermia, with AZFa deletions being the most severe. DEAD-box RNA helicase 3 Y-linked (DDX3Y) is one of two genes in the AZFa region. It is hypothesized that loss of DDX3Y causes the infertility, which we will confirm functionally with *Ddx3y* knockout mice. We will use CRISPR/Cas9 gene editing to generate mouse models and examine the function of two DDX3 subfamily members, *Ddx3y* and *Ddx3x*, in spermatogenesis and fertility.

- Title: *Immunogenic Roles of the DNA-Sensing Pathway in Ovarian Cancer*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Ovarian cancer (OC) is the most aggressive type of gynecologic malignancy. Standard treatment currently combines surgery and chemotherapy with platinum-based drugs (cisplatin). Recent studies demonstrate that immune-based therapies can improve clinical outcome in OC. We are testing the hypothesis that cisplatin, while inducing tumor involution, can act as an immune adjuvant by triggering the cGMP/AMP synthase/stimulator of interferon genes (cGAS/STING) pathway. The cGAS/STING axis acts as a DNA sensor and triggers inflammation via type I interferon. We further postulate that targeting the cGAS/STING axis can increase the therapeutic potential of cisplatin and the efficacy of immune therapy via immune checkpoint blockade.

- Title: *Regulation of Meiosis and Fertility in Male Mice by Testosterone Signaling in Sertoli Cells*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Our results will define the interlinked network of testosterone regulated Sertoli cell signals and responding germ cell mRNA and protein targets that are required for maintaining spermatogenesis and male fertility. These studies will provide long-needed new strategies to treat male infertility and develop male contraceptives. In addition, our findings may be applied to improve the understanding of testosterone-regulation of overall male health as limited testosterone-signaling is linked to an increased risk of developing chronic and age-related conditions, such as obesity, metabolic syndrome, diabetes. heart disease and early death.

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Monell Chemical Senses Center ($129,462) – 1 Project

Research Projects:

- Title: *Does Switching Between Macronutrients Exacerbate Obesity?*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: We will test the hypothesis that the severity of obesity produced by eating high-calorie foods depends on the sequence that carbohydrate and fat are eaten. We will test (a) whether mice given a choice between a high-carbohydrate, low-fat diet and an equicaloric low-carbohydrate, high-fat diet get fatter than mice given either diet alone, and (b) whether this "extra" obesity also occurs if the diets are presented one-at-a-time but switched daily. According to NIH, 300,000 deaths per year in the U.S. are directly attributable to obesity. This project will establish an animal model useful to investigate the "extra" obesity caused by choosing among foods, which is a ubiquitous component of human behavior but is absent from other rodent models.

Penn State University ($5,238,380) – 16 Projects

Research Projects:

- Title: *Potent Inhibition of Opportunistic Viruses: Pursuing a Pre-clinical Model*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The purpose of this project is to test the properties of a lead antiviral compound in mice. This compound targets a cellular protein that although important for multiple different viral infections, is not essential for cell viability because the cell has redundant proteins that compensate for its inhibition. This important finding provides us with the ability to develop a highly potent antiviral with minimal cellular toxicity. It also leads to the possibility that the compound can be administered as a prophylactic, previously not possible due to the high toxicity of the currently approved therapies. These studies will test the bioavailability and stability in an animal model as well as demonstrate its antiviral efficacy in an animal model.

- Title: *Digital Environmental Monitoring of Human Water Supply Watersheds by High-Throughput Phenomics of Plankton and Meiofauna*
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: We will develop digital phenotyping of whole millimeter-scale organisms including meiofauna and plankton across all of their component cell types and tissues, for early detection of potential human toxicity caused by environmental contamination. We will perform 'environmental biopsies' through utilizing microCT as a tool to identify for phenotypic changes in macrofauna, meiofauna and planktons. A digital library will be curated and serve as an atlas for the organisms imaged, to be used as a reference and educational tool, for researchers, teachers, the public and policy makers.

- Title: *Roles of the Cyclooxygenase Metabolites in the Venous Distension Reflex*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Our prior work in humans has shown that vascular distension of peripheral limb

veins evokes a powerful sympathoexcitatory reflex (venous distension reflex, VDR). However, the mechanisms are not understood. The purpose of this project is to determine the role played by cyclooxygenase (COX) metabolites of arachidonic acid in evoking the VDR. We hypothesize that acute blockade of COX system will markedly attenuate muscle sympathetic nerve activity (MSNA) and arterial blood pressure responses to limb venous distention. We will also examine if an accentuated VDR contributes to "orthostatic hypertension".

- Title: *Pathway-Specific and Cell-type Specific Glutamate Transmission in the Accumbens Shell; Implications in Opioid Addiction*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Opioid-induced context associations (environments that become associated with the rewarding properties of opioids following repeated opioid use within that environment) are controlled by excitatory glutamatergic input in the nucleus accumbens shell (NAcSh). The NAcSh receives excitatory glutamatergic input from the infralimbic prefrontal cortex (ILC), basolateral amygdala (BLA), ventral hippocampus (vHPC), and paraventricular nucleus of the thalamus (PVT). The purpose of this project is to determine whether the strengthening or weakening of specific projections from one or multiple brain regions causes opioid-context associations to be maintained.

- Title: *Mechanisms Mediating Heroin-Induced Devaluation of Natural Reward*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of the study is to use preclinical research to generate new knowledge related to the etiology and treatment of opioid addiction and, in so doing, to gather essential preliminary data to strengthen our R01 application to the NIH. Specific Aim 1 will use microdialysis and HPLC Mass Spectroscopy to determine the neurochemical profile in the nucleus accumbens of vulnerable rats when waiting for access to heroin. Specific Aim 2 will explore cue-induced craving, which is thought to contribute to the etiology of the disease. Finally, Specific Aim 3 will challenge our need-state hypothesis by testing whether treatment with a 'satiety' agent will reduce responding during a known potent need state, sodium appetite.

- Title: *Integrative Genomics Approaches to the Study of ARDS*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The Acute Respiratory Distress Syndrome (ARDS) is a complication of critical illness that results in the rapid accumulation of pulmonary edema fluid and respiratory failure, with a mortality rate in excess of 30%. The goals of this project are to perform high-throughput molecular profiling of the transcriptome, metabolome and microbiome of critically ill patients in order 1) to identify transcriptional biomarkers associated with ARDS diagnosis and prognosis; and 2) to identify networks of interactions between molecular biomarkers that will provide additional insights into the pathobiology of ARDS.

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- Title: *The Brain Network Dynamics of Odor-Visual Association in Humans*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: This research will fill a gap in knowledge about brain mechanisms, through which visual information modulates the olfactory perception. Behaviorally, visual information increases the likelihood of detecting and identifying odor objects of interest. Emphasis will be on differentiating respective system dynamics, selectivity and representation to elucidate the neural processes that are involved in synthesizing cross-modal information. Olfactory deficits are very common in early stage Alzheimer's disease (AD) and Parkinson's disease (PD) patients. A better understanding of the biological basis of olfactory function, including multi-sensory integration, will help pinpoint the fundamental mechanisms by which different neurological diseases start in the brain.

- Title: *Mapping Oxytocin Receptor in a Mouse Model of Autism*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Autism spectrum disorder (ASD) is a debilitating neurodevelopmental disorder that leads to significant, lifelong social behavioral impairments. Despite its significance, we lack specific knowledge of the neurobiological mechanisms underlying the disorder, which further limits the development of treatments for autistic symptoms. Our goal is to determine how the oxytocin receptor (OTR), an important regulator of the social behavioral development, is changed in an environmental animal model of ASD using our highly innovative brain mapping technique.

- Title: *Identifying Subgroups among E-Cigarette Users on Their Progression to Established Use of Tobacco Products*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: As an emerging popular device of delivering nicotine and other toxic compounds to a vast population, e-cigarette has the potential to change the landscape of consumption of various types of tobacco products, with profound ramification on public health. The purpose of this study is to subgroup the experimenting e-cig user population, to describe and compare those subgroups' risk profiles, and to investigate their progression to deepened addiction to one or more tobacco products.

- Title: *Agonist-specific Mechanisms of Cannabinoid Tolerance*
  Type of Research: Health Services
  Focus: Neurosciences
  Purpose: One of the primary cannabinoids in cannabis, delta-9-tetrahydrocannabinol (Δ^9-THC), has been increasingly used by cancer patients for its analgesic properties as well as for the treatment of nausea secondary to cancer chemotherapy. However, tolerance represents a significant disadvantage for cannabinoid therapies and has been demonstrated clinically in heavy use of cannabis prescribed for cancer pain treatment. Successful completion of this research project will address our novel concept that cannabinoid tolerance occurs through agonist-specific mechanisms, providing novel insight about the

mechanisms of cannabinoid tolerance and advancing the knowledge base needed to develop improved and innovative therapeutic strategies.

- Title: *Targeted Approaches for Cancer Therapies for Clinical Trial Development*
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: Therapeutic approaches to specifically target cancer cells are in great demand. This is due to the great potential to minimize or eliminate damage to normal cells observed with older chemotherapies. Approaches being developed for this purpose include; 1) identification and development of natural, endogenous compounds that specifically target cancer cells, 2) targeting cancer stem cells, and 3) combinatorial approaches that utilize immunotherapies. The purpose of this project is to create novel therapies using preclinical models to provide evidence to support future clinical trials for a variety of cancers that are of high prevalence in central Pennsylvania.

- Title: *Differential Regulation of SLE Autoimmune and Pathogen-Targeted Responses*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Systemic lupus erythematosus (SLE) is characterized by high-affinity autoantibody production followed by inflammation in multiple organs. SLE patients are primarily treated with non-specific immunosuppressive agents, which often predispose patients to recurrent infection and death. Current B-cell-targeted therapy indiscriminately depletes both autoreactive and pathogen-targeted B cells, leaving patients susceptible to lethal infection. A major roadblock to developing therapeutics that can specifically target autoimmune cells is our poor understanding of divergent mechanisms between autoimmunity and pathogen-directed immunity. The purpose of this project is to delineate the divergent mechanisms that regulate SLE autoimmune and pathogen-directed responses.

- Title: *REDD1-Dependent Control of Cell Death in Response to UVB*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: UVB-irradiation, the main carcinogen that causes skin cancer, activates a stress response in cells. This research project will examine the role of the protein REDD1 in cells exposed to UVB. REDD1 responds to genotoxic stress by inhibiting the mTORC1 pathway but has poorly understood mTORC1-independent effects. The purpose of this project is to characterize a mechanistic link between loss of REDD1 and increased sensitivity to UVB-induced cell death. Understanding the pathways that control the UVB stress response will aid in the design of more effective approaches to prevent and treat skin cancer.

- Title: *DNA Polymerase Kappa Activity during DNA Damage Response*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: DNA polymerase κ is a low fidelity polymerase that plays a critical role in the

cell's DNA damage response. (1) We will identify if N^2-(4-ethynylbenzyl)-2′-deoxyadenosine (N^2-EBn-dA) triphosphate can act as a probe for DNA polymerase kappa activity. (2) The ability of pol κ to contribute to DNA synthesis after DNA adduct bypass will be examined (i) by in vitro experiments using purified polymerases and (ii) in cells using DNA fiber experiments. (3) The sequence-specific activity of pol kappa will be evaluated with next generation sequencing experiments.

- Title: *Structural Investigation of the NMDA Receptor/CaMKII Super Complex*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of the research project is to use state-of-the-art cryo-electron microscopy methods to investigate protein-protein interactions responsible for clustering glutamate receptors within the membrane of neurons, as well as structural mechanisms of feedback between the receptors and their binding partners. The project will focus on the N-methyl-D-Aspartate (NMDA)-type glutamate receptor and the calcium/calmodulin (CaM)-dependent kinase II (CaMKII), two molecules hypothesized to form a super complex in vivo that is essential for normal synaptic function.

- Title: *Innovative Approach to Missing Longitudinal Data in Clinical Trials*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Missing longitudinal data due to dropouts are common in clinical trials, where weighted generalized estimating equations are often applied. There is limited work on model selection of marginal mean regression or correlation structure to address the issue of missing longitudinal data. To fill these gaps, we propose innovative information criteria based on empirical likelihood, joint empirical Akaike information criteria (AIC) and joint empirical Bayesian information criteria (BIC). In this project we consider two scenarios: 1) longitudinal data with missing outcomes only; 2) longitudinal data with missing outcomes and covariates. Also, we will provide rigorous theoretical proof to assess their asymptotic properties for further evaluations.

Salus University ($42,703) – 1 Project

Research Projects:

- Title: *Protein Interactions Related to LCA12 and rd3 Retinal Degenerations*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Research project that integrates diverse laboratory and clinical data related to inherited retinal degenerative disease. The main purpose of the project is to elucidate biochemical processes related to the retinal degeneration using in vitro studies and animal models.

Temple University-of the Commonwealth System of Higher Education ($2,239,881) – 6 Projects

Research Projects:

- Title: *Correlation of Bone Strength with MR Imaging and Spectroscopic-Derived Composition*

Type of Research: Biomedical
Focus: Musculoskeletal, Oral and Skin Sciences
Purpose: Bone fracture risk increases with age, disease, and certain therapies. Factors that contribute to fragility include bone architecture, mineral density and crystallinity, water, and collagen quality. To date, however, prediction of bone strength using finite element models (FEMs) have primarily used architecture based on magnetic resonance imaging (MRI) or micro CT data. Here, we will quantify micron-level bone compositional parameters using molecular-based spectroscopic imaging and develop FEMs of bone strength that incorporate this data. Comparison of FEMs of bone strength based on compositional vs MRI-determined architecture data will enable patient-specific fracture risk assessment to guide therapeutic protocols.

- Title: *In Vitro Effects of Commensal Oral Bacteria on Oral Squamous Cell Carcinoma Cell Lines*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of the study is to identify commensal oral bacteria with anti-cancer properties that can be potentially used in the treatment/prevention of oral squamous cell carcinoma (OSCC). We propose a screening study in which a panel of health-associated species, identified from previous microbiome analysis studies, will be tested against an OSCC cell line in vitro to assess their effect on cell proliferation as well as expression of representative genes involved in proliferation, inflammation, stemless and invasion. The effect of promising strains will be explored more comprehensively used RNA sequencing to elucidate mechanisms of action.

- Title: *Clinical Implications of the Colon Cancer Microbiome*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The bacteria and other microorganisms that normally reside in the human gastrointestinal tract (the microbiome) are known to contribute to colon cancer development through mechanisms that remain incompletely understood. Based on preliminary experiments, we have developed the new hypothesis that specific components of the microbiome contribute to colon cancer development by triggering abnormal DNA methylation, an epigenetic process that controls cellular identity. This hypothesis has implications for colon cancer classification and this project will lead to new treatment approaches through better selection of patients for chemotherapy and/or immunotherapy.

- Title: *Linkage of Racial Disparities in Colon Cancer to Microbiome-Mediated Epigenetic Changes*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Colorectal cancer mortality rates for African American men and African American women are higher than for Caucasian men and women. Our hypothesis is that much of the racial disparity between African Americans and Caucasians in colon cancer incidence and outcomes are due to environmental differences (dietary and other factors

such as smoking and physical activity) between the two groups that influence the epigenome through differences in the gut microbiome composition. We will test this hypothesis in this pilot project by comparing DNA methylation levels in the normal colon mucosa of cancer patients and patients without cancer, stratified by race, as well as identifying race-associated and cancer-associated "marker species" in the microbiome.

- Title: *Research Infrastructure Project: TBI Lab Facilities*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to renovate a space in the Biological Life Sciences (Biolife) facility that is presently used for computational research to a Traumatic Brain Injury (TBI) research laboratory, which will include a small animal surgical and behavioral room and a room to house small research animals.

- Title: *Stress-Related Predictors of Disparities in Health Outcomes*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The primary purpose of this project is to investigate the biologic, social, behavioral and environmental factors associated with stress that contribute to poor health outcomes in urban populations. Potential differences among racial/ethnic groups will be examined. Given the increased morbidity and mortality among minority groups specifically related to cardiovascular disease, cancer, and diabetes, the role of obesity-related inflammation as a mediator of these associations will also be assessed.

Thomas Jefferson University ($1,890,887) – 4 Projects

Research Projects:

- Title: *Investigations into hematopoietic cell death*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Alterations in hematopoiesis in the bone marrow can cause hematopoietic cell deficiencies, bone marrow failure, and predisposition to hematologic cancers. The purpose of this project is to investigate how a gene that protects cells from death contributes to hematopoietic cell development, survival, and development of T cell lymphoma.

- Title: *High Throughput Screening for New Oncogenes*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: We have previously developed technology that has enabled us to identify novel oncogenes that are potential targets of new therapies for cancer. However, this method is extremely labor intensive and slow, which has impeded our ability to apply it more widely. This project will modify and optimize this technology further to permit screening for new oncogenes in a more high-throughput fashion, with a goal of facilitating the discovery of new oncology targets for the development of therapies across multiple cancer types.

- Title: *Study of the Nuclear Pore Complex Contribution to Lethal Prostate Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project aims to study the mechanisms behind the deregulation of the Nuclear Pore Complex (NPC) in advanced prostate cancer (PC). The project will focus on the analysis of PC cell models via high resolution video microscopy and immunofluorescence combined with gene expression and functional analysis. These studies will permit us to dissect the impact of NPC deregulation and of its genetic and chemical manipulation on survival of aggressive cells to current standard chemotherapy. The overall goal is to understand the contribution of the NPC to PC progression and find new potential treatment options.

- Title: *Novel Chimeric Fusion Protein Therapeutics Promoting Natural Killer Cell Anti-Tumor Responses*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Natural killer (NK) cells are innate immune cells that play a central role in the elimination of tumor cells without prior tumor antigen sensitization. Surface molecular components within the tumor cellular milieu can suppress NK cell responses and so permit tumor escape and cancer progression. This project will explore novel immunotherapeutic strategies that can counter this suppression, focusing on the design of multifunctional fusion proteins targeting NK activating and inhibitory receptors, with the goal of restoring NK cell anti-tumor functions.

The Trustees of the University of Pennsylvania ($6,162,800) – 10 Projects

Research Projects:

- Title: *Assessment of Young Adult Cancer Survivors' Outcomes*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project will describe physical, psychosocial, and behavioral outcomes achieved by survivors of young adult (YA) cancer diagnosed between 18-39 years of age. We will assess constructs which include unmet needs; disease, treatment, symptom, and functional status; knowledge about disease, treatment, screening recommendations and other aspects of survivorship care; health behaviors; and perceptions of care received. These variables will be assessed with a mind toward refining survivorship care planning interventions and defining targets for future intervention studies. As well, we will explore potential moderators of outcomes such as demographic, disease, and treatment variables. The project will employ a cross-sectional single-group design and survey 1000 YA cancer survivors obtained through the Abramson Cancer Center Registry (n=900) and clinics (n=100).

- Title: *Mechanisms of Collagen-Mediated Lung Metastasis*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project is based on our observation that tumor-associated collagen can promote metastatic disease in soft tissue sarcomas. Recently, multiple independent groups

have confirmed these findings in additional cancer contexts. The goal of this project is to define the precise mechanisms underlying this phenomenon and to identify potential therapeutic targets for the treatment of metastatic disease

- Title: *Improved Immunotherapy of Cancer Using Synthetic KIRs*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Solid tumors utilize multiple mechanisms to resistance to T cell-based immunotherapy. This project evaluates a novel synthetic immunoreceptor design based upon a naturally occurring multi-chain immunoceptor of a killer immunoglobulin-like receptor (KIR) family. T cells that are genetically engineered to express a KIR-based chimeric antigen receptor (KIR-CAR) are capable of eradicating large tumors in pre-clinical murine models that are otherwise resistant to T cell immunotherapy using a CD3zeta-based chimeric antigen receptor with either 4-1BB or CD28 costimulatory domains. This research aims to reveal the mechanism(s) that underlie the enhanced in vivo activity of T cell immunotherapy that uses KIR-CARs that will provide valuable insight in future CAR design.

- Title: *Targeting PPT1 to Improve the Efficacy of Immunotherapy*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this research is to gain new knowledge about the role of PPT1 within the tumor microenvironment and the effects of PPT1 inhibition alone and in combination with PD1 Ab. This project will test the hypothesis that PPT1 inhibition can augment the efficacy of PD1 Ab. Upon successful completion it will provide new preclinical rationale to explore new combinations of PD1 Ab and PPT1 inhibitors in the clinic.

- Title: *Hospital Type and Utilization, Prices, and Financial Burden for Cancer Surgeries*
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: The purpose of this research project is to examine the relationship between hospital type and utilization, prices, financial burden and spending for major cancer surgeries among privately-insured patients in the Commonwealth of Pennsylvania. We will examine the difference, if any, in utilization and spending associated with care from different types of hospital providers: National Cancer Institute (NCI) Designated Cancer Centers, National Comprehensive Care Network (NCCN) member institutions, and members of the Council on Teaching Hospitals (COTH). This research will reveal fundamental knowledge about health outcomes and financial burden experienced by cancer patients treated in various hospital settings.

- Title: *Research Infrastructure - Levy Research Animal Vivarium Renovation*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The renovation of the cage wash area and associated support areas of the Levy vivarium of the University of Pennsylvania, School of Dental Medicine (SDM) will

improve the quality of research animal care and will expand the types of studies that can be done by facilitating clean "barrier" rodent housing and the study of infectious disease in dental health. The Levy vivarium is the only research animal housing area dedicated to studies relevant to dental and oral research. SDM research requires studies in animals that include basic research, applied research and many different approaches to improving dental health.

- Title: *Cigarette Smoking Products and Pre-metastatic Niche*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Gen
  Purpose: To determine the harmful effect of cigarette smoking products on the formation of the pre-metastatic niche in the lungs and subsequent stimulation of lung metastases of malignant melanoma and pancreatic cancer. These studies will be undertaken to discover new knowledge that can potentially lead to development of new approaches to adjuvant treatment of metastatic cancers.

- Title: *Mechanism of Cryptosporidium Host Cell Invasion*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The protozoan parasite *Cryptosporidium* is one of the most important causes of severe diarrheal disease. The parasite is resistant to water chlorination and the CDC links more than 50% of U.S. waterborne disease outbreaks to *Cryptosporidium*. Zoonotic outbreaks including the 2017 farm outbreak in Easton, Pennsylvania are also frequent. In patients suffering from immunosuppression as a consequence of HIV/AIDS, organ transplantation, or cancer *Cryptosporidum* produces chronic and potentially fatal disease. Currently there are neither drugs nor vaccines available. In this project we will analyze host cell invasion and we will link key parasite organelles to infection flagging them as targets for future intervention.

- Title: *Virtual Cortical Resection for Epilepsy Using Stereo EEG*
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this study is to develop new methods to map epileptic networks in the brains of people with medication-resistant epilepsy. In this project, we will develop new engineering techniques, based upon stereo EEG, to improve targeting of epilepsy surgery, laser ablation and implantable devices, and to improve patient outcome. We will integrate engineering and network neuroscience research with new therapies to improve the lives of patients with medication-resistant seizures.

- Title: *Towards Improving Glycemic Control through Behavioral Feedback in Type 1 Diabetes*
  Type of Research: Clinical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: There is a critical need to improve the control of patients with diabetes. The purpose of this project is to test whether providing behavioral feedback to type 1 diabetes

patients can improve their glycemic control. Findings from this research may have important implications for both improving adherence in type 1 diabetes and for improving treatment strategies.

University of Pittsburgh-of the Commonwealth System of Higher Education ($6,162,800) – 7 Projects

Research Projects:

- Title: *McGowan Research Institute Laboratory Infrastructure Upgrades*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The McGowan Research Institute building at the University of Pittsburgh is a 44,592-square-foot research facility made up of a neuroimaging lab, a high-field imaging center, and core neurobiology laboratories. The purpose of this project is to replace aging infrastructure systems and provide the McGowan Institute with reliable and redundant heating, ventilation, and air conditioning (HVAC) systems that are required to support the research facility and keep it operating at a high and uninterrupted level. These upgrades will continue to support the existing and expanding research needs of critical programs within the facility.

- Title: *Auto-Antiviral Vaccination with TLR-7 Agonist to Achieve Functional Cure*
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: A human immunodeficiency virus (HIV) cure is needed to curb the epidemic, yet most of the explored strategies did not provide acceptable results. In this project, we will test a new strategy to naturally boost anti-simian immunodeficiency virus (SIV) immunity in macaques receiving antiretrovirals by performing repeated episodes of brief treatment cessation (BTC) combined with toll-like receptor (TLR)-7 stimulation. Our goal is to elicit better control of viral replication and a functional cure during a final analytical treatment interruption (ATI). We optimized the assays needed and established strategic collaborations with academic and industry leaders in this field. If successful, our strategy may lead to functionally cured HIV-1 infection, which will spare those infected with HIV the burden of prolonged medication (costs, side effects, viral resistance).

- Title: *Cortical Control of Muscles of Vocalization*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this project is to characterize the pathways that underlie cortical control of muscles of vocalization using an animal model. Specific muscles of respiration and phonation—subsystems central to vocalization control—will be explored to define the cerebral cortex regions that are involved in voluntary control and the extent to which these cortical control substrates for individual muscles overlap. Findings are of high relevance to understanding the neurobiological underpinnings of vocalization. Further, the results of this project will provide a foundation for the future identification of potential cortical therapeutic targets in patients with neuromuscular breathing and speech breathing disorders.

Health Research Formula Grants – State Fiscal Year 2017-18

- Title: *Using a Cell-Based Approach to Reverse Pathological Disinhibition in the Auditory System*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The project will characterize the degree to which precursor inhibitory neurons transplanted into the auditory midbrain will produce a long-lasting increase in neuronal inhibition. This added inhibition may counteract pathological disinhibition, which typically develops after noise-trauma and in aging and which is thought to be a major factor underlying central auditory processing deficits. The potential of embryonic medial ganglionic eminentia (eMGE) cells to counteract pathological disinhibition will be tested in a mouse model using ultrastructural, electrophysio-logical, and behavioral techniques. Project results may inspire further development of cell-based treatment strategies for central auditory processing deficits following hearing loss or aging.

- Title: *Requirement for Cyclin-Dependent Kinase Activity in Platelets for Melanoma Metastasis*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project will test whether blocking cyclin-dependent kinase 4 (cdk4) in platelets will inhibit the ability of melanoma cells to spread to the lungs and grow. Although platelets are best known for making blood clots, they also provide critical support to melanoma cell metastasis by providing pro-tumorigenic signals. We have discovered that cdk4 is in platelets and is involved in signals that are important for platelet-cancer interactions. Drugs that target both cdk4 and cdk6 (e.g., palbociclib) are in clinical use for breast cancer and in trials for melanoma. This project will use a genetic knockout of cdk4 in platelets to determine whether cdk4 in platelets is required for melanoma metastasis and for palbociclib effectiveness against melanoma.

- Title: *Novel STAT3 Inhibitors for the Treatment of Colorectal Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Colorectal cancer (CRC) remains a major public health problem. When metastatic disease is diagnosed, CRC is associated with poor prognosis, with five-year survival rates around 10 percent. Thus, there is an urgent need to identify and develop more effective therapies. This project seeks to fully characterize the mechanism(s) of action of bruceantinol and other quassinoids against human CRC. Our preliminary data suggest that quassinoid compounds inhibit signal transducer and activator of transcription 3 (STAT3) and suppress downstream signaling pathways. Development of effective STAT3 inhibitors remains an exciting opportunity as no inhibitors have yet been approved for the treatment of CRC or any other human cancer.

- Title: *Estrogen Receptor Dependency in Metastatic Breast Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to develop a mechanistic understanding of

estrogen receptor gene (*ESR1)* fusions to provide new concepts for the treatment of endocrine-resistant breast cancer.

University of the Sciences in Philadelphia ($22,390) – 1 Project

Research Projects:

- Title: *Real-time Imaging and Control of Biomolecules with In Vivo Bioreactors*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Imaging devices will be used to directly interact with cells and tissues. These microfluidic devices allow one to perfuse in drugs and molecules to directly interact with cells and tissues for the study of mechanisms regulating cancer metastasis and wound healing. In this study, a device will be used to reverse the cellular polarity of cells. This process will be used to investigate the signaling pathways that are involved in cancer, specifically cancer cell migration/metastasis, with the goal of elucidating critical signaling pathways and finding new therapeutic targets.

The Wistar Institute of Anatomy and Biology ($1,486,259) – 3 Projects

Research Projects:

- Title: *Transcriptional Control of Normal and Aberrant Myelopoiesis by the Integrator Protein Complex*
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: This project is a basic investigation in the area of gene expression and epigenetics that will reveal critical information about the molecular determinants of myelopoiesis and disclose new druggable nodes for Acute Myeloid Leukemia (AML) and other myeloproliferative diseases.

- Title: *Small Molecule Modulation of IFNAR1- IFN Signaling*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this project is to identify and develop novel small molecule modulators of the IFNAR1-IFN signaling axis. The type I interferons (IFNs) are an important family of cytokines involved in the innate immune response to infection, developing tumors, and other inflammatory stimuli. IFN has a function different than other type I interferons and can exhibit distinct functional properties and has been shown to bind IFNAR1 in an IFNAR2 independent manner to generate signals that control the transcription of a unique group of genes that do not require activation of STAT1 for their expression. This is important and has substantial biological and, possibly, clinical-translational implications.

- Title: *Understanding the Effect of Anti-CTLA4 Antibodies on Peripheral Immunity*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Anti-CTLA4 is approved for the treatment of advanced, metastatic melanoma, and clinical trials have begun with a next-generation anti-CTLA4 antibody. This next

generation anti-CTLA4 antibody has enhanced ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC). This is significant because in murine models the anti-tumor effect of anti-CTLA4 antibodies has been shown to be dependent on ADCC. However, anti-CTLA4 antibodies can also induce significant severe adverse events. Thus, our purpose is to understand the role of CTLA4 blockade versus anti-CTLA4-mediated ADCC on activation of the peripheral immune system in anti-CTLA4 treated mice.