Health Research Formula Grants – State Fiscal Year 2015-16

Twenty-eight organizations received health research formula grants totaling $30,179,100 for the state fiscal year 2015-16. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2016 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 ($99,079) – 2 Projects

Research Projects:

- Title: *Representations of the Phantom Limb in Individuals with Amputation*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Most individuals with amputation have a phantom limb endowed with sensory properties such as touch and pain. The purpose of this study is to test three hypotheses about the causes of phantom limb pain. The hypotheses focus on the relationship between the individual's capacity to voluntarily control the phantom limb and the phantom pain they experience.

- Title: *Remote Monitoring of Symptoms and Cognitive Function using Telehealth: **T- Liver** Project*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: End-Stage Liver Disease (ESLD) is one of the ten leading causes of death in US. It is marked by episodic acute exacerbations of the underlying liver disease which often leads to severe symptoms, poor quality of life, mental deterioration and repeated hospitalizations. The overall purpose of this project is to introduce a telehealth-based intervention (involving remote monitoring of symptoms and weight, with periodic cognitive function assessment) initiated at the time of discharge of ESLD patients. This will support enhanced clinical care and improve self-management in ESLD population. In addition, it will reduce healthcare utilization, improve medication adherence and overall health outcomes.

Allegheny Singer Research Institute ($63,809) – 1 Project

Research Projects:

- Title: *Opioid Polymer Hybrids*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Despite the addictive nature and harmful side effects that result from opioid usage, they remain the most popular class of drugs for the management of chronic pain. Strategies to manage chronic pain include slow release transdermal patches and intrathecal pumps for targeted spinal delivery of opioids. These solutions have critical drawbacks that include variable release rates which can lead to overdose, significant implantation cost, risk of infection and need for frequent medical visits. There is a prominent medical need for a new class of therapeutics that can effectively treat and manage pain without respiratory system depression or the tendency to become addicted.

American College of Radiology ($1,661,159) – 4 Projects

Research Projects:

- Title: *Assessing Important Oncology Research Questions using NRG/RTOG Clinical Trial Data*
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: For over 40 years, the Radiation Therapy Oncology Group (RTOG) was funded by the

National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. RTOG's research has been incorporated into a newly funded NCI clinical trials program, NRG Oncology, which is a member of the NCI National Clinical Trials Network. Drawing upon this vast resource of demographic, treatment, biospecimen, and outcome data from RTOG trials, researchers will develop hypotheses and explore associations that were not defined in the treatment protocols for patients with brain tumors, head and neck, pancreas, esophageal, and prostate cancers, which may inform and/or lead to future protocols.

- Title: *Prevention and Assessment of Missing PRO Data to Enhance the Success of Clinical Trials*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project aims to enhance the success of clinical trials by evaluating automatic email reminders and past due notifications as a method to prevent missing patient-reported outcome (PRO) data on clinical trials, assessing reasons patients are not consenting to PRO components on clinical trials, and assessing the robustness of commonly used analysis techniques on PRO data in which missingness is a concern.

- Title: *Using New Technology and Big Data Analytics to Improve Radiotherapy Treatment for NSCLC*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to develop new technology to define precise target(s) and organ-at-risk (OAR) definitions as well as for personalized, knowledge-driven radiotherapy (RT) treatment planning to enable us to produce an optimal dose pattern for each patient's adaptive RT. We hypothesize that limiting the dose to normal tissue and/or enabling safe escalations of the RT dose will result in improvements to the treatment of patients with lung cancer. The aim is to improve local control of the tumor, resulting in longer survival for lung cancer patients undergoing radiotherapy treatment.

- Title: *A Pennsylvania State Multisite Database of Patients with Actionable Focal Masses on Imaging*
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: Actionable focal masses representing possible cancer are commonly detected on imaging exams. Yet radiologists variably describe the malignant potential of these masses in reports and inconsistently provide follow-up recommendations. This contributes to delayed or missed cancer diagnoses. The primary aim of this project is to improve patient care through a) implementing standardized radiology report language clearly categorizing masses as benign, indeterminate and suspicious for malignancy and b) creating an automated database that reliably captures all patients with actionable (i.e., indeterminate and suspicious) masses. Additional project outcomes will include tracking follow-up imaging and cancer diagnoses associated with these masses.

Carnegie Mellon University ($928,997) – 2 Projects

Research Projects:

- Title: *Development of a Novel Visceral Measure of Cigarette Craving*
  Type of Research: Biomedical
  Focus: Health Populations, Behavioral and Biobehavioral Processes
  Purpose: Self-report assessments of cigarette craving are widely used, but they only weakly predict actual smoking behavior. This may be due to limitations in how craving is assessed - asking smokers to translate craving experiences into words may disrupt the craving experience

itself and distance people from the underlying state (because of "verbal overshadowing"), thereby reducing the predictive utility of such self-reports. The purpose of this project is to: (1) determine whether verbal overshadowing effects occur during traditional self-reports of craving, and (2) test whether a novel "visceral" approach to assessing craving that does not rely on language processing (squeezing a dynamometer) better predicts smoking behavior than traditional self-reports.

- Title: *Computational and Biological Approaches to Define the Neural Basis of Trial-and-Error Learning*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: How motor skills are learned is not well understood. In an effort to better understand the process, this project will examine phenomena at several neural scales ranging from the molecular to cellular to ensembles of neurons.

The Children's Hospital of Philadelphia ($5,887,731) – 1 Project

Research Projects:

- Title: *Pediatric Big Data Project*
  Type of Research: Clinical Research
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to use big health data methods to elucidate novel factors related to the causes of pediatric asthma, childhood obesity, early childhood caries, and avoidable hospitalizations. Asthma, obesity, and caries are among the most common chronic conditions affecting children, and avoidable hospitalizations are one of the most costly types of pediatric healthcare events. Across the city of Philadelphia from 2001-2017, children's electronic health records, birth records, health insurance claims, environmental data that characterize the social and physical environments of residential neighborhoods, and data concerning the natural environment will be integrated, mined, and statistically analyzed.

Drexel University ($1,559,434) – 20 Projects

Research Projects:

- Title: *An Ultrastructural Analysis of Axonal Translation*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: In this project we will investigate the previously unexplored phenomenon of axonal protein synthesis in two populations of neurons in the rodent brain. This protein synthesis is dysregulated in the autism-related disorder Fragile X syndrome, but the details of this dysregulation are unclear. The purpose of these studies is to elucidate the basic biology of axonal translation as well as how alterations in this phenomenon contribute to the symptoms of autism-related disorders. The findings from these and/or follow-up studies may suggest therapeutic targets to ameliorate these symptoms.

- Title: *Gulf War Illness as a Neuroinflammation-based Tauopathy*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of the proposed one-year study is to use human induced pluripotent stem cells (hiPSCs) derived from blood of veterans of the first Gulf War to test the hypothesis that neurodegeneration resulting from Gulf War Illness (GWI) is due (at least in part) to microtubule (MT) deficiencies resulting from neuroinflammation-induced tauopathy.

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- Title: *Targeted Discovery of Novel Antibiotics*
  Type of Research: Biomedical
  Focus: Infectious Disease and Microbiology
  Purpose: The purpose of this study is to identify new compounds with utility as antibiotics against bacterial infections that are refractive to current available therapies.

- Title: *Development of In Vitro Assay to Measure Vaccine Effectiveness*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Follicular helper T cells (Tfh) are critical in eliciting antibody affinity maturation and instructing isotype switching. Thus, harnessing Tfh cell functions is critical in developing effective and protective vaccines. Because Tfh cells primarily reside in lymphatic tissues, it becomes increasingly difficult and impractical to measure their functions and numbers in response to vaccines. The major objective of this project is to develop a new assay to monitor and measure vaccine immunogenicity and effectiveness. Findings from this application will lead to the development of an invaluable tool to accelerate the development of vaccines and immunotherapeutics.

- Title: *The Implications of Multiple Axial Contacts in Sickle Hemoglobin Polymers*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Sickle cell disease arises because a genetic mutation allows normally-isolated hemoglobin molecules to form stiff, multistranded polymers. It is our hypothesis that the contacts thought to exist between molecules within the polymers are significantly incomplete, because the polymer structure is incorrect. This work will test our hypothetical new structure, which could provide new molecular contact sites that can be targeted by small-molecule therapeutics. Our methods employ site-directed mutagenesis at the putative sites, and kinetic studies by which the response to mutation is dramatically amplified and thus readily quantified.

- Title: *Prefrontal Cortical Control of Social Behavior and Aggression*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The project aims to determine the role of the prefrontal cortex (PFC) in aggression control and to dissect the specific effects of dopamine (DA) receptors on social behaviors in a cell-type specific manner. This study will eventually bridge a gap in the literature given that we aim to offer causative evidence of the “social neural circuit” containing prefrontal dopamine D1 receptor- and D2 receptor-expressing neurons in regular social interaction and escalated aggression.

- Title: *The Role of Astrocyte-synapse Interactions in Neural Circuit Formation*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: In this study, we will examine the role of astrocytes, the predominant glial subtype in the central nervous system, in regulating cortical circuit organization and function during early postnatal development. Whereas a large body of knowledge on the role of neuronal activity and function shapes our current understanding of circuit formation, the role of glial cells in these processes remains poorly understood. Compelling evidence now shows that astrocytes are critical for synapse formation and function. Here, we will examine whether astrocyte dysfunction impairs cortical circuit organization and function.

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- Title: *Novel Signal Processing for Combinatoric Neural Electrodes to Increase Yield by Orders of Magnitude*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: There is a significant need for better electrode technologies. A major current constraint on electrode design is that each wire or trace terminates in a single recording site. We have proposed and patented methods to use multi-site wires in braided combination arrangements to transcend this limitation. These open lattice braids also produce much less local inflammation, gliosis and neural death in the brain if compared to a single standard 50-micron microwire electrode. Fully leveraging this new design strategy requires improved signal processing methods that also fully leverage the signal separation opportunities in the new designs. We here propose to further develop the novel signal processing tools needed to fully leverage the new designs.

- Title: *Role of Chloride Intracellular Channel (CLIC) in Regulating Mitochondrial Structure/function and Life Span*
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Aging is a degenerative process and is associated with decrease in physiological functions and increase in risk of neurodegenerative and cardiovascular diseases, and cancer. Ion channels are canonically considered as targets but not causatives in aging process. We have identified mitochondrial anion channel [Chloride intracellular channels (CLICs)] playing a possible role in determining the life span *via* mitochondria. CLICs are associated with cardiopulmonary function, tumorigenesis, cell cycle and apoptosis. Establishing CLICs as mitochondrial ion channels regulating life-span will provide novel therapeutic targets for a vast array of pathophysiological conditions.

- Title: *Intravenous Hemostatic Nanoparticles to Survey, Control and Halt Internal Bleeding*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Trauma is the leading cause of death for individuals between ages 1-44, and many of these deaths are because of excessive hemorrhage. One-third of civilian trauma casualties and 80% of battlefield casualties occur before the patients ever reach a hospital. While there are a few methods for hemostasis, such as pressure dressings, tourniquets, QiukClot, or HemCon, they cannot be used for internal bleeding (noncompressible). The purpose of this project is to develop a novel intravenous hemostatic nanoparticle system with ultra-long blood circulation half-lives to survey, control and halt internal bleeding.

- Title: *Molecular Engineering of Cartilage with Biomimetic Proteoglycans*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Regeneration of osteoarthritic cartilage has been a largely unmet biomedical challenge for the past fifty years. In a pilot animal study, we have molecularly engineered the cartilage tissue using novel biomimetic proteoglycan aggrecan (BA). With these promising results, we are poised to explore the mechanisms underlying this interesting phenomenon and expand the study to include human osteoarthritic specimens. Elucidation of these mechanisms will enable us to better understand and further explore the molecular repair strategy for osteoarthritic cartilage and further expand the strategy to other degenerative tissues.

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- Title: *The Role of Fucosyltransferase 8 in Altering Hepatocyte Physiology*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The incidence of hepatocellular carcinoma (HCC) is increasing in the United States; HCC is usually lethal. Development of anti-HCC therapies has been hampered by an incomplete understanding of factors that influence HCC development. Recently, alterations in the addition of fucose residues onto hepatocyte proteins were identified as biomarkers for, and possible contributors to, HCC development. We will assess the role of fucosyltransferase 8, the enzyme that fucosylates proteins, in altering hepatocyte physiology. Our studies could define new methods for detecting, treating, and/or preventing HCC.

- Title: *Novel Allosteric Modulator of Glutamate Transporter EAAT2 for Neuroprotection after Brain Trauma*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this project is to examine the effects of a novel compound that can be developed into a therapy for traumatic brain injury (TBI). Safe and effective pharmacological treatments for TBI patients are lacking, as earlier approaches have failed in the clinic. Our novel compound, GT949, is a positive allosteric modulator (PAM) of the glutamate transporter EAAT2. Modulation of the activity of EAAT2 is a promising and innovative strategy for diseases/conditions in which glutamate excitotoxicity is involved, including TBI. Specifically, we will provide *in vitro* and *in vivo* proof of efficacy of this PAM and will determine the best dose and route of administration in a clinically relevant animal model of TBI.

- Title: *Role of Maf1 as a Critical Regulator of Lifespan Extension*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We will establish the role of Maf1 as a critical target of the mTOR pathway, which plays a central role in controlling cell growth, proliferation, metabolism, ultimately regulating cellular lifespan and senescence. This pathway has significant clinical relevance; mTOR inhibition ameliorates multiple age-related diseases in animal models including Alzheimer's disease, Parkinson's disease, and idiopathic senile cardiomyopathy. On a University level, Drexel is developing a provisional patent application on the use of mTOR inhibitors for the treatment of dermal atrophy. Thus, the identification of additional mediators of mTOR will provide novel drug targets that may be valuable in several disease states.

- Title: *Functional Profiling of Novel Tools for Dissecting Pathophysiological Mechanisms of Cardiovascular Disorders*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The main goal of this research is to define the biological consequences of acutely inhibiting heterotrimeric G proteins associated with G protein coupled receptors (GPCRs), using chemical biology approach. Heretofore, studies investigating the role of G proteins in normal physiology and disease have relied on genetic manipulation. This approach, however, is limited by activation of compensatory mechanisms because many GPCRs can couple to more than one G protein in the same cell. This study will determine whether newly synthesized small molecule inhibitor ligands can be used as tools to study the acute effects of blocking G proteins while avoiding the activation of compensatory mechanisms.

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- Title: *Promoting Vascularization In-vivo in Magnetically Actuated Scaffolds*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The strategy described in this project will provide a means to obtain pre-vascularized tissue constructs and facilitate integration of these constructs with the host tissue due to accelerated anastomosis between host blood vessels and pre-vascularized structures of the tissue construct. In the future, this methodology will allow generation of pre-vascularized cardiac patches that will result in efficient cardiac cell retention, survival, and function in an infarcted heart, contribute to a novel clinical treatment of heart failure patients, and add to our current knowledge of infarct healing.

- Title: *Investigation of the Pathological Tau Phenotypes and Tau Spreading in hiN Cells from FAD*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Familial Alzheimer's Disease (FAD) is a human-specific neurodegenerative disease caused by abnormal tau species. No effective treatment is available due to lack of knowledge of the mechanisms underlying the disease. Rodent models fail to recapitulate tau phenotypes seen in humans because of differences between rodent and human tau. In this project, human induced neurons (hiNs) will be derived (via direct reprogramming) from the skin cells of unaffected individuals (UND) and FAD patients. These cells will be used to investigate mechanisms of pathological tau phenotypes in FAD and to screen for therapies.

- Title: *Rapid Antimicrobial Susceptibility Test*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Drug resistant bacteria cause 2 million US infections annually and cause > 23,000 deaths. Rapid determination of the antimicrobial susceptibility profile of patient isolates is critical to determine which antibiotics will effectively treat the infection, and to prevent bacterial strain spread. Current antimicrobial susceptibility testing (AST) methods require days of culture and > 10 hr of incubation with the antibiotic drugs. We will assess a novel, incubation-free, little-culture, piezoelectric plate sensor (PEPS) AST for instantaneous minimum inhibitory concentration (MIC) determination for each drug tested. Such rapid AST results will permit better treatment of patients with infections and prevent spread of multi-drug resistant organisms.

- Title: *The Role of MK2 Kinase Signaling in Inflammatory Breast Cancer*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this study is to characterize the role of the p38-MAPKAP kinase 2 (MK2) signaling pathway in the progression of inflammatory breast cancer (IBC). As relatively little is known regarding the molecular mechanisms that drive this particular type of breast cancer, these studies will address this knowledge gap and may provide new targets for therapeutic intervention.

- Title: *Control of Catheter-Associated Urinary Tract Infection and Biofilm*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this study is to develop an antibacterial and anti-adhesive coating for urinary catheters to effectively prevent catheter-associated urinary tract infections (CAUTI). Current coatings are either not significantly effective or are only effective for several days. A

catheter coating that can reduce the infection rate for longer duration will greatly reduce the rate of CAUTI and associated morbidity and mortality of patients. We propose to study whether sustained release of minocycline, a safe and effective broad-spectrum antibiotic, in combination with an anti-adhesive coating capable of inhibiting bacterial adhesion, can effectively inhibit CAUTI for at least a month. This research will help to discover new knowledge leading to prevention of CAUTI.

Duquesne University of the Holy Spirit ($125,372) – 2 Projects

Research Projects:

- Title: *Fully Functionalized Small-molecule Probes for Oncology Drug Discovery*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to begin producing an optimal collection of "fully functionalized small-molecule probes" (FFSMPs) for integrated phenotypic screening and target identification studies in cancer cells. FFSMPs are compounds that can be immediately used as bait to capture their protein targets under the same assay conditions used for phenotypic screening, thus avoiding lengthy synthetic modification of biologically active "hit" compounds. Recognizing that target identification is the crucial, rate-limiting step in oncology drug discovery, and providing for its completion from the outset, we expect to facilitate rapid identification of new chemical probes and drug targets for the treatment of cancer.

- Title: *Crosslinking/Mass Spectrometry (CXMS) Studies of Glycine Receptor Allostery*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The proposed research is relevant to public health because knowledge of how ionotropic receptors function at a molecular level is necessary to understand their allosteric modulation and their interactions with anesthetics, drugs and therapeutics. In particular, the proposed innovative collaborative research on state-dependent crosslinking of the glycine receptor has the potential to transform our understanding and ability to modulate neuronal communication.

Geisinger Clinic ($184,737) – 1 Project

Research Projects:

- Title: Evaluation of System-wide Medication Prior Authorization Process
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This specific aims of this project are: (1) to identify difficulties that providers and patients are currently experiencing with the prior authorization process; (2) to develop solutions to help patients and providers navigate this process more efficiently; and (3) to evaluate this modified medication prior authorization process.

Hepatitis B Foundation ($385) – 1 Project

Research Projects:

- Title: *Hepatitis B Prevalence and Factors Associated with Infection among High-risk Asian Americans and Pacific Islanders in Philadelphia*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to establish baseline data for hepatitis B virus (HBV) status among Philadelphia Asian Americans and Pacific Islanders (AAPIs) to better understand the picture of HBV in high-risk AAPI communities in Philadelphia. This includes understanding the

demographic and personal/family history characteristics of persons who are HBV infected; as well as factors that are associated with HBV infection.

The Institute for Cancer Research ($1,876,002) – 7 Projects

Research Projects:

- Title: *Comparing CBP and p300 Residue Acetylation Preference*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We will focus on dissecting the molecular and biochemical differences between cyclic adenosine monophosphate (cAMP)-response element binding protein (CBP) and p300, two highly similar lysine acetyltransferase to address the factors that regulate their site-specific targeting on histones. This investigation will aid in our understanding of why these enzymes cannot compensate for each other *in vivo* and in turn why, if lost, can lead to a number of the leading causes of death, including heart disease, cancer, as well as neurodegenerative diseases, including Alzheimer's.

- Title: *Regulation and Function of Interferon-activated Necrosis in Antiviral Innate Immunity*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this project is to identify the mechanism by which interferons, a class of antiviral cytokines, activate necrotic death of virus-infected cells, and to determine the relevance of this form of death to interferon-mediated clearance of virus-infected cells and resolution of respiratory viral disease in vivo.

- Title: *Identification of Bioactive Small Molecule Compounds that Regulate Ciliary Dynamics*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The primary goal of the project is to identify new therapies for cancers that depend on intact cilia: structures that protrude from the plasma membrane, and that serve as signaling hubs for soluble cancer-promoting ligands that include Sonic Hedgehog (SHH), platelet derived growth factor (PDGF), and Wnts. This class of cancers includes hard-to-treat malignancies such as medulloblastoma, glioblastoma, and basal cell carcinoma. We will use unique cellular models, high throughput screening approaches, and chemical libraries of bioactive compounds and cancer-relevant small molecules, developed at Fox Chase Cancer Center/Temple University School of Medicine (FCCC/TUSM) to identify drugs that affect ciliary dynamics.

- Title: *The Role of Chitinase-like Protein YKL40 in Inflammation and Cancer*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of current project is to study the rather unexpected role of chitinase-like protein Chi3l1/YKL40 in the induction of tumor –elicited inflammation in colon cancer and its role in colon cancer progression. We have recently generated unique cellular and genetic tools to analyze the role of YKL40 in preclinical models of colon cancer. YKL40 can be produced by various cell types and can signal to several different cellular populations within the tumor microenvironment. Therefore, in this project, we will gain insights into the role of YKL40 produced by epithelial/cancer cells and by myeloid cells.

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- Title: *Pathogenesis of Neurological Damage Induced by Peripheral Infection*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Brains of individuals who died from a number of central nervous system disorders, including multiple sclerosis, amyotrophic lateral sclerosis, and autism show evidence of neuroinflammation, though no pathogenic trigger has been identified for any of these chronic central nervous system (CNS) disorders. This project is based on preliminary studies that support the emerging principle that the site of pathogen replication can be uncoupled from the site of immune-mediated damage. Should this be true for any of the human CNS diseases with inflammatory hallmarks, this would substantially affect how prophylactic and interventional modalities are conceived and developed.

- Title: *Improving BH3-mimetic Effectiveness in the Treatment of Acute Myeloid Leukemia*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Acute myeloid leukemia (AML) is an aggressive, chemotherapy resistant blood cancer with very poor (<25%) 5-year survival rates. These unsatisfactory outcomes underscore the urgent need for new, more-effective therapies. BH3-mimetics are a new class of compounds that are showing effectiveness in a variety of human cancers, including AML. However, although most patients initially respond to BH3-mimetic treatment, many patients relapse with a therapy resistant disease. The purposes of this study are to first identify molecular pathways that promote BH3-mimetic resistance and then develop strategies for pharmacologically targeting them.

- Title: *Methods to Enhance CRISPR-Mediated Gene Targeting*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to develop novel methods to enrich cells whose genes have been specifically targeted by the clustered regularly-interspaced short palindromic repeats (CRISPR)-Cas9 technology. It is based on the method that our lab has previously developed and published to enrich successfully targeted cells. We will extend this method to other cell lines commonly used in cancer research. In addition, we will develop a new method to facilitate the sequential targeting of multiple genes for the study of their genetic interactions.

Lankenau Institute for Medical Research ($121,269) – 1 Project

Research Projects:

- Title: *Determining the Basis of IDO1-Mediated Support of Neovascularization*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The tryptophan catabolizing enzyme IDO1 is emerging as a promising immuno-oncology target that promotes tumoral immune escape in the context of chronic inflammation where it may represent one of the earliest determinants for directing the immune response towards supporting rather than eliminating tumors. Recently, we made the unexpected discovery that loss of IDO1 can negatively impact neovascularization. The current project aims to probe the underlying cellular and molecular basis for the involvement IDO1 has in supporting this key aspect of tumor outgrowth, informing not only the clinical development of IDO1 inhibitors in oncology but also suggesting a completely new use for such agents in the treatment of ocular diseases.

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Lehigh University ($105,676) – 1 Project

Research Projects:

- Title: *Optofluidic Nanocytometry for Characterization of Whole Particle Viruses*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The overall objective of this research program is to develop an optofluidic analyzer for quantitative characterization of whole particle extracellular bio-nanovesicles in a suspension, functioning in a similar fashion as flow cytometry but targeting particles orders of magnitude smaller. To our knowledge, the proposed platform will be the first to allow analysis of whole viral and exosome particles in a simple flow-through process for fast diagnosis of various diseases and detection of biological hazards. Furthermore, this platform is expected to revolutionize virology and exosome biology like how flow cytometry has greatly impacted cell biology.

Lincoln University-of the Commonwealth System of Higher Education ($12,364) – 1 Project

Research Projects:

- Title: *Genetic Variants and Gender Differences in Lung Cancer Risk*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: We hypothesize that lung cancer risk is associated with carcinogen levels, and that the risk is modified by differences in detoxification of carcinogens due to genetic variants in carcinogen-metabolizing genes. We aim to identify genetic variants in the genes associated with carcinogen metabolism and lung cancer risk and determine if there is a gender difference in these risks. The findings will result in a significant advance in our understanding of lung cancer and help to identify high-risk individuals for the development of lung cancer screening and prevention strategies. For example, individuals with these variants may benefit from more frequent screening or personalized chemoprevention or intervention programs smoking.

Magee-Womens Research Institute and Foundation ($1,195,949) – 9 Projects

Research Projects:

- Title: *Mechanisms of Adipocyte Death*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Although fat cells (adipocytes) are crucial contributors to metabolic health and disease, to date, very few studies addressed the physiological control of adipocyte death. Our preliminary studies show that down-regulation of the nuclear receptor PPAR□ (Peroxisome Proliferator-Activated Receptor □) in adipocytes leads to their rapid death *via* a novel, non-apoptotic, non-necrotic mechanism. Here, we will investigate this mechanism through the use of a unique *in vivo* marking system designed to identify, isolate and analyze adipocytes from whole fat pads and a cell culture simulation as they are dying upon induced loss of PPAR□. This study will significantly enhance the knowledge of adipocyte dynamics in health and disease.

- Title: *Lipids, Inflammation and Placental Malperfusion*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Cardiovascular disease (CVD) is the leading cause of death among women in the United States. Women with pregnancies complicated by preeclampsia, preterm birth and fetal growth restriction have higher cardiometabolic risk and excess CVD in the years after pregnancy. A common pathophysiologic feature of these adverse pregnancy outcomes is evidence of placental malperfusion, characterized by incomplete vascular remodeling or vessel wall impairments similar to atherosclerosis. Surprisingly, little is known about maternal precursors to these placental

vascular lesions. We hypothesize that mid-gestational atherogenic markers measured in maternal serum will be associated with placental malperfusion lesions. To test this hypothesis, we will utilize placental samples and stored serum samples collected as part of the MOMI Biobank (100 with malperfusion lesions and 100 without malperfusion lesions). We will measure lipids, inflammation markers, and asymmetric dimethylarginine (ADMA) in serum collected at mid-gestation and relate these atherogenic markers to the presence of placental malperfusion lesions.

- Title*: Identifying Targets for Developing Interventions to Prevent Perpetration of Intimate Partner Violence Among Boys and Young Men*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Intimate partner violence (IPV) is a prevalent problem associated with negative health consequences for victims, perpetrators, and child witnesses. The scientific effort to date has focused primarily on female victims of IPV. Focus on batterers—the individuals who actually cause the problem—has lagged far behind the focus on victims, both in research and in prevention and intervention. Through prior research, we have accessed data about and from clients of two community battering intervention programs for adult male perpetrators of IPV. The purpose of this proposal is to use this existing data to increase understanding of human service utilization and criminal justice involvement among battering intervention program (BIP) clients and intervention components that BIP clients indicate represent key targets for developing IPV perpetration prevention programs for boys and young men.

- Title*: Interaction of Long Non-coding RNAs, miRNA and mRNAs in Primary Human Trophoblasts*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: One of the main purposes of this study is to investigate the interaction between long non-coding RNAs (lncRNA), miRNAs, and mRNAs in primary human trophoblasts (PHT cells) cultured under standard or hypoxic conditions and search for putative miRNA and lncRNA regulators for mRNA targets in PHT cells. In addition, we will examine the expression of the selected RNA species in maternal plasma from normal pregnancies and pregnancies with fetal growth restriction. The results from this study will enhance our understanding of the mechanisms of placenta injury and suggest new tools for diagnosis and prevention of pregnancy complications.

- Title: *Genetic Dissection of Endometriosis-Associated Ovarian Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: In this exploratory proposal, our research plan centers on *ARID1A* and *PIK3CA*, two of the most frequently mutated genes in endometriosis-associated ovarian cancer (EAOC). We will use our CRSIPR-Cas9 genome editing tool to dissect genes regulated by mutated *ARID1A* and *PIK3CA* in an endogenous and physiological background and determine how these genes contribute to EAOC initiation and progression. We will establish a double-conditional *Arid1a* knockout and *Pik3ca* H1047R mutation knockin mouse model to dissect their roles in EAOC tumorigenesis *in vivo*. Information gleaned from our data may not only shed new light on EAOC pathogenesis but may also identify new therapeutic targets and biomarkers.

- Title: *Defining the Role of Apical Vaginal Support in Pelvic Organ Prolapse*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: To define the role of apical vaginal support in maintaining the anatomical positions of pelvic organs by dynamically monitoring apical position and function with a combined use of

MRI imaging and a customized colpometer in a non-human primate model. This study will not only explore new technology but also collect reviewer-requested preliminary data for a favorably scored NIH R01 proposal to investigate whether the loss of apical support, likely impacted by pregnancy, mode of delivery, and parity, increases the risk of pelvic organ prolapse. The study will utilize an established interdisciplinary team with expertise in tissue mechanics, tissue analysis, non-human primate research, imaging, and urogynecology.

- Title: *Identification of Changes in Tumor Transcriptome and Immune Surveillance in Metastatic Ovarian Cancer*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The high mortality rate in ovarian cancer is due to the fact that 75% of patients are diagnosed late, when the tumors have spread throughout the peritoneal cavity or to distant organs. Current therapy includes surgery and cytotoxic drugs, a combination that is often unable to eradicate the metastatic tumors. Although the biology of loco-regional tumor expansion has been partially deciphered, much less is currently known about the metastatic disease resulting from hematogenous spread to distant organs. In this project, we aim to identify molecular changes that trigger tumor spread and modulate immune responses at primary and metastatic sites. Our studies have the potential to reveal new therapeutic venues for metastatic ovarian cancer.
- Title: *Construction of Transgenic Mice to Study Testosterone-mediated Health and Fertility*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: This project will produce unique transgenic mouse models that will greatly increase our knowledge of the molecular mechanisms by which testosterone impacts major health issues including male and female fertility, bone fragility, cardiovascular disease, muscle wasting, obesity and prostate cancer. The transgenic mouse models will identify physiological processes in testosterone responsive tissues that are regulated by either the classical or non-classical pathways of testosterone action. This information will be useful to develop therapies for many pathologies associated with defects in testosterone signaling. Our mouse models also will used to develop therapies for male infertility and identify novel targets for male contraception research.

- Title: *Regulation of Meiotic Double-Strand Break Formation*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: During the specialized cell division of meiosis, parental chromosomes swap DNA in the process known as crossover recombination. This process begins with the formation of a double-strand break by the enzyme SPO-11. However, our understanding of how SPO-11 is recruited to specific regions of the genome and how its activity is regulated is still quite rudimentary. Our studies using the nematode *C. elegans* will use genetic and cytological approaches to attain new knowledge about the protein complexes that regulate break formation. These studies have the potential to identify genes and pathways that lead to human aneuploidy and therefore may identify targets for therapeutic purposes.

Monell Chemical Senses Center ($258,825) – 2 Projects

Research Projects:

- Title: *Identifying the Genetic Basis of Isolated Congenital Anosmia*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to identify candidate causal genes for isolated congenital

anosmia (ICA), a condition in which people are born without a sense of smell but are otherwise completely healthy. To date, only a single gene has been implicated in the development of ICA in two brothers with this disorder. Knowledge of the genetic basis of this disorder will provide avenues for its diagnosis and treatment which are currently unavailable for patients with ICA.

- Title: *Expression and Function of Taste-like Chemosensory Pathway in Choroid Plexus of the Brain*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Recent studies have shown that taste receptors and their downstream signaling components are expressed not only in taste buds but also in various extra-oral tissues. Emerging evidence suggests that the extra-oral taste-like chemosensory pathway, composed of taste receptors and their signaling components, is involved in sensing nutrients, toxic compounds, microbes, and parasites. Our preliminary data suggest that choroid plexus of the brain expresses taste receptors and their signaling components. The purpose of the project is to confirm the expression of sweet, umami, and bitter receptors and their signaling molecules in choroid plexus and to determine the role of taste-like chemosensory pathway in the regulation of immune responses in the brain.

National Disease Research Interchange ($60,530) – 1 Project

Research Projects:

- Title: *Susceptibility Genes for Microvascular Complications in Patients with Type 1 Diabetes*
  Type of Research: Health Services
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: The overall goal of this project is to identify the genes and mechanisms that are major contributors to microvascular complications of Type 1 Diabetes (T1D). We are specifically searching for shared familial pathogenic mechanisms that predispose to T1D complications but that are not necessarily related to T1D susceptibility. Identifying such mechanisms will allow us to predict which patients are at greatest risk for the blindness, kidney failure and nerve disease caused by diabetic microvascular disease and eventually lead to understanding the origins of complications susceptibility and provide pathways for developing treatments or prevention.

NSABP Foundation, Inc. ($670,736) – 1 Project

Research Projects:

- Title: *Assessment of the Immune Microenvironment in Cancer*
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this study is to investigate the immune microenvironment in colon and/or breast tumors, with the aim of understanding its role in: determining prognosis, predicting benefit from therapy, and identifying potential new strategies for treatment. An examination of the cell-types, quantity, and location of immune cells in the tumor and the surrounding stroma, in conjunction with a characterization of the expression of critical immune molecules may allow for the discovery of new monitoring and treatment strategies. Our unique access to colorectal cancer (CRC) tumor tissue from the MPR-1 living patient registry and our clinical studies also opens up the prospect of future clinical trials for cancer patients.

Penn State University ($6,873,203) – 19 Projects

Research Projects:

- Title: *Mucosal Macrophages and Post-Infectious IBD*
  Type of Research: Biomedical

Focus: Digestive Sciences
Purpose: Inflammatory bowel disease (IBD) is the result of exacerbated immune response against commensal or "good" bacteria, whereas various gastrointestinal (GI) infections caused by "bad" bacteria such as *Salmonella* can initiate the onset and relapse of IBD. The purpose of this project is to understand the regulatory role of macrophages in simultaneous protection against "bad" microbes and control of exacerbated immune response against "good" microbes.

- Title: *Discovering the Genetic Profiles of Chronic Inflammation: An Ulcerative Colitis Model*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The wide variety of symptoms displayed by Ulcerative Colitis (UC) patients creates a challenge for clinical diagnosis and treatment. To meet this challenge, we have assembled an experienced multidisciplinary team of Penn State research scientists, genome scientists and clinicians to test the hypothesis that each patient's diseased organ has developed unique genetic changes that impact clinical presentation. The purpose of this pilot study is to understand how genetic changes arising within pre-cancerous tissues of UC patients contribute to cancer progression. We will develop novel genomics and computational approaches for detecting mutations within patient tissues and interpret how the acquisition of somatic mutations contributes to UC pathogenesis.

- Title: *Obesity Related Breast Cancer Risk Reduction Using Liposomal DHA*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: We demonstrated the preferential role of docosahexaenoic acid (DHA), a component of fish oil, in reducing breast cancer risk in obese women. To provide better understanding of the role of DHA in breast cancer prevention, we will compare protein profiles in archived plasma samples of obese *vs.* lean women given fish oil. We developed a liposomal formulation of DHA which withstands pH fluctuations and oxidation and showed its superior anti-tumor activity in human breast cancer cells to that of free DHA. Prior to testing chemoprevention efficacy, we will perform PK/PD studies to demonstrate the superiority of liposomal formulation in the delivery of DHA to the target organ (mammary tissues).

- Title: *Effect of Flavorings on Free Radical Production in Tobacco Smoke*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The goal of this research is to determine the effect of menthol and other flavorings on the production of reactive free radicals in mainstream smoke from cigarettes, little cigars and cigarillos. Free radicals and other oxidants produced from combustible tobacco products are thought to play a key role in the development of many tobacco related diseases including cancer and cardiovascular diseases. Little is known regarding the production of toxicants including free radicals from flavoring agents added to tobacco prior to combustion. This information is critical in understanding the potential harm which may result from use of these flavored products.

- Title: *Novel Mutations and Chromosomal Landscape in Familial and Sporadic Nonmedullary Thyroid Cancer*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Each year over 62,000 people are diagnosed with thyroid cancer; between 5 and 10% of these cases are hereditary, although the causative gene has not been identified. We recently discovered a mutation in the DUOX2 gene in a family with highly penetrant hereditary thyroid

cancer. This project aims to determine whether dysregulation of DUOX2 and associated proteins contributes to thyroid cancer and to identify large-scale chromosomal structural variations that occur in thyroid cancer. The knowledge gained through this project may reveal novel strategies to prevent thyroid cancer, identify new therapeutic targets, and facilitate the selection of patients who will maximally benefit from existing treatments.

- Title: *Mechanism of Chromatin Structure Unfolding During NETosis*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to understand the molecular mechanism of chromatin unfolding during NETosis - an abrupt unfolding of DNA in neutrophil granulocytes in form of Neutrophil Extracellular Traps (NETs). NETosis plays an important role in fighting bacterial infections but has adverse effects for cystic fibrosis, autoimmune disorders and deep vein thrombosis and pulmonary embolism. Understanding the molecular events leading to induction of NETosis at nano- and molecular level may lead to designing new pharmacological drugs capable of controlling excessive NETosis as well as regulating DNA compaction in the cell nucleus.

- Title: *Influence of the Microbiome and Epigenetics on Childhood Obesity*
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this study is to identify changes in the gastrointestinal (GI) microbiome and epigenetic regulation that are associated with childhood obesity. Though genetics and the microbiome are known to play a role in adult obesity, their patterns of expression in the first two years after birth remain uncertain. We plan to identify changes in the GI microbiome that are associated with fluctuations in fecal micro ribosomal nucleic acid (miRNA). Furthermore, we will determine if these factors are affected by environmental influences such as family context, psychosocial influences, and demographic factors. Such information will enhance our understanding of the development of childhood obesity and inform strategies aimed at its prevention.

- Title: *Big Data Integration, Statistical Analysis, and Computational Approaches to Benefit Biologists and Clinicians*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The biomedical community faces continuing challenges as the field becomes more data intensive. The growing complexity of data analyses and computational demands are substantial barriers for researchers without statistical and informatics expertise, whereas the heterogeneity of existing data makes it difficult for statisticians and bioinformaticians to develop effective tools. Our purpose is to address these challenges by characterizing several common human diseases in multiple dimensions, developing novel tools for data analysis and integration to leverage complex information in understanding diseases, and making such tools widely accessible to biomedical and clinical researchers.

- Title: *Calcium Phosphosilicate Nanoparticles: Imaging and Drug Delivery for Prostate Tumors*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The overall purpose of the project is to develop biocompatible nanoparticles (specifically calcium phosphosilicate nanoparticles: CPSNPs) which incorporate imaging or therapeutic agents for targeted delivery to prostate tumor cells. Our hypothesis is that prostate tumor growth can be suppressed by delivering chemotherapeutic drugs, such as docetaxel, directly to cancer cells using

a targeted nanoparticle delivery system. Secondly, we propose to encapsulate imaging agents, such as near-infrared (NIR) and MRI imaging agents, into CPSNPs. Finally, we will assess whether a DNA aptamer with high affinity for the CCK-B receptor, a protein found on prostate cancer cells, improves nanoparticle up-take by prostate tumor cells in vitro and in vivo.

- Title: *Risk Factors and Early Life Contributors to Childhood Obesity*
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Though 25% of children aged 2-5 years are *already* overweight or obese in the US, we struggle to understand the causes and identify solutions. This research will further explore risk factors shown to be associated with obesity across the life course related to pregnancy and the home environment. These factors influence overweight and rapid weight gain during infancy and also co-morbidities including hypertension, coronary heart disease, and diabetes. This research will also explore new epigenetic mechanisms as infancy and the prenatal period are critical periods of developmental plasticity with long-lasting consequences.

- Title: *Precision Medicine for Melanoma Treatment*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The overarching goal of this project is to develop more precise therapies based on the biology of melanoma that can overcome current limitations. The central hypothesis for the project is that unraveling the biology of the disease can be used to design precision therapeutic approaches for patients that would be more effective with fewer side effects.

- Title: *β-Adrenergic Blockade Combined with High Dose Interleukin-2 for Treatment of Melanoma*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: This project seeks to increase the population of melanoma patients who will benefit from high dose interleukin-2 (IL-2) therapy. IL-2 therapy induces responses in about 16% of Stage IV melanoma patients with a durable complete response rate of 4%. As there is a clear role for stress in suppression of anti-tumor immunity, we will alleviate the impact of stress using pharmacologic antagonists that reduce β-adrenergic signaling. Under these conditions of reduced stress, we will investigate the mechanisms by which excessive β-adrenergic signaling impedes the anti-tumor immune response and determine whether a reduction in signaling can improve the efficacy of high dose IL-2 therapy that correlates with clinical response.

- Title: *Renal Medullary Oxygenation and Blood Flow During Sympathetic Activation in Humans*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The purpose of this project is to investigate the effect of graded sympathetic activation on renal medullary oxygenation and blood flow in healthy humans. The sodium and fluid retention associated with diseases such as congestive heart failure may partly be due to exaggerated sympathetic nerve activity directed to the renal medulla. Understanding the basic physiology behind this neural control in healthy humans is the critical first step in addressing this issue. Therefore, we will use magnetic resonance imaging and Doppler ultrasound to measure renal medullary oxygenation and blood flow, respectively, during graded sympathetic activation via lower body negative pressure application in healthy humans.

Health Research Formula Grants – State Fiscal Year 2015-16

- Title: *Novel Optogenetic and Chemogenetic Model for Parkinson's Disease*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of the project is to study a reversible model of Parkinson's disease using novel optogenetic and chemogenetic techniques. Such a model will allow a comprehensive assessment of therapies that has never before been possible and allow us to make advances in the care of patients with Parkinson's disease. The techniques themselves may offer opportunities to become therapies in patients with Parkinson's disease or for complications of neurological disorders that have dysregulation of dopamine.

- Title: *In Situ Structural Analysis of Membrane Proteins by NMR*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Structural information about proteins in biological environments is scarce. To date, most membrane structure determinations have been carried out in detergent preparations and synthetic lipid bilayers, despite the known importance of the membrane environments in supporting the native structure, dynamics, and function of membrane proteins. We recently demonstrated the feasibility of using magic-angle spinning (MAS) solid-state nuclear magnetic resonance (ssNMR) to directly characterize a recombinant protein in native Escherichia coli (E. coli) membranes. In this project, we will develop and apply this in situ approach to characterize the structure of □-secretase (BACE1), a prime target for treatment of Alzheimer's disease (AD).

- Title: *Cancer Risk Stratification of Endometrial Hyperplasia by Next Generation Sequencing*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Endometrial hyperplasia is the abnormal, exuberant growth of the inner lining of the uterus. The condition is common and is the setting in which the majority of uterine cancers arise. Despite this, it is currently difficult to predict which women with endometrial hyperplasia will go on to develop cancer. It has recently been shown that a subset of endometrial hyperplasias harbors mutations in the same set of genes altered in endometrial cancer. This project aims to perform next generation sequencing on a series of endometrial hyperplasia cases to determine if mutational profile in endometrial hyperplasia is predictive of cancer risk. This will be done as a case-control study on retrospective materials.

- Title: *Cannula with Integrated LV Volume and Pressure Sensing for LVAD Control*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Left Ventricular Assist Devices (LVADs) are mechanical blood pumps that are used to support the left ventricle (LV) in patients with end-stage heart failure. Currently, there is no practical means to automatically adjust LVAD speed in response to a patient's physiologic need. The purpose of this research is to incorporate wireless pressure and volume sensors into an LVAD system so that heart function can be continuously measured and used to control LVAD speed. This will prevent excessive suction on the heart and dangerous arrhythmias and will allow the LVAD to pump higher flow when needed, thereby improving health and exercise tolerance.

- Title: *Linking Viral Genetic Variations to Outcomes in Pathogenesis and Disease*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Viruses constitute a major force in human disease, both in acute infections and in longer-term chronic infections. Improving our knowledge of these pathogens will assist in identifying

viral variants associated with the greatest risk of disease and requiring the most aggressive intervention. Conversely, we may identify safe or weakened viral variants that could be used in vaccine development. We will investigate the degree to which genetic variation in viruses affects the multifaceted outcomes of disease in people. We will explore viral pathogen variation both within and between infections, to uncover potential sources of variation in clinical outcomes, and we will link these variations to putative biological functions.

- Title: *DNA Damage Landscape*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The goal of this research is to create a methodology to determine the position of DNA damage in the genome. While much work has gone into measuring the levels of DNA damage caused by carcinogens, we have limited knowledge concerning where the damage is located in the genome. The hypothesis underlying this work is that the location of damage, caused by compounds such as the environmental carcinogen benzo[a]pyrene, plays a role in cancer etiology, while the location of damage caused by cancer therapeutics such as cisplatin plays a role in therapy.

Salus University ($41,363) – 1 Project

Research Projects:

- Title: *Experimental Models for Studying Congenital Retinal Diseases*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Several types of human congenital blindness found in patients in the United States and worldwide have been linked to mutations in a gene coding for retinal guanylyl cyclase, RetGC1. These mutations either disable the function of RetGC1 or cause abnormal regulation of the enzyme in the retina. The purpose of this short-term pilot study is to find, by utilizing mouse retinas, the functional link between the multiple mutations and the photoreceptor dysfunction in order to better understand the physiological changes in photoreceptors that lead to blindness. A part of the study will also focus on designing genetic constructs capable of reducing or preventing the development of blindness in mouse models.

Swarthmore College ($24,006) – 1 Project

Research Projects:

- Title: *Ambivalence as a Catalyst for Changing Health Behaviors*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Ambivalence, the simultaneous experience of positive and negative feelings, may be a critical catalyst for changing health behaviors, while also distracting attention away from healthy decision making. This project aims to explore these two hypotheses, as well as an intervention that may diminish the deleterious effects of ambivalence on attention: specifically, acknowledging an ambivalent state may allow an individual to focus on subsequent tasks and improve decision making. Examining the neural signatures of these processes and studying how individual differences (e.g., personality) affect the experience of ambivalence may also shed light on the positive role that ambivalence can play in changing health behaviors.

Temple University-of the Commonwealth System of Higher Education ($2,631,111) – 6 Projects

Research Projects:

- Title: *Nanoplasmonic Imaging Agents, Biosensors, and Therapeutics*
  Type of Research: Biomedical

Focus: Bioengineering, Surgical Sciences and Technology
Purpose: The scientific objective of this project is to develop plasmonic copper nanoparticles (CuNPs) as sensors for biomedical imaging, diagnostics and therapeutic applications. Current state-of-the-art plasmonic sensors show simple, color-based diagnostic responses, but rely upon expensive gold and silver metals, which limit their applicability and accessibility for poverty-level population groups. While copper offers a less expensive alternative, it is also highly sensitive to oxygen, requiring the development of biocompatible protective coatings. The purpose of this study is to produce CuNPs with optimized sensitivity for *in vivo* and *in vitro* diagnostics and biosensing, while protecting the CuNPs against oxygen.

- Title: *Synthetic Chemistry for the Improvement of Human Health by Fostering a Cleaner Earth*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Toxins and pathogenic microbes in the environment pose a significant risk to human health. The proposed research seeks to use synthetic chemistry to prepare and characterize chemical compounds that have implications for 1) green energy and the removal of environmental toxins and 2) eradication of disease in vivo and in the environment.

- Title: *Health Data Science Research Project*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose is to upgrade the facilities to incorporate a dedicated computational analytic cluster to support health data storage, networking, and end use; to create a portal based on the hub that provides a conduit to a health data warehouse; and develop virtual research facilities to connect faculty working on health data science across multiple campuses. The newly designed facility will host the data storage and analytical needs associated with the development and use of novel techniques for examining temporal, spatial, and health information.

- Title: *The Molecular Mechanisms of Overnutrition Induced Insulin Resistance*
  Type of Research: Clinical
  Focus: Research Infrastructure Project
  Purpose: Overnutrition is associated with obesity, insulin resistance (IR) and diabetes. We showed that men exposed to overnutrition experienced a rapid onset of oxidative stress (OS) followed by IR. In adipose tissue, proteomics studies showed that the OS resulted in carbonylation and loss of function of a major glucose transporter (GLUT4). Also, adipocytes exposed to byproducts of OS showed similar GLUT4 modifications. Therefore, using proteomics technology, we propose to study the role of GLUT4 carbonylations in producing IR. These studies will enhance our understanding of the mechanisms by which overnutrition produces IR via GLUT4 carbonylations and how these changes can be prevented or reduced.

- Title: *Psychopathology, Disordered Eating, Impulsivity and Weight Loss after Bariatric Surgery*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The main purpose of the study is to assess the relationship between psychopathology, disordered eating, impulsivity, and changes in body weight following bariatric surgery. Secondary outcomes include changes in weight-related comorbidities, dietary intake, physical activity, and psychosocial functioning.

- Title: *Community-Based Obesity Treatment in African American Women after Childbirth: A Randomized Controlled Trail of WIC Mothers*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Individuals from underserved populations are profoundly affected by obesity and its comorbidities. They also are less likely to be provided access to empirically supported weight loss interventions. The purpose of the proposed study is to determine whether a lifestyle intervention to promote postpartum weight loss in obese African American women will have positive "ripple" effects on their untreated infants, e.g., lead to changes in eating/activity/sleep behaviors and weight status.

Thomas Jefferson University ($2,592,323) – 9 Projects

Research Projects:

- Title: *Mechanism and Consequence of Tumor Suppressor Alterations in Advanced Prostate Cancer*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Preliminary findings demonstrate that the prevalence of CRPC (castration resistant prostate cancer)-specific TP53 mutations in advanced prostate cancers is higher than previously appreciated and these events occur in a “hotspot” cluster that are likely to deregulate one or more key functions of the p53 protein that are essential for p53-mediated tumor suppression. These findings suggest that expression of the CRPC-specific R248Q and R273C p53 mutants will promote aggressive CRPC phenotypes and that delineating the specific contributions of these mutants will allow for development of precision medicine and identification of a unique subclass of prostate cancer patients characterized by increased genomic instability.

- Title: *Exosomal Integrin-mediated Radioresistance*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This project addresses an important area of research that is under investigated and has significant unmet clinical need. The challenge is to develop effective treatment for advanced prostate cancer “with no available curative therapy”. The results will provide insights in the understanding of the molecular mechanisms by which Neuroendocrine Prostate Cancer (NEPC) alters the response to radiation therapy and provides insight into intrinsic and acquired resistance to therapy.

- Title: *Breast Cancer Cell Dormancy is Orchestrated by Osteoblasts in the Bone Niche*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Breast cancer has a predilection for bone metastasis, where the five-year survival rate is bleak. Disseminated breast cancer cells invade bone and can remain undetectable and untreatable during a period of proliferative quiescence. Little is known about the bone niche during indolent breast cancer cell residence. To investigate this, we will use a dormancy model of metastasis-suppressed breast cancer cells in addition to novel mechanistic approaches in-vitro and in-vivo. We will specifically focus on understanding alterations in breast cancer cell-osteoblast signaling via exosomes, cellular microRNAs, and exosomal microRNAs. This project is innovative and likely to have high impact in understanding mechanisms promoting breast cancer dormancy.

Health Research Formula Grants – State Fiscal Year 2015-16

- Title: *Genetic Modification of the Relationship between Body Mass Index and Prostate Cancer*
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to determine which genetic factors modify the effects of obesity on advanced prostate cancer (PCa) and poor outcomes.

- Title: *Psychosocial Stress and Hepatic Inflammation in Patients with Chronic HBV Infection*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of the project is to explore the link between stress and liver inflammation in patients with chronic HBV infection.

- Title: *Genetic Evaluation of Men – the GEM study*
  Type of Research: Clinical
  Focus: Renal and Urological Sciences
  Purpose: Prostate cancer is one of the most heritable cancers, yet genetic testing has lagged behind other cancers due in part to lack of clinical genetic testing data. Necessary data include the spectrum of genetic alterations, carrier frequency estimates among tested individuals, and variant annotation for potential functional role in prostate cancer predisposition. The GEM study will implement clinical genetic counseling and genetic testing for prostate cancer patients and will uncover the germline variant spectrum and carrier frequency using multifaceted approaches. The results will inform a larger genetic testing study and eventual development national guideline for optimal genetic evaluation of this highly heritable cancer.

- Title: *Targeting Chemokine Receptors in Cancer Progression*
  Type of Research:
  Focus: Oncological Sciences
  Purpose: Skeletal metastases are detected in >90% of patients with advanced prostate cancer and current standards of care do not effectively treat this aspect of the disease. While the mechanisms that mediate skeletal metastasis have not been fully defined, several studies suggest that interfering with the chemokine receptor CXCR4 could be effective in both preventing and treating this process. This project will address whether CXCR4 is a viable target in treating prostate cancer. We propose to develop more effective drugs for inhibiting CXCR4 function in prostate cancer cells and evaluate these drugs in prostate cancer cell migration models.

- Title: *Novel Treatment for Ovarian Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Epithelial ovarian carcinoma (EOC) is a highly lethal cancer of women. EOC spreads early to the peritoneal cavity (PC), where it remains mostly confined at advanced stages. Because current treatments for EOC are mostly ineffective, it may be necessary to develop new approaches to conquer it. Our proposed research study will develop and test a new strategy for the effective management and potential cure of EOC in mice. If successful, this approach could lead to translational studies and potential new treatment strategies in humans.

- Title: *Roles of HuR and Innate Cells in Autoimmune Neuroinflammation*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this project is to investigate the function of RNA-binding protein HuR in

innate cells in autoimmune neuroinflammation and to identify novel therapeutic target for treatment of multiple sclerosis refractory to current approved interventions.

Treatment Research Institute ($187,047) – 1 Project

Research Projects:

- Title: *Developing an Intervention to Engage Treatment Court Participants in Preventive Healthcare*
  Type of Research: Clinical Research
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Given the increased susceptibility to a range of physical illnesses and low rates of non-emergency healthcare utilization among drug court clients, the development of brief and effective interventions to improve their utilization of preventive healthcare is critical. The current study seeks to test a brief health promotion intervention to help drug court clients connect to primary and preventive healthcare to facilitate the identification and treatment of medical conditions. Connecting this medically vulnerable population to preventive healthcare may have significant implications for both the individual (e.g., improved health, longer life) and society (e.g., reduced spread of infectious diseases; reduced healthcare costs).

The Trustees of the University of Pennsylvania ($8,086,121) – 8 Projects

Research Projects:

- Title: *Defining ATRi- and BPDE-Associated Breakpoints across the Human Genome*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Polycyclic aromatic hydrocarbons (PAHs) are the main cause of mutations from cigarette smoke. Although the mechanisms underlying PAH-driven point mutations as well as general aspects of their association with DNA have been documented, how and where PAHs cause double-strand breaks (DSBs) is poorly characterized. Herein, we hypothesize that PAHs generate DSBs through the persistent stalling of DNA replication forks at particular sequences, which in aggregate leads to a reliance on the ATR kinase to suppress fork collapse into DSBs. We will investigate the mechanism and sites of chromosome breakage from PAH exposure and examine how ATR inhibitors (ATRi) may be optimally applied to treat lung cancer in the clinic.

- Title: *Research Infrastructure: Psych-Bio Vivarium Space Renovation and Expansion*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is complete an upgrade and renovation of 5641 square feet of small animal vivarium space to standards appropriate for a 21st century laboratory supporting research in the biological and psychological sciences at the University of Pennsylvania, School of Arts and Sciences. This construction will reconfigure and expand the existing small animal vivarium facility in the Lynch Laboratory facility to allow the laboratory space to accommodate a new population of animals as we work to consolidate our Psychology Department into the new Life Sciences Quadrant.

- Title: *Health Behaviors and Smoking among Head and Neck Cancer Patients*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Head and neck cancers affect more than 59,000 Americans annually and are primarily mediated by health behaviors both in terms of etiology and long-term outcomes. Moreover, the population demographics are rapidly shifting due to human papillomavirus (HPV) infection, making it difficult to plan and target effective behavioral interventions for this rapidly changing

population. This project describes health behaviors, smoking, and their demographic and psychosocial predictors as a first step in developing appropriate interventions to improve health behaviors and, ultimately, outcomes among head and neck cancer survivors.

- Title: *Defining Rare Somatic Stem Cell Populations through Single Cell Analyses*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Stem cells hold great promise for tissue regeneration in a variety of organ systems. Tissue maintenance and regeneration in adult mammals is governed by multipotent, tissue-resident somatic stem cells. These cells are exceedingly rare, but extremely powerful, as they are capable of giving rise to all of the differentiated functional cell types comprising the respective tissues in which they reside. Despite their importance, the scarcity of somatic stem cells has hindered our ability to understand their molecular identity and the mechanisms governing their identity. Here, we propose bring together investigators based in the Institute of Regenerative Medicine to apply cutting-edge single cell profiling technologies to reveal these mechanisms with the ultimate goal of harnessing the power of somatic stem cells in order to promote tissue regeneration.

- Title: *Empowering Basic and Translational Research with Human iPSC-Derived Cells*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Advances in stem cell biology and technology have created unprecedented opportunities to rigorously mimic in vivo developmental processes using in vitro models. This project includes five investigator-initiated aims designed to address timely research challenges while empowering new inquiries relevant to the broad themes of cell differentiation and intercellular communication. This project has two overarching goals: 1) to understand and optimize iPSC and reprogramming differentiation pathways in 3 cell types (cardiac, endothelial, and hepatocyte), and 2) to lay foundational data and collaborative interactions that enable novel inquiries into the intercellular dynamics which contribute to developmental and disease processes in humans.

- Title: *EGFR Palmitoylation Regulates Receptor Activation*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The purpose of this project is to determine the mechanism and biological function of epidermal growth factor receptor (EGFR) regulation by protein palmitoylation. Inhibition of EGFR depalmitoylation with small molecules could have therapeutic potential for treating EGFR driven cancers.

- Title: *Impact of Tobacco on the Oral Microbiome and Cancer*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The use of tobacco has been shown for decades to be a strong contributor to the development of lung carcinomas. Additionally, tobacco use has also been linked to incidence of oral cancers and increased incidence of HPV-related cervical cancers as well as oral squamous cell cancers. Therefore, this makes tobacco use a major factor in development of human cancers. We will investigate the changes in the oral microbiome due to tobacco exposure and compare the tobacco smokers and non-smokers' oral microbiome and their incidence of oral squamous cell carcinomas. The changes in the microbiome will provide new information for development of potential early interventions strategies.

- Title: *Neurological Filtering of Sensory Signals Related to Need and Decision Making*
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: To better understand the emergence of appropriate appetitive decisions this research study proposes experiments that involve: mapping the circuitry of neurons sensing nutrient-need, identifying how factors that lead to abnormal feeding behavior alter the circuits responding to nutrient-need, and investigating how neurons sensing other survival needs interact with feeding circuitry. Integrating a molecular and cellular analysis of neural circuitry with behavioral assessment of neural function, this research will address, at a neural circuit level, how the brain filters sensory signals of need to effect behavioral decisions in a complex environment.

University of Pittsburgh-of the Commonwealth System of Higher Education ($8,086,121) – 5 Projects

Research Projects:

- Title: *Research Infrastructure: 11.7T Installation in the McGowan Institute*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to renovate space in the McGowan Institute Building on the University of Pittsburgh campus to install a Bruker AVANCE III HD 11.7 Tesla 89-mm microimaging MRI scanner.

- Title: *Establishment of a Nonhuman Primate Model of Ataxia Telangiectasia*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The goal of this project is to generate a nonhuman primate model of ataxia telangiectasia (A-T) by knocking out a gene called ATM. In children, the absence of ATM results in progressive cerebellar degeneration and profound motor difficulties. A mouse knockout of ATM exists but does not display the motor disorders characteristic of the debilitating disorder and, therefore, is an inappropriate model for testing new therapies for children. We have chosen marmosets as our nonhuman primate model because of their small size and ability to reproduce quickly. After we create the knockout, we will characterize, monitor, and maintain this unique resource.

- Title: *Population-Based Study of Lung Cancer Screening*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Lung cancer is the leading cause of cancer death in the U.S. and in Pennsylvania. The Pittsburgh Lung Cancer Screening Study (PLuSS) was initiated in 2002 to examine whether low-dose computed tomography (CT) could improve lung cancer detection. Subsequent work in the national lung cancer screening study demonstrated a 20 percent reduction in lung cancer deaths through the use of CT screening. This finding has since been adopted as a standard of care to reduce lung cancer deaths. This project seeks to expand the PLuSS cohort further, and to use the collected specimens to determine whether ultrasensitive methods for detection of cancer-specific DNA methylation in plasma and sputum can improve the early detection of lung cancer.

- Title: *Role of Mitotic Translation Regulation in Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Cancer cell survival is highly dependent on active synthesis of new proteins required for cell division. mTOR signaling is known to regulate protein synthesis, and several new classes of

chemotherapeutic mTOR inhibitors act by preventing cancer cell protein synthesis. We recently found a new, mTOR-independent pathway that cancer cells use to regulate protein synthesis during cell mitosis, involving cyclin dependent kinase 1 (CDK1). This project will investigate the role of CDK1 inactivation of eukaryotic initiation factor 4E-binding protein (4E-BP1) in cancer cell growth. Mitotic 4E-BP1 phosphorylation may be an important biomarker for cancer aggressiveness and resistance to chemotherapy.

- Title: *Genome-Wide Detection of Pathological Gene Fusions in Clinically Intractable Breast Cancers*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Recurrent gene fusions in breast cancer have been poorly studied due to the limitations of genomics and bioinformatics techniques. We have developed innovative bioinformatics techniques integrating several different data types to reveal recurrent pathological gene fusions, and preliminary results indicate that they may be more frequent and more significant in breast tumorigenesis than previously thought. In this project, we will discover recurrent gene fusions in clinically intractable breast cancers based on large-scale analysis of transcriptomic and genomic sequencing data sets from The Cancer Genome Atlas (TCGA) to reveal robust new drug targets and establish new biomarkers for effective, individualized treatment.

University of the Sciences in Philadelphia ($13,009) – 1 Project

Research Projects:

- Title: *Investigating Anti-Cancer Compounds Selectively Cytotoxic Against Triple Negative Breast Cancer Cells*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The data from this study will establish novel anti-cancer compound(s) that can complement existing therapy regimens for Triple Negative Breast Cancer (TNBC). Current therapies for TNBC are associated with poor prognosis and toxic side effects. The compounds discovered from this research study will complement the current drugs for TNBC treatment and will assist in reducing toxic side effects on normal breast cells.

The Wistar Institute of Anatomy and Biology ($1,721,478) – 3 Projects

Research Projects:

- Title: *Epigenetics of Ovarian Clear Cell Carcinoma*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: This project will investigate the molecular basis of ovarian carcinogenesis by defining the mechanistic role of ARID1A and the SWI-SNF complex in ovarian epithelial cells. ARID1A, a SWI-SNF component, is the most mutated protein in Clear Cell and Endometrioid Ovarian Carcinomas, however it is unknown how loss of ARID1A leads to impaired SWI-SNF activity and ultimately to cell transformation. This project will recapitulate the early molecular events that follow loss of ARID1A in epithelial cells and pinpoint the critical genes and regulatory elements implicated in tumorigenesis.

- Title: *ATRX-RNA Interactions in Gene Regulation: Significance to Glioblastoma Cancers*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: ATRX is a chromatin remodeling factor that regulates non-coding RNAs (ncRNA) association to transcriptional repressors such as the Polycomb Repressive Complex 2 (PRC2).

ATRX is frequently mutated in many cancer types with a high prevalence of mutations occurring in glioblastomas. Understanding ATRX function and the consequence of its loss to ncRNA pathways in a neuronal model system is therefore critical to identify causes of glioblastoma development and will help identify new diagnostic markers and therapeutic targets in this deadly cancer.

- Title: *Investigating the Role of FOXO1 in Limiting T Cell Function*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this project is to further investigate the role of FOXO1 in limiting T cells responses. Others and I have found that FOXO1 is required for proper differentiation and function of T regulatory cells, but limits differentiation of T follicular helper cells and CD8 memory cells. In this project we will investigate the role of FOXO1 in regulating T cell function post differentiation and in regulating T cell dysfunction that occurs in T cells responding to chronic stimulation. Thus, this research will help us to design effective strategies to target FOXO1 to modulate immune responses for new treatments