Health Research Formula Grants – State Fiscal Year 2016-17

Twenty-eight organizations received health research formula grants totaling $30,364,000 for the state fiscal year 2016-17. Grants may support one or more research projects and research infrastructure projects. The grants started on 1/1/2017 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 ($68,832) – 2 Projects

Research Projects:

- Title: *Priming Brain Stimulation with Aerobic Exercise: Physiological and Behavioral Effects*
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: Recovery of arm function after stroke involves re-learning of activities of daily living with the weaker hand. This relearning is achieved through repetitive task practice during therapy that leads to brain changes (i.e. neuroplasticity) imperative for recovery. Applying weak electric currents to specific brain regions using noninvasive transcranial direct current stimulation (tDCS) during practice improves motor skill learning, although the magnitude of these benefits has been relatively small and clinically nonsignificant. Recent exciting evidence suggests that aerobic exercise which challenges the cardiorespiratory system also promotes brain plasticity by increasing vasculature, augmenting neurotropic factors and neurotransmitter mechanisms. In this preliminary study, we will determine if high-intensity aerobic exercise (AE) administered prior to anodal tDCS over motor cortex (M1) augments the upregulating effects of anodal tDCS on motor cortical excitability and motor performance in 20 patients with chronic stroke.

- Title: *Personalizing care with Patient Reported Outcomes Assessment in Routine Hepatology Practice*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: In this project, we will integrate measurement of Patient Reported Outcomes (PRO) as an intervention for patients with liver disease due to any cause. The results of PROs will be shared with providers and patients right before the office visit, and the clinical effectiveness will be assessed through provider and patient surveys, and changes in quality of life. The surveys will assess any changes in patient management, and patient directed discussion on symptoms and issues that matter to them. Quality of life will be assessed using Chronic Liver Disease Questionnaire at baseline, 3 and 6 months.

Allegheny Singer Research Institute ($50,522) – 1 Project

Research Projects:

- Title: *In Vivo Characterization of Novel Opioid Receptor Agonists with Potential for Limited Abuse*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The opioid abuse crisis has gripped many counties and cities in the

Commonwealth of Pennsylvania. Diversion and abuse of prescription drugs is a major challenge. Databases that track prescription drug use and prescriptions can help prevent opioid diversion, but they do not address the fundamental challenge of the ability of prescription opioids to induce euphoria and cause addiction. The Neuroscience Disruptive Research Lab has been creating novel opioids that can prevent the sensation of pain but are predicted to not penetrate the blood brain barrier, thereby treating pain without the risk of addiction. The purpose of this project is to study the *in vivo* antinociceptive behavior of the novel opioids as well as the pharmacokinetics and blood brain barrier permeability.

American College of Radiology ($391,618) – 1 Project

Research Projects:

- Title: *Optimizing Cancer Diagnosis and Treatment through Predictive Models with Radiomics Biomarkers*
  Type of Research: Health Services
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: This project will leverage the extensive clinical trial datasets from the legacy Radiation Therapy Oncology Group (RTOG) and the American College of Radiology Imaging Network (ACRIN) to develop radiomics biomarkers from multi-modality image data and to establish predictive models incorporating the radiomics biomarkers. The American College of Radiology's (ACR's) Data Archive and Research Toolkit (DART) will be used as the research platform for data analysis. If successful, the creation of predictive, clinically useful, validated models can be used to customize and optimize cancer diagnosis and treatment for individualized precision medicine.

Carnegie Mellon University ($517,991) – 2 Projects

Research Projects:

- Title: *Predicting Short Time Scale Neural Reorganization During Learning*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Motor control is one of the most important tasks the brain performs, and disorders of motor control affect millions of people. Although a wealth of psychophysical studies has led to good descriptions of the phenomenological processes underlying motor control and motor learning, the neural implementations of these processes are not well understood. One problem is that motor control is inherently a neural population phenomenon: movements are generated by groups of neurons that must work in a coordinated fashion to produce precisely timed muscle activation patterns. Using brain-computer interfaces, we will study how the structure of neural population activity reorganizes during short-term learning.

- Title: *Binding Studies of Huntington's Disease Gene Modulators by Nuclear Magnetic Resonance*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The overall goal of this research project is to use nuclear magnetic resonance to demonstrate the viability of a programmable molecular platform for targeting r(CAG)-

repeat expansions, in an attempt to develop therapeutic invention for Huntington's disease. The approach is general and, if successfully developed, could be applied to the treatment of a number of other neurodegenerative diseases including myotonic dystrophy, fragile X syndrome, Friedreich's ataxia, spinocerebellar ataxia, and possibly amyotrophic lateral sclerosis (ALS).

The Children's Hospital of Philadelphia ($4,632,839) – 1 Project

Research Projects:

- Title: *Frontiers in Leukodystrophy Initiative (FrontLINe)*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: This approach is meant to demonstrate a pathway for translational research in the leukodystrophies at the Children's Hospital of Philadelphia. Leukodystrophies are heritable disorders of the central nervous system white matter most often affecting children. This underserved patient population, with high morbidity and mortality, will benefit from both innovative bench research on disease mechanisms and biomarkers, as well as improved diagnostics and standards of care. Together these approaches are expected to yield a shift in clinical care in leukodystrophies based on evidence, more specifically Alexander disease, Aicardi Goutieres Syndrome and Hypomyelination with Atrophy of the Basal Ganglia. This program is expected to serve as a model for future advances in additional leukodystrophies.

Drexel University ($1,027,656) – 11 Projects

Research Projects:

- Title: *Advancement of First-in-Class Macrocyclic HIV-1 Inactivators for Therapeutics and Cure*
  Type of Research: Biomedical
  Focus: AIDS and Related Research
  Purpose: Macrocyclic peptide triazoles (cPTs) are easily accessible and highly potent HIV-1 inactivators. We have shown their effectiveness against fully infectious as well as laboratory-adapted pseudoviral HIV-1 forms using different cell lines. In this project, we will evaluate our cPTs against primary infected T cells as well as human-derived infected cells. This project will also investigate the potential of using a combination of cPT and a latent reversing agent (LRA) to work synergistically *in vitro*, on latent cell models, as a "shock & kill" small molecule combination. Data generated form these studies will advance and facilitate the developments of cPT as potential curative agents for HIV-1.

- Title: *Mechanisms of Olfactory Hypersensitivity in Fragile X Syndrome*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: In this project, we will investigate the mechanistic basis for olfactory hypersensitivity in the autism-related disorder Fragile X syndrome. This sensory hypersensitivity impacts social behavior and leads to poor diets and overall worse health. Our goal is to understand this hypersensitivity, how it relates to the normal function of the olfactory system, and how treatments may normalize these responses. The findings from this and follow-up studies may suggest therapeutic targets to ameliorate olfactory

symptoms in patients with Fragile X syndrome and, potentially, other autism-related disorders.

- Title: *Chronic Pain and Cardiovascular Disease*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: The purpose of this research is to examine the relationship between chronic neuropathic pain and the development of cardiac disease. Using rodent models of chronic neuropathic pain and the analytical *in vivo* methods of cardiovascular and hemodynamic assessment, this project will expand on preliminary results suggesting that chronic pain neuropathic has a profound impact on and compromises the cardiovascular system. We will investigate these relationships in detail to determine whether these effects are gender related and whether the development of cardiomyopathies can be prevented by pharmacological treatments that attenuate the development of pain.

- Title: *How Bacteria Utilize Environmental Fatty Acids*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Bacteria require fatty acids for their membranes, co-factors, quorum sensing molecules, and natural products. Most bacteria can biosynthesize fatty acids de novo from acetate units using the fatty acid synthase, but some can efficiently take up fatty acids from their environment. We identified and characterized an enzyme that is essential to this process and allows bacteria to circumvent anti-bacterials targeting fatty acid biosynthesis. We will further characterize fatty acid utilization pathways using classical microbiology and mass spectrometry techniques. An understanding of these processes in bacteria is of broad interest, especially in the context of antibacterial development and metabolism- and microbiome-associated diseases.

- Title: *A Novel in vitro 3D Liver Sinusoid Model for Hepatitis B Virus Studies*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The studies in this project are designed to advance a dual-chamber microchannel liver sinusoid model for the study of human liver disease. The device will be configured so that hepatocytes and non-parenchymal liver cells can be cultured in a layered format that mimics the architecture of a human liver sinusoid and allows long-term culture of these cells, which is not possible in other model systems. We will demonstrate the utility of this model system in testing potentially curative treatments for chronic hepatitis B virus (HBV) infection, which will require eradication of cccDNA, a stable HBV replication intermediate that is not targeted by current HBV therapies.

- Title: *Novel Compositions for Treating or Preventing Age-Related Dermal and Epidermal Disorder*s
  Type of Research: Clinical
  Focus: Biology of Development and Aging
  Purpose: The purpose of this research study is to determine the efficacy of a topical application of rapamycin for dermal atrophy and seborrheic keratoses. We have

developed a proprietary composition for the topical delivery of this compound and evaluating its efficacy will allow us to explore its utility in the prevention and treatment of age-related conditions, such as dermal cutaneous atrophy with resultant decubitus ulcers in the geriatric population, and cosmetic changes, such as fine rhytides and seborrheic keratoses.

- Title: *Analytics on Real-Time Biometrics from Passive Wearable Smart-Garments*
  Type of Research: Clinical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Typically, Radio Frequency Identification (RFID) data is used for inventory management purposes, but passive RFID interrogation data can be mined as time-series data with biomedical inferences drawn from relative changes in signal strength of the interrogation. It is difficult to extract biomedical meaning from this noisy RF data because it is infeasible to train machine learning algorithms on anomaly class data (i.e., non-breathing), and because the data consists of RF attributes, rather than biomedical signals. This project addresses each of these challenges via the creation of a real-time signal processor and data fusion framework for use in clinical experimentation, to monitor infant respiration, maternal uterine activity, and extremities movement for Deep Vein Thrombosis (DVT) alerting.

- Title: *Effects of GSK-3β on the Prefrontal Dopamine System*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The project aims to determine a cell type-specific role of glycogen synthase kinase-3β (GSK-3β) in dopamine signaling pathway in the prefrontal cortex (PFC) at cellular and molecular levels by using a new conditional knockout mouse model. This study will reveal where (on D2 receptor-expressing neurons) and how (through genetic modification) GSK-3β regulates NMDA receptor-associated synaptic and cognitive functions. The results generated from this project may reveal new targets for treatment of dopamine-related diseases.

- Title: *O-GlcNAc Regulation of Acetate Metabolism in Glioblastoma*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: This study will further our understanding of how the metabolism is reprogrammed in cancer cells to further drive cell growth and survival and to elucidate the connection between nutrient sensor O-GlcNAc transferase (OGT) and acetate metabolism in lipid-dependent cancers such as glioblastomas. It will also establish for the first time OGT as potential therapeutic target for treating glioblastomas. In addition, this project brings together unique expertise at Drexel to uncover the molecular mechanism by which OGT regulates acetate metabolism via regulation of enzyme ACSS2 in brain tumors.

- Title: *The Mechanisms of Visual and Decision Processes in Cancer Histopathology Interpretation*
  Type of Research: Biomedical
  Focus: Oncological Sciences

Purpose: Cancer image interpretation from whole slide imaging of histologic tissue has ushered in a new era of diagnostic potential that prominently features computer-aided diagnostics (CAD). Using advanced image processing and machine learning, CAD promises to improve cancer detection and diagnosis. Despite these advances, it remains unclear whether the improvements in diagnostic accuracy promised by CAD are realized and in what ways CAD can best supplement the natural limitations of the human brain. We propose a series of experiments to reveal how pathologists view whole slide images in order to better understand these limitations, and ultimately to guide CAD development and to model its impact on diagnostic accuracy.

- Title: *Local Delivery of Minocycline and Glypican to Promote Protection and Repair after Spinal Cord Injury*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this study is to develop an effective and clinically-applicable approach to promote both protection and repair after traumatic spinal cord injury (SCI) by co-delivery of minocycline (a potent anti-inflammatory and neuroprotective drug for protection) and glypican (for repair). Sprouted/regenerated fibers often do not form functional synapses that lead to functional recovery. Glypican has been shown to promote functional, excitatory (likely positively impacting recovery) synapse formation *in vitro* and enhance neurite outgrowth and functional recovery after brain injury. This study will for the first-time test whether exogenous glypican will enhance the ability of axons to regenerate and/or form synapses after SCI to improve behavioral recovery.

Duquesne University of the Holy Spirit ($129,002) – 2 Projects

Research Projects:

- Title: *Investigation of the Molecular Basis of Neuroinflammatory Pain Associated with Cancer and Cancer Therapy*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Pain associated with cancer emerges from a complex inflammatory dialog between nerves, supporting glia cells and immune cells. Nanoparticles (droplets less than 200nm in size), appropriately designed to carry specific dyes, can label immune cells that can then be visualized in live animals to reveal neuroinflammation associated with pain, while also providing pain relief. Remarkably, the dose of drug needed to provide pain relief in this way is thousands-of-fold less than what would be needed to provide equivalent relief by conventional oral drug delivery. Here, we propose to initiate a novel exploration using this targeted drug delivery platform to more deeply assess the molecular basis of neuroinflammatory chronic pain. We will also explore the affect that the targeted delivery of ultra-low-dose drug has on the molecular dialog of inflammation.

- Title: *Site-directed Delivery of Ticagrelor as Anti-Platelet Therapy in Vascular Environment*
  Type of Research: Biomedical
  Focus: Cardiovascular Sciences
  Purpose: Ticagrelor is a common anti-platelet therapy recommended by the American

College of Cardiologists for up to 12 months' post-implantation of both bare metal and drug-eluting stents. Here, stent materials used for coronary artery implantation will be chemically modified with small molecule linkers to present Ticagrelor on the surface of the stent for direct delivery to the area of concern to decrease or eliminate systemic drug delivery. These modified stents differ from current drug eluting stents which target endothelization.

Franklin and Marshall College ($10,803) – 1 Project

- Title: *The Role of Maternal Exercise in Drug Abuse Susceptibility*
  Type of Research: Biomedical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project plans to shed light on a cost-effective measure that may help reduce drug abuse among humans. Simply, mothers that exercise during gestation may be able to confer protection against the reinforcing effects of illicit drugs to their offspring. The prenatal development represents a critical period in the embryo that is greatly influenced by the same environmental events at the mother. Consequently, if a mother is regularly exercising, the fetus is effectively "exercising" and is developing in a manner consistent with those healthy activities. This project will test this hypothesis in rats. Women, generally, believe exercise can be harmful to the fetus, but in reality, they may be lowering their child's drug addiction risk in a healthy way.

Geisinger Clinic ($140,437) – 1 Project

Research Projects:

- Title: *Clinical Phenotypes Associated with CFTR Carriers*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Individuals with cystic fibrosis (CF), which is caused by carrying two copies of abnormal cystic fibrosis transporter conductance regulator (*CFTR*) gene, classically develop chronic lung, sinus, and pancreatic disease and are also recognized to have increased risk of gastrointestinal malignancy. In contrast, it is unknown if heterozygote carriers of one *CFTR* mutation, which occurs in 4-5 percent of the population, share similar health risks. This project will use genetic resources of the Geisinger MyCode program, coupled with rich clinical data, to examine whether *CFTR* heterozygotes share similar risks of the clinical disorders seen in CF, including malignancy and chronic lung and sinus disease.

Hepatitis B Foundation ($209) – 1 Project

Research Projects:

- Title: *Processes for Developing A Community-Based Coalition for Addressing Hepatitis B Among Asian American Communities in Philadelphia*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project assesses and documents the processes and strategies for developing an effective community-based coalition to address the health disparities associated with hepatitis B infection among Asian Americans in Southeastern PA. Study results could

significantly impact future interventions to improve hepatitis B screening and linkage to care rates in these highly impacted, hard to reach communities.

The Institute for Cancer Research ($1,179,993) – 4 Projects

Research Projects:

- Title: *Maintenance of Genomic and Epigenomic Stability at CpG Sites*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The purpose of this project is to understand how the base excision repair enzyme Thymine DNA Glycosylase (TDG) not only protects cytosine-phosphate-guanine (CpG) sequences from transition mutations and wards off endogenous deamination events, but also mediates DNA demethylation and transcriptional activation. This dual role in genomic and epigenomic stability of CpG sites is likely to be important for cancer formation, given the frequent occurrence of CpG to cytosine-phosphate-adenine (CpA) or thymine-phosphate-guanine (TpG) point mutations and hypermethylation of tumor suppressor genes in cancer. We will study the role of TDG in two contexts, genomic imprinting, and normal and leukemic hematopoiesis. Knowledge accumulated in this project may lead to novel strategies for cancer prevention.

- Title: *Impact of Electronic Cigarette Vapor on Risk for Lung Cancer*
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: A dramatic increase in the use of electronic cigarettes (e-cigs), particularly among youth, has raised significant concern regarding their safety. Use of e-cigs by smokers in areas where smoking is prohibited has led to dual use of e-cigs and conventional cigarettes. While the adverse properties of nicotine are documented, inhalation of heated nicotine is unprecedented and its health risks unknown. Furthermore, the stabilizers in e-cigs have carcinogenic properties and can cause throat irritation. The proposed studies investigate the effect of e-cig vapor on young naïve mice (mimics youth who never smoked) and mice at increased risk for lung cancer due to lung mutations induced by tobacco smoke (mimics former/current cigarette smokers). The results will aid in determining the risks associated with e-cig use and inform the development of federal policies to guide e-cig use.

- Title: *Evaluating AMH as a Modifier for Lung Cancer Therapeutic Response*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Approximately 16 percent of all cancer deaths are due to lung cancer, with the five-year survival rate at only ~16 percent. This reflects the failure of current therapies to control advanced disease. In preliminary studies, we identified elevated expression of Anti-Mullerian Hormone (AMH) in a significant subset of non-small cell lung cancer (NSCLC) cell lines as a regulator of response to targeted and cytotoxic chemotherapies. AMH is a member of the transforming growth receptor beta (TGF□) superfamily, known to regulate therapeutic response; autocrine AMH signaling has never previously been demonstrated in any tissue outside of the gonad. Given the recent development of clinical

grade reagents targeting AMH and its receptor AMHR2, our purpose is to evaluate the potential for therapeutic targeting of AMHR2 as a way to improve clinical treatment of NSCLC.

- Title: *Dysregulation of Mitosis in the Transformation of Neural Progenitor Cells into Glioblastomas*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Glioblastoma (GBM) is a highly aggressive, heterogeneous disease. Despite this multifaceted approach patients usually relapse; median survival is approximately 14 months. A confounding issue is the existence of a sub-population of tumor-initiating cells (TICs) or 'cancer stem cells' that are inherently resistant to conventional chemotherapy and radiation. Although aneuploidy is a common feature of GBMs, whether they arise from TICs that exhibit chromosome instability (CIN) has not been investigated. The proposed project will use multiple and complementary approaches to test whether CIN in neural progenitor cells can drive the formation of GBM. Understanding the origin of GBM will provide opportunities for early detection as well as developing treatment strategies and recurrence prevention.

Lankenau Institute for Medical Research ($95,725) – 1 Project

Research Projects:

- Title: *Blood-based Assay as Predictor of Chemotherapy-induced Nausea*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Chemotherapy, though medically necessary to treat many forms of cancers also cause side effects such as chemotherapy-induced nausea and vomiting (CINV) the side effect most feared by patients. Lacking markers of nausea creates uncertainties regarding what anti-emetic to prescribe and to whom. Traditionally, clinicians rely on subjective patient characteristics such as gender and age producing approximately 50 percent accuracy. We have developed a blood-based assay we believe can predict who will suffer from delayed nausea, the most unpredictable form of nausea. In a preliminary study, we have demonstrated that we can identify older men who will experience nausea and younger women who will manage with minimal intervention. Preventing nausea will improve the general health of patients and motivate them to complete their life-saving therapy.

Lehigh University ($102,934) – 3 Projects

Research Projects:

- Title: *Outcomes of an Opioid Treatment Program that Includes a Time Banking Exchange Component*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to evaluate an innovative opioid use disorder treatment program that is being administered by a local federally qualified health center. This program employs medication assisted therapy (e.g., Suboxone) and community-

based care. In addition, patients are invited to join a "time bank" – a community-based platform for exchanging services that is designed to empower members and increase social integration. Our assessment will include patient evaluations of the program, indicators of patient empowerment, quality of life, health behaviors, and social integration. We plan to assess these indicators longitudinally over a 12-month period, and we will test whether these outcomes are influenced by the quantity and quality of participants' engagement with the treatment program and time bank.

- Title: *3D-Printed Scaffolds to Guide Osteochondral Interface Tissue Formation*
  Type of Research: Health Services
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: Osteoarthritis is a degenerative joint disease characterized by the loss of lubricating cartilage at the ends of the bones. Osteoarthritis affects 70% of adults over age 65 and nearly 3 million Pennsylvanians, for an age-adjusted prevalence rate of 25.7%, which is the 12th highest rate in the nation. As the disease progresses, patients may experience debilitating pain and seek relief through total joint replacement, which is a costly burden on the health system. Currently, no interventions have been proven to truly regenerate cartilage and obviate the need for joint replacement. The purpose of this project is to apply 3D printing technology to fabricate biodegradable polymer scaffolds that can be adapted to promote cellular activity that may lead to cartilage regeneration and restoration of joint health, thereby enabling more pain-free years of active independent mobility.

- Title: *Assessment of the Implementation of the Center of Excellence for Opiate Use Disorders*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose is to understand the factors that influence the successful implementation of a community care model for opioid addiction treatment.

Magee-Womens Research Institute and Foundation ($996,679) – 7 Projects

Research Projects:

- Title: *Social Networks to Lessen Drug Use and High-Risk Behavior in Pregnant Women with Opioid Use Disorder*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this research is to a) identify the types, functions, and structural characteristics of the social networks of pregnant women with opioid use disorder, b) describe their influence on drug use and high-risk behavior and c) explore changes in the function and characteristics of network members over time. An evaluation of social network influences on health behavior is necessary to design interventions that not only provide immediate benefit to the individual, but that are resilient to social undermining and last beyond the period of healthcare engagement. Moreover, pregnancy may also represent a critical period of engagement with social network members linked to the subject (e.g., partner, family, friends) who also may be receptive to health behavior change due to increased focus on improving maternal and infant outcomes.

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- Title: *Lactate Metabolism in Placental Development and Injury*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Lactate has traditionally been considered a dead-end waste product of glucose metabolism in conditions of limited oxygen, including life at high altitudes, enhanced physical activity, or interruption in tissue blood flow. However, recent findings implicate lactate as both an important signaling molecule that regulates the response to hypoxia and as an alternate energy source in extreme physical conditions. Our own published and preliminary findings implicate lactate metabolism in development and hypoxic stress of the placenta. Building on these findings, the purpose of this project is to advance scientific knowledge of placental lactate metabolism and its roles during normal and complicated pregnancies.

- Title: *Oncogenic Pathways and Tumor Inflammation in Ovarian Cancer*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Ovarian cancer represents the most aggressive type of gynecologic malignancy. Current therapy combines surgery and a platinum/taxane drug combination. Despite an initially favorable response to chemotherapy, the tumor invariably recurs. The overall 5-year survival rate remains low (at 44%) and has not improved in more than 3 decades. New developments in immunotherapy, especially with immune checkpoint blockers, demonstrate significant clinical responses in small patient subsets. To increase efficacy, new combination therapies are needed. We test here the hypothesis that tumor-driving pathways modulate anti-tumor immunity and that the *in vivo* efficacy of immune therapy can be increased through combination regimens tailored to the cancer cell molecular framework. This project has the potential to advance our ability to treat ovarian cancer.

- Title: *Preservation of Female Fertility in Cancer Chemotherapy through Safeguarding Oocyte Centrosomes*
  Type of Research:
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Dramatic advances in cancer therapies now provide many girls and women long, largely healthy lives. This project targets an aspect of cancer treatment of importance to these female cancer survivors -- the opportunity to have children biologically their own by avoiding damage to their ovaries and oocytes during chemotherapy. Specifically, this project will investigate hitherto unexplored intracellular targets of the chemotherapeutic drug cisplatin and its fertoprotective agent, imatinib, in ovarian oocytes, using a mouse model. Knowledge in this area has the potential to improve cancer treatment while preserving girls' and women's long-term fertility so that they may enjoy long and full lives.

- Title: *Perinatal Marijuana Use, Tobacco Co-Use, Pregnancy Outcomes, and Use of Social Services*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes

Purpose: Perinatal marijuana has been associated with various negative outcomes, including stillbirth, preterm delivery, and neurocognitive deficits. However, many of these early studies have been criticized for methodological concerns, such as reliance on participants' self-report of perinatal marijuana use; limited assessment of type, frequency, and amount of marijuana use; and no assessment of the impact of co-occurring use of tobacco. The proposed project will address these research gaps by using our existing data to (1) assess perinatal marijuana use by examining the concentration of marijuana metabolites; (2) explore co-use of perinatal marijuana and tobacco; (3) examine how co-use impacts pregnancy outcomes; and (4) assess post-pregnancy child protective services or early intervention service utilization among pregnant women who use marijuana.

- Title: *Optimization of CRISPR/Cas9-Mediated Homologous Recombination for Generation of Transgenic Animals*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: The CRISPR/Cas9 system is a powerful new tool for gene editing in mammalian cells. However, it is much easier to mutate and inactivate genes using this technology than it is to introduce precise genetic modifications or large insertions because target cells tend to repair Cas9-induced double strand breaks, using error-prone non-homologous end joining (NHEJ) rather than the more precise homologous recombination pathway. This project will optimize CRISPR/Cas9 methods for precision gene editing by iterative testing of the single guide RNAs (sgRNAs) that guide the Cas9 nuclease (one sgRNA versus two), the donor DNA template (single stranded versus double stranded), and NHEJ inhibitors (Scr7 and Nu7441). As a model system, we will insert the *mCherry* reporter into the *Gfra1* locus in mouse embryos to produce *Gfra1-mCherry* reporter

- Title: *Identification of lncRNA Signatures During the Differentiation of Trophoblasts*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: In this project, we will examine the expression of long non-coding RNAs (lncRNAs) during the differentiation of primary human trophoblasts. More specifically, we will analyze RNA-seq data to explore the relations between trophoblast differentiation and the expression of protein-coding RNAs (mRNAs) and determine the regulatory relations between lncRNAs and mRNAs. In a second phase, we will undertake the functional characterization of a selection of lncRNAs. The results from this study will enhance our understanding of the molecular mechanisms during placental development and suggest new avenues of research to improve the diagnosis and treatment of placental insufficiency.

Monell Chemical Senses Center ($160,043) – 1 Project

Research Projects:

- Title: *Disease Related Olfactory Signals and Their Molecular Mechanisms*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The purpose of this study is to identify the extracellular, intracellular, and

metabolic signals that are involved in the production of disease-related volatiles. It is currently known that mammals have different volatile profiles during inflammation, infection, and illness. However, it is unknown how these volatile profiles arise or how much specific health information they contain. By understanding the molecular mechanisms involved, the analysis of volatile profiles can be better used as a low-cost medical diagnostic tool.

Penn State University ($4,636,240) – 20 Projects

Research Projects:

- Title: *Lysine-specific Demethylase 1 as Therapeutic Target for Retina Degeneration*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The goal of this project is to develop the use of epigenetic modifiers to treat an array of neurodegenerative diseases. Specifically, we will determine the effect of the histone demethylase inhibitor tranylcypromine (TCP) on retina degeneration in Rd1 and Rd10 mouse models by physiological and histological analysis of the retina and by analysis of gene expression in retina after TCP treatment. We will also identify retinitis pigmentosa patients, collecting baseline vision loss data and testing measures of progressive loss, in preparation for clinical studies of TCP. The studies in this project will provide both proof of principle and a protocol to begin testing one such treatment in an important blinding disease.

- Title: *Gender Bias in Lupus; Role of the Inactive X Chromosome*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder that affects >1.5 million people in the US, 90% of whom are female. Despite treatment advances, mortality remains high, at least in part because underlying mechanisms are not fully understood. X-linked genes are clearly implicated in SLE etiology. This project seeks to test the novel hypothesis that gender bias in lupus is in part caused higher expression of X-linked genes in females due to their inability to be silenced by X chromosome inactivation. To test this hypothesis, we will evaluate inactive X gene expression and epigenetic landscape in SLE patient cells and determine whether small molecule inhibitors of epigenetic modifiers modulate inactive X gene expression in SLE cells.

- Title: *Role of SP-R210 (Myosin 18A/CD245) in Influenza A Virus Infection and Epigenome Modification of Human Alveolar Macrophages*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: Pathogenic influenza A virus (IAV) strains that arise frequently cause exuberant inflammation and lung injury with high morbidity and mortality. We have uncovered a new IAV-macrophage interaction that exaggerates inflammation in mice. We found that IAV infection through SP-R210 receptor isoforms alters expression of the pioneer transcription factor PU.1 which can impact histone modification and PU.1 chromatin occupancy disrupting the balance of pro- and anti-inflammatory responses. We will

validate our findings in human lung macrophages to develop therapeutic interventions that alleviate development of influenza induced lung injury by harnessing epigenetic responses to infection in lung macrophages.

- Title: *Development and Testing of an Enhanced Decision Aid for Patients Who Present to the Emergency Department with Chest Pain*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The objective of this project is to develop and test an enhanced decision aid (one that provides information on patient's risk status and test characteristics) for emergency department (ED) patients with chest pain but no objective evidence of ischemia (lack of blood flow to the heart). We will test the decision aid product against usual care in ED patients with low-risk chest pain. The study will take place over a 12-month period. The primary endpoints will be compared between the decision aid and usual care groups and include: 1) the percentage of individuals in each group who undergo stress testing in the subsequent 30 days, 2) length of stay during the ED visit, 3) knowledge about risks/benefits/alternatives to stress testing, and 3) decisional conflict.

- Title: *Measurement of Autonomic Nervous System Function to Predict Excessive Alcohol Intake and Weight Regain after Bariatric Surgery*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this translational pilot study is to understand neuro-biological mechanisms of binge eating and binge drinking and to identify preoperatively factors which are associated with an increased risk of alcohol use following Roux-en-Y Gastric Bypass (RYGB), the most common weight-loss surgery. An improved understanding of the biology of binge behaviors (compulsive reward-seeking) will provide potential targets for intervention in the general population and also improve patient outcomes in the large population of RYGB patients.

- Title: *The Role of Parental Emotion Regulation in Parent-Child Conflicts*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Current Attention Deficit Hyperactivity Disorder (ADHD) treatments reduce symptoms but do little to improve long-term functioning. Improving the long-term functioning of ADHD youth has proved to be a sizable challenge. Recent work has found that negative parenting behaviors (NPB), such as criticism and yelling, predict the persistence of behavior problems in children. We theorize that parental emotion regulation capacity (ER) moderates the connection between a child's behavior and NPB with stressed parents with impaired ER being more likely to engage in NPB. We will test this association using objective ER measures and examine if parental ER predicts response to behavioral parent training, with the aim of developing new therapies to improve the long-term course of ADHD.

Health Research Formula Grants – State Fiscal Year 2016-17

- Title: *Effect of CD4+ T-cell Exosomes on Airway Epithelial Inflammation in Asthma*
  Type of Research: Biomedical
  Focus: Respiratory Sciences
  Purpose: Asthma is an inflammatory disease that involves communication between airway epithelial cells and immune cells. This project will determine whether particles (exosomes) secreted from T-cells carry genetic material (microRNAs) that can be taken up by airway epithelial cells to promote an inflammatory response. We will demonstrate that this exchange occurs in tissue culture as well as *in vivo* using mouse studies. In addition, we will identify the cellular and functional changes that occur in exosome-treated airway cells.

- Title: *Mind-Body Strategies to Increase Physical Activity in Rural Breast Cancer Survivors*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to elicit barriers to and preferences for a yoga-based mind-body physical activity program targeted to rural breast cancer survivors living within the Penn State Cancer Institute catchment area. Qualitative methods will be used to inform the cultural-adaptation of a mind-body physical activity intervention. A community partnership will be formed and used to establish the feasibility of recruiting rural breast cancer survivors within the Penn State Cancer Institute catchment area to participate in the intervention.

- Title: *Topical Naltrexone Treatment for Diabetic Dry Eye*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: This project involves the study of a novel treatment for chronic dry eye syndrome (DES), a common complication of diabetes. Funding will support animal testing of efficacy and safety of the new formulations. Subsequent studies to examine FDA required drug distribution, long-term safety, and dose-dependent systemic effects will also be conducted if the formulation is found efficacious.

- Title: *Research Infrastructure: Human Smoking and Addiction Laboratory*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The project will renovate an existing facility in the Clinical Research Center to build a new Human Smoking Testing Laboratory. This will allow for studies on the pharmacokinetics of exposure to diverse tobacco products, behavioral studies of nicotine addiction including puffing profiles and randomized trials of behavioral responses to nicotine delivery devices, and collection of biological samples to measure exposure to tobacco toxins from different tobacco and nicotine-delivery products. These studies are necessary to inform the FDA in their authority to reduce harm from tobacco.

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- Title: *Regulation of Genomic Stability by PARP10-mediated Mono-ADP-Ribosylation*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Correct DNA replication in S-phase is essential to maintain genomic stability and suppress carcinogenesis. DNA damaging agents such as tobacco smoke and UV radiation from sunlight induce DNA adducts and other lesions. If unrepaired prior to S-phase, these lesions can block the progression of replicative polymerases and thus induce stalling of the replication machinery. Stalled forks need be stabilized and eventually restarted, to avoid the toxic outcomes (chromosome breaks, translocations and rearrangements) caused by the collapse of the replication machinery at stalled replication forks. Our goal is to understand the replication fork restart process, which is essential to suppress genomic instability and carcinogenesis.

- Title: *Noninvasive Negative Pressure Chest Wall Ventilation in the Neonate*
  Type of Research: Biomedical
  Focus: Respiratory Sciences
  Purpose: The purpose of the study is to develop and test a new technology for assisting natural breathing noninvasively. Mannequins for in vitro testing and optimizing the technology will also be made as part of the project.

- Title: *Analysis of the Efficacy of a Novel Prostaglandin D12PGJ3 in the Treatment of Acute Myeloid Leukemia in Murine and Human Xenograft Models*
  Type of Research: Biomedical
  Focus: Hematology
  Purpose: Acute myeloid leukemia (AML) is one of the most common forms of leukemia. Unfortunately, it also has the lowest 5-year survival rate. The number of treatment options is limited, and these treatments lack the ability to induce a long-lasting remission. In addition, the incidence of AML increases with age. Many elderly patients cannot withstand the standard high-intensity chemotherapy regimen. We have identified a novel prostaglandin compound, Δ^{12}-Prostaglandin J_3 (D12PGJ3) that is highly effective in treating chronic myeloid leukemia (CML) in murine models. The purpose of this project is to test the efficacy of D12PGJ3 in treating AML in a murine model and analyze its mechanism of action. In addition, we will test D12PGJ3 in AML patient samples in vitro and in xenograft models in vivo.

- Title: *Bioproduction of 3D Functional Pancreatic Beta Cell Clusters from Adipose Derived Stem Cells*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The long-term goal of this project is to bioengineer adipose stem cell derived functional human pancreatic beta cells in vitro that are suitable for insulin replacement therapy. Stem cells have the potential to develop into many different cell types and may offer the ability to generate replacement cells. Patients afflicted with type 1 diabetes could potentially be cured by transplantation of engineered beta cells. This project will: 1) differentiate human adipose derived stem cells (ADSC) into functional beta cells in vitro

utilizing a new 3D differentiation protocol. 2) Co-culture ADSCs with patient specific endothelial cells to generate vascularized islets. 3) Bioprint patterned engineered-islets into a fibrin device to engineer a perfusable pancreas-on-a-chip model.

- Title: *Development of a Subarachnoid to Sagittal Sinus CSF Drainage System*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The proposed shunt system is an improvement over the standard ventriculoperitoneal shunt. This is a simple and easy to deploy system that reproduces biology utilizing a minimally invasive procedure. The shunt will be made of barium-impregnated silicone tubing with microfilaments embedded into the walls of the device, which would allow for drainage of cerebrospinal fluid into the cerebral venous sinus system. It will be initially used as an alternative to the standard cerebral shunt system currently in use. The overarching goal is for the system to be the gold standard for the treatment of hydrocephalus across different age groups and disease processes.

- Title: *Mechanisms of T Lymphocyte-Mediated Immunotherapy for Cancer*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: Despite major advances in the use of immunotherapy for cancer treatment, only a small proportion of patients experience durable complete responses to therapy. We will define the cellular and molecular characteristics associated with T lymphocyte-based immune therapy that promote the regression and durable control of established cancers. Using models of both prostate and brain cancer, we will define the gene expression patterns induced at the tumor site following the application of immunotherapy that associate with long-term tumor control. In addition, we will define the characteristics and role of persisting T cells following either durable or transient anti-tumor responses in order to improve immune-based therapies.

- Title: *The Role of GABAergic Signaling Mechanisms in the Outer Retina*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The project is centered on the development of a novel genetic approach using a powerful model system (zebrafish) to explore the impact of removing GABA, an important inhibitory signaling molecule, and testing whether GABA contributes to the origins and formation of sensory processing in the retina. GABA has been proposed to contribute to the origins of sensory processing in the outer retina. Previous studies have relied heavily on drugs that are not very specific, and have drawn inconclusive results, making interpretation of GABA's role very difficult. Instead, this study attempts to use genetics to tease apart GABA's role using zebrafish.

- Title: *Studies of the Interaction of Malaria Merozoites with a Complement Regulator*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: The hypothesis to be tested in this research project is that merozoites of Plasmodium falciparum, the deadliest malaria parasite, bind to a soluble *unspecified*

molecule in serum or plasma and that this interaction increases the resistance of merozoites to complement activation *(molecule is considered confidential and we'll call it "X")*. To do this, we will allow merozoites to egress from the red cell into serum and plasma and determine whether X is pulled down by the merozoites using Western blotting. Confocal microscopy will be used to co-localize X to the merozoite surface. Finally, we will evaluate the role of X in protecting merozoites from complement activation by determining whether inhibition of X binding to merozoites increases the in vitro susceptibility of merozoites to complement-mediated damage.

- Title: *Biomolecular Structure Characterization to Advance Biomedicine*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: New avenues have been opened by the availability of detailed structural descriptions of proteins and enzymes involved in the normal (or abnormal) functioning of the human body and associated pathogens. In particular, this information provides a better understanding of the basis by which different proteins achieve selectivity and specific binding to their cognate ligands and drugs. Indeed, several marketed drugs in recent years have been developed using structure-based methods, targeting a wide range of disease such as AIDS, leukemia, cancers and venous thromboembolic events. Our understanding of biological function and its impact on human health will be advanced in this study utilizing our new cryo-electron microscopy capability.

- Title: *Brainstem Circuits Controlling Gastrointestinal Functions in a Parkinson's Disease Model*
  Type of Research: Biomedical
  Focus: Digestive Sciences
  Purpose: Recently it has been recognized that severe gastrointestinal (GI) dysfunctions are prodromal to the diagnosis of Parkinson's disease (PD). Their pathophysiology is unclear, which hampers their diagnosis and clinical treatment. Many studies show that prolonged environmental exposure to toxins predisposes individuals to the development of PD. This project aims to investigate the neural pathophysiology of gastric dysmotility induced by exposure to subthreshold doses of environmental factors known to induce PD at significantly higher doses. Our results will provide important translational information that will be used to target gastric dysfunctions in PD patients and provide a potential means by which vulnerable patients may be identified *a priori*.

Salus University ($32,241) – 1 Project

Research Projects:

- Title: *Physiology of Photoreceptors Affected by CORD6 Congenital Blindness*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: To understand how the mutation causing congenital autosomal dominant cone-rod dystrophy (CORD6) in guanylyl cyclase alters the physiology of the affected photoreceptors and leads to blindness.

Health Research Formula Grants – State Fiscal Year 2016-17

Temple University-of the Commonwealth System of Higher Education ($1,960,548) – 9 Projects

Research Projects:

- Title: *Research Infrastructure for Research Neuroimaging Facility*
  Type of Research: Clinical
  Focus: Research Infrastructure Project
  Purpose: The project will support the establishment of a multi-modal research neuroimaging facility, serving an inter-disciplinary community of researchers at Temple University's main campus. The facility will provide investigators with access to cutting edge Magnetic Resonance Imaging (MRI) technology, and to a host of integrated and complementary tools that enable this technology to be applied toward behavioral- and mental-health focused research. Accordingly, this facility will allow active investigators to maintain, enrich, and extend the high-level work being carried out in association with externally-funded research at our institution.

- Title: *Alterations in Mitochondrial Calcium Signaling Drive Alzheimer's Disease*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Alzheimer's disease (AD) is projected to increase ~40% over the next 10 years with a projected cost of $315 billion/year for dementia related disorders, representing an enormous health and economic burden on the US. AD is characterized by a decline in memory and cognitive skills due to neural degeneration that is debilitating and ultimately fatal. We will test the central hypothesis that mitochondrial calcium ($_{m}Ca^{2+}$) overload is a primary contributor to AD pathology by eliciting neuronal cell death and metabolic dysfunction and that enhancing $_{m}Ca^{2+}$ efflux will impede AD progression. The proposed studies are the first genetic examination of $_{m}Ca^{2+}$ exchange in AD-associated neurodegeneration and may discover new therapeutic targets.

- Title: *Neural Reward Responsivity, Inflammatory Biomarkers, and Risk for Adolescent Depression*
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: This project will elucidate mechanisms that may contribute to risk for adolescent depression. It involves a novel investigation of the associations between inflammatory biomarkers and neural reward responsiveness in adolescents with depression or at familial or environmental risk for depression compared to low-risk adolescents. The design will allow new knowledge about whether attenuated neural reward responsiveness and inflammation are vulnerabilities to, or consequences of, depression. As such, it may have implications for the development of novel interventions that reduce inflammation to address blunted reward function and depressive symptoms such as anhedonia, fatigue, inactivity, and social withdrawal.

- Title: *Chronic Stress Regulation of Attention Circuits*
  Type of Research: Clinical
  Focus: Neurosciences
  Purpose: Sustained attention—the process of continuously monitoring situations for rare

and unpredictable events—is critical for many cognitive processes and disrupted in disorders, including, schizophrenia, attention deficit hyperactivity disorder (ADHD), and Alzheimer's disease. Chronic stress worsens the symptoms of these disorders, yet the neurobiological processes by which chronic stress alters sustained attention are unknown. This project will determine in rats how chronic stress alters neurotransmitters critical for attention and the structural plasticity of neurons within attention circuits. These studies may identify new targets that can be manipulated therapeutically to improve attention in stressed patients with a variety of disorders.

- Title: *Children's Selective Attention and Brain Responses to Tactile Stimulation*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: This project will investigate relations between children's cognitive control skills and neural indices of anticipatory selective attention. The purpose is to understand the influence of early environment on cognitive and neural development and how anticipatory brain responses across different modalities (tactile, auditory or visual) relate to broader cognitive skills. The project will shed new light on the understanding of how attention is selectively and flexibly deployed, with implications for behavioral, educational, and health-related interventions.

- Title: *Nrf-2 Translation Activators as Therapeutic Leads for Alzheimer's Disease*
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: Alzheimer's disease is an irreversible, progressive brain disease that impairs cognitive functions. This project is aimed at identifying drugs that reduce oxidative stress, which is known to increase toxicity and chronic inflammation in brain cells and contributes to neuron and synaptic deterioration in Alzheimer's disease. The activation of the endogenous cellular defense against oxidative stress is regulated by nuclear factor-erythroid 2 related factor 2 (Nrf2). We have discovered a novel unconventional mechanism by which cells activate Nrf2 and, based on this knowledge, we were able to identify novel compounds that increase Nrf2. The goal now is to select compound(s) with optimal pharmacological properties to prevent/block the progression of Alzheimer's disease.

- Title: *Research Infrastructure Project: Core Animal Facilities*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The purpose of this project is to fund laboratory and core facility infrastructure and to remediate existing damaged floors within core facility animal/procedure rooms, as well as service support areas in essential animal core facilities, by installing reinforced fiberglass paneling (RFP) in such areas, as well as emergency power supply to the large animal surgical suites in these core facilities. The installation of RFP on animal housing and procedure room walls will help sustain long term integrity of the walls, reduce maintenance costs and improve sanitizing capabilty. Furthermore, emergency power access would be installed in both surgical rooms to provide support for surgical lights and life support monitoring equipment.

- Title: *A Combined Complementary Cannabinoid Treatment Strategy for Spinal Cord Injury*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Spinal cord injury leads to long lasting motor, sensory, and autonomic dysfunction, each of which produces drastic impairments quality of life. We have demonstrated that the phytocannabinoid cannabidiol (CBD) attenuates neuropathic pain in a mouse model of SCI and decreases T cell activity. We did not observe a significant effect of CBD treatment on locomotor or bladder function. In contrast we have found that a synthetic cannabinoid CB2 receptor agonist significantly improves locomotor and bladder function and decreases microglial activation in the injured cord. The purpose of the research study is to determine the combined effects CBD and CB2 agonist treatment to provide maximum recovery from spinal cord injury.

- Title: *A Novel Approach for Preferential Brain Cooling to Mitigate Consequences of Traumatic Brain Injury*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The purpose of this study is to provide a novel, practical approach to rapidly and preferentially induce and maintain brain cooling and to control rewarming in order to optimize therapeutic hypothermia for the mitigation of consequences of traumatic brain injury. Further, we will develop new brain thermal mapping and temperature gradient algorithms as well as unfold new understanding of the role that therapeutic hypothermia plays on mechanical properties of the brain to contribute to neuroprotection.

Thomas Jefferson University ($1,797,867) – 5 Projects

Research Projects:

- Title: *Understanding the Role of Stress Granules in KRAS-driven Cancers*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The overarching goal of this project is to mechanistically decipher the capacity of mutant KRAS cancer cells to upregulate stress granules and investigate whether stress granule upregulation, as a KRAS-driven stress resistance platform, contributes to tumor evolution.

- Title: *The Effects of Comorbidity and Concurrent Medication Use on Health Outcomes among Cancer Patients*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to quantify the effects of comorbidities and co-medications on life expectancy, the risk of adverse events, and various health outcomes among cancer patients.

- Title: *Tumor Cell Biology and Biomarker Discovery Studies in T-cell and NK-cell Neoplasms*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The overall purpose of this research project is to gain knowledge on the molecular basis of T/NK-cell lymphoma development, on the mechanisms underlying disease progression, and on candidate tissue and blood-based biomarkers that may predict prognosis and guide therapy in these malignancies.

- Title: *Localizing Seizure Onset Sites Using Surrogate Markers of a Specific Imbalance in Excitatory-inhibitory Signaling during Low Voltage Fast Activity*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: One third of patients with focal epilepsy continue to experience seizures despite treatment with anti-seizure medicine. For these patients, resective surgery of the epileptogenic brain region can produce seizure freedom. To localize the epileptogenic brain regions, it is necessary to record brain activity using intracranial electrodes. When seizures are recorded, the locations of the electrode recordings showing the earliest changes, *i.e.* seizure onset zone, are used to target the resection. Localization of the seizure onset zone can be challenging. To aid clinicians and improve patient outcomes, we will investigate an electrophysiological surrogate marker of the location of seizure onset that is present only where dramatic changes in excitatory-inhibitory balance occur.

- Title: *The Developmental Programs that Build a Central Synapse in Drosophila*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: The precise coordination of communication between neurons in the brain requires properly functioning connections between these neurons at a specialized site called a synapse. Many neurodevelopmental disorders and intellectual disabilities can be traced to failures of synapses to properly develop or function normally. To date, though, our knowledge of how central synapses form has been limited. The research study proposed herein will determine how the synapses in a model neuronal circuit in the brain develop. It will first map how synapses form normally using newly pioneered technology and then assess the genes and circuit mechanisms that enable development. This will provide critical new insight on brain development and a critical foundation for designing ameliorative approaches for neurodevelopment disorders.

The Trustees of the University of Pennsylvania ($5,454,400) – 8 Projects

Research Projects:

- Title: *Development of Computational Techniques for Analysis of High-Dimensional Dynamic Single Cell Data*
  Type of Research: Biomedical
  Focus: Cell Biology, Biological Chemistry, Macromolecular Biophysics, Genomes and Genetics
  Purpose: Recently, it has become possible to acquire large-scale high-dimensional data from individual cell measurements leading to fundamental biomedical questions such as:

"How many functionally different cell types are in an organ?" and "What are the fundamental mechanisms of cellular programming for each cell type?" The answers to these questions will lead to a better understanding of developmental disorders that cause human diseases as well as better design of cell therapeutic reagents. While technologies have been rapidly advancing for instruments that can make these measurements, the development of computational analysis tools appropriate for these data is lagging. The goal of this project is to develop a new theoretical framework and data analysis tools for large-scale high-dimensional data from individual cell measurements

- Title: *Stemmler Hall Building Renewal – Research Infrastructure Facility Renovation Project*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: The Stemmler Hall Building Renewal Research Infrastructure Facility Renovation Project is a multi-phased wholesale renovation of this essential and aged health research laboratory resource and is aligned with the research program, building use and capital planning strategies of the Perelman School of Medicine (PSOM) at the University of Pennsylvania. This work will support research programs of the Department of Orthopaedic Surgery, with missions to conduct high quality fundamental and translational research and to train the next generation of leaders in the field. Health research projects include foci in creating and evaluating potential treatment modalities of tendon and ligament injury, healing, repair and regeneration.

- Title: *Examine Evidence-Based Practices to Reduce Unnecessary Hospitalizations and ED Visits*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Our purpose is to develop the essential pre-implementation qualitative data to elucidate barriers to acceptance of and adherence to evidence-based strategies to reduce avoidable hospitalizations and ED visits. The primary evidence-based practice we will revise is the Come Home Program, an evidence-based approach to reducing hospitalizations and ED visits by patients receiving care in community medical oncology practices. However, there are challenges to scaling this approach to fit into an academic or integrated medical center in its current form. Moreover, in its current form, a major barrier to implementation of the Come Home Program is provider acceptance and adherence to its pathways. Thus, we will collect data to adapt the Come Home Program and we will explore the use of social comparison strategies to maximize uptake of the revised program.

- Title: *Impact of Obesity and Dietary Fat on the Genomic Landscape of Primary Breast Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: The hypothesis that weight loss can prevent breast cancer recurrence in women is predicated on the assumption that the mechanisms responsible for the impact of obesity on recurrence risk are largely reversible. In contrast, if primary tumors arising in obese

women harbor collections of mutations that differ from those found in non-obese women, this would raise the possibility that at least some effects of obesity on recurrence risk may not be reversible by behavioral interventions. Therefore, the purpose of this project is to determine whether obesity or dietary fat alter the genomic landscape of primary tumors using an integrated genome-wide analysis. The results of this project will yield new knowledge that could lead to a better understanding of the impact of obesity on breast cancer recurrence and suggest approaches to prevent it.

- Title: *Personalized Treatment of GBM via Image-Guided Predictive Modeling of Recurrence*
  Type of Research: Biomedical
  Focus: Bioengineering, Surgical Sciences and Technology
  Purpose: The purpose of this project is to leverage advanced imaging analytics to develop personalized treatment plans for patients with glioblastoma (GBM), which is the most aggressive brain cancer. Recent technologies have allowed us to develop predictive maps of tumor infiltration and recurrence beyond the visible margin of the tumor, which currently forms the basis for neurosurgical resection and subsequent radiation. By utilizing predictive maps of tumor recurrence, we will develop an optimized plan for intensive yet targeted radiation therapy, aiming at focused targeting of brain tissue that is most likely to recur, while relatively sparing tissue that is less likely to recur.

- Title: *Novel Population Health and Behavioral Economic Approaches in Colorectal Cancer Screening*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: Colorectal cancer (CRC) screening is effective, but underused in low-income populations. The purpose of this project is to test novel approaches to engage patients to overcome social, economic, and structural barriers and advance a national goal to increase screening uptake to "80% by 2018." We will combine population health and behavioral economic approaches leveraging health information technology to engage with patients, providers, community stakeholders, and health system leaders. Also, despite the Affordable Care Act (ACA), Medicare does not waive the 20-25% co-insurance for a screening colonoscopy if it results in a biopsy, polyp removal, or is done to work-up a positive screening test. Cost-sharing is a substantial barrier for low-income or minority patients who may not have supplemental insurance to cover out-of-pocket costs.

- Title: *Predicting Therapeutic Response in Acute Myeloid Leukemia*
  Type of Research: Health Services
  Focus: Oncological Sciences
  Purpose: Acute myeloid leukemia (AML) is a highly fatal cancer of the blood. Approximately 350-400 Pennsylvanians will die of AML this year. AML is typically treated with high dose chemotherapy that requires a month-long hospital stay and is highly expensive. However, such therapy is curative in only 35% of patients. We are interested in improving the ability to predict response to chemotherapy allowing clinicians to use this therapy only when it is likely to improve survival. To this end, we propose to build a database of molecular information that we have already collected and will

generate as part of this project. Database will include information about patients treated for AML at the University of Pennsylvania and molecular information about these patients' leukemic cells. We will use bioinformatics to build a better predictor for response to chemotherapy.

- Title: *Novel Targets for Smoking Cessation*
  Type of Research: Clinical
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: There is a critical need to identify better treatments for nicotine dependence and evidence supports negative affect and cognitive deficits as potential therapeutic targets for new interventions. The purpose of the project is to examine the repurposing of an existing FDA-approved medication (metformin) to attenuate negative affect and cognitive deficits during nicotine withdrawal. Findings from this research may have important implications for helping more smokers quit by increasing the number of available treatment options.

University of Pittsburgh-of the Commonwealth System of Higher Education ($5,454,400) – 10 Projects

Research Projects:

- Title: *Infrastructure: Biomedical Science Tower 3 (BST3) 6th Floor Gnotobiotic Lab*
  Type of Research: Biomedical
  Focus: Research Infrastructure Project
  Purpose: Our goal is to generate a state-of-the-art gnotobiotic ("germ-free") facility to provide a reliable, reproducible pipeline for testing hypotheses generated from The Center for Medicine and the Microbiome (CCM) projects like large patient cohort studies. Gnotobiotic mice provide an important mechanism where a microbiome of known composition can be added to a mammalian model and perturbed in a specified way. The interactions between the microbiome and the host can be monitored in a tractable manner. The ability to maintain a germ-free environment requires development of a new specialized facility dedicated to this line of experimentation and testing. Results from these experiments will be critical to translating research findings toward diagnostics and therapeutics for commercialization.

- Title: *The Role of Interleukin-22 in Influenza, Bacterial Super-Infection*
  Type of Research: Biomedical
  Focus: Immunology
  Purpose: The influenza virus infects millions each year with widely variable severity. Influenza is the cause of thousands of pneumonia cases associated with bacterial super-infection, often resulting in severe illness and/or death. This project addresses the host immune mechanisms by which the lung protects itself against bacterial super-infection and deficiencies in host defense driven by influenza-induced lung injury. The goal of the project is to define molecular pathways of epithelial-mediated innate host defense and determine novel therapeutic approaches. The focus is on a specific pathway in immunity, Type 17, and the mediator interleukin (IL)-22. Herein, we plan to evaluate the therapeutic potential of targeting IL-22 in a preclinical animal model of influenza, *Staphylococcus aureus* super-infection

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- Title: *Unraveling Innate Immunopathways of Healthy Longevity in a Mouse Model*
  Type of Research: Biomedical
  Focus: Biology of Development and Aging
  Purpose: This is a "human-to-mouse translation" project. We will test the idea that long-term survivorship in late life is dependent on innate or natural immunity. It is an idea stemming from our human studies that showed favorable health and high functional status among older adults are linked to the acquisition of innate armaments. Here, we will use long-lived mice deficient in pregnancy-associated plasma protein A (PAPPA) as experimental models. We will build on our seminal finding that old PAPPA-deficient mice are protected from acute toxicity to high-doses of lipopolysaccharide, a bacterial product that is lethal to old normal mice. Our primary goal is to examine the innate determinants of immune protection from bacterial infection. This project will provide insight into translational efforts to develop age-appropriate immune-based strategies to promote healthy longevity.

- Title: *Development of Anti-FoxO1 Small-Molecule Drugs for Diabetic Hyperlipidemia*
  Type of Research: Biomedical
  Focus: Endocrine, Metabolism, Nutrition and Reproductive Sciences
  Purpose: Our goal is to develop better therapeutic agents for clinical treatment of diabetic hyperlipidemia. Diabetic hyperlipidemia is characterized by markedly elevated blood fat levels, resulting from increased lipid production in the liver and decreased lipid clearance in the blood. Diabetic hyperlipidemia, which usually strikes people with morbid obesity and type 2 diabetes, is a major risk factor for cardiovascular disease—a leading cause of death in the U.S. To date, there is no cure for diabetic hyperlipidemia, and chronic intake of currently available lipid-lowering drugs is associated with various side effects. To address this clinical limitation, our project focuses on developing better lipid-lowering small-molecule drugs for treating diabetic hyperlipidemia and preventing cardiovascular disease in at-risk subjects with obesity and diabetes.

- Title: *Blood Signature of Reactivation Tuberculosis Risk*
  Type of Research: Biomedical
  Focus: Infectious Diseases and Microbiology
  Purpose: This project seeks to use a novel paradigm in tuberculosis (TB) to improve current tools that would be used as diagnostic and predictive measures of outcome. Using a pre-existing set of samples stored from a cohort of well-characterized animals, we will identify an immune signature of reactivation risk. Our ultimate goal is to develop new tools that will predict an individual's risk of severe forms of tuberculosis. If successful, these tests will lead to preventive interventions and, ultimately, reduce the number of deaths attributed to TB. It will also lead to more effective and efficient methods of treatment to reduce infection rates. Lastly, this method may provide more precise and individualized methods of risk assessment, catapulting the field into the modern medical era.

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- Title: *Determining Pathogenic Mechanisms of Amyotrophic Lateral Sclerosis (ALS)*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: ALS is a late onset neurodegenerative disorder characterized by the loss of upper and lower motor neurons. FUS and TDP-43 are DNA/RNA binding proteins found to be mutated in both sporadic and familial forms of ALS. In our project, we will systematically identify components of cytoplasmic stress granules under disease conditions in ALS patient cells. We will also test whether disintegrating stalled stress granules help in reducing FUS-related neurodegeneration. We will also investigate molecular mechanisms of muscleblind-mediated suppression of mutant FUS toxicity in *in vivo* models. Our proposed studies are expected to provide novel insights into the molecular mechanism of FUS-related ALS that would help in developing therapeutic interventions for ALS, for which currently no cure is available.

- Title: *Dose-seeking and Efficacy Study of Pembrolizumab Plus Vemurafenib for Therapy of Advanced Melanoma*
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this study is to determine the safety and identify the maximum tolerated dosage of vemurafenib administered in concurrent combination with standard-dose pembrolizumab for patients with unresectable stage III and stage IV melanoma. In addition, this study aims to assess overall response rate (ORR) with the combination of pembrolizumab and vemurafenib, compared to historical benchmarks.

- Title: *First-In-Human Study of BMS-986207 Alone and in Combination with Nivolumab in Advanced Solid Tumors*
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: Programmed death 1 (PD1) blockade results in durable remissions in 30-40 percent of advanced melanoma patients, but primary and secondary nonresponse is an intractable problem. Data from multiple investigators, including a University of Pittsburgh immunologist, suggest targeting alternative immune checkpoints—particularly TIGIT (T-cell immunoreceptor with Ig and ITIM domains)—may mediate this. Translational efforts have resulted in the development of a TIGIT monoclonal antibody (mAb), BMS-986207, that will be evaluated in this first-in-human study. Patients receive BMS-986207 alone or in combination with PD1 mAb nivolumab, and pre- and on-treatment biopsies are mandated. Multiplatform evaluation of paired biopsy samples will illuminate mechanisms of response/nonresponse to next-generation immune checkpoint inhibitors.

- Title: *Phase I Trial of VX-970 in Combination with Irinotecan in Patients with Advanced Solid Tumors*
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The purpose of this phase I trial is to identify the maximum tolerated dose (MTD), recommended phase II dose (RP2D), and dose-limiting toxicities (DLTs) of VX-

970 in combination with irinotecan in patients with advanced solid tumors. Although the clinical benefit of these drugs in combination has not yet been established, the intent of this treatment is to provide a possible therapeutic benefit. For this reason, patients will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Anti-tumor activity will be measured by overall response rate (ORR) and progression-free survival (PFS).

- Title: *Phase II Trial of Atezolizumab in Advanced NSCLC Patients Previously Treated with PD-1-directed Therapy*
  Type of Research: Clinical
  Focus: Oncological Sciences
  Purpose: The therapeutic landscape of previously treated advanced non-small cell lung carcinoma (NSCLC) in the absence of an actionable oncogenic driver has shifted from a cytotoxic approach to modulation of the immune checkpoints. This phase II clinical trial is evaluating the efficacy of PD-L1 inhibition with atezolizumab in advanced NSCLC patients previously treated with anti-PD-1 therapy. The primary objective is to estimate the best overall response of atezolizumab in these patients, while secondary objectives include estimating duration of response, progression-free survival, overall survival, and safety. This trial is critical in evaluating the efficacy of sequencing PD-L1 inhibition in patients with stable or progressing disease on PD-1 directed therapy and to the identification of candidate biomarkers of response and resistance to PD-1/PD-L1 directed therapies.

University of the Sciences in Philadelphia ($11,039) – 1 Project

Research Projects:

- Title: *Physical Activity and Nutrition Needs of Low-Income Cancer Patients and their Caregivers*
  Type of Research: Health Services
  Focus: Health of Populations, Behavioral and Biobehavioral Processes
  Purpose: The purpose of this project is to characterize physical activity (PA) and nutrition-related beliefs, behaviors, and knowledge of low-income cancer survivors and caregivers to determine the unique needs of these understudied populations. Improving PA and dietary quality can enhance recovery from cancer treatments, improve quality of life, decrease cancer mortality, and reduce the risk for cardiovascular disease. The long-term goal is to utilize findings from this project to reduce disparities in modifiable behaviors that contribute to cancer risk and recurrence. This goal may be accomplished by leveraging mobile technologies to deliver and assess a physical activity and nutrition program for low-income cancer survivors and their caregivers.

The Wistar Institute of Anatomy and Biology ($1,362,421) – 2 Projects

Research Projects:

- Title: *Positive Allosteric Modulators of Glutamate Transporters for Glioma and CNS Diseases*
  Type of Research: Biomedical
  Focus: Neurosciences
  Purpose: Increases in extracellular glutamate are observed in the brain during and after

severe debilitating Central Nervous System (CNS) conditions, such as traumatic brain injury, stroke, epilepsy, and Amyotrophic lateral sclerosis (ALS). The vast majority of primary brain tumors derive from glial cells and are collectively called gliomas. Glioma growth is restricted by the skull. They release glutamate to cause excitotoxic death to surrounding neurons to vacate healthy tissue for tumor expansion. The purpose of this project is the development of positive allosteric modulators of the glial glutamate transporter EAAT2 as an effective means to remove excess glutamate in synaptic clefts as a novel approach to the treatment of CNS diseases due to excess glutamate, and most importantly to halt glioma growth and invasion due to glutamate excitotoxicity.

- Title: *Targeting Acetyl-CoA synthetase 2 as a Novel Therapeutic Modality in Colorectal Cancer*
  Type of Research: Biomedical
  Focus: Oncological Sciences
  Purpose: Our recent work has highlighted that acetate capturing enzymes frequently undergo gene amplification in colorectal cancer. In addition, the natural microbiota of the human colon produces a large amount of acetate from fermentation of dietary fibers and other indigestible carbohydrates. Therefore, we propose that the localized high concentrations of acetate in the human gut and selective amplification of acetate capturing genes work together to support colorectal tumor growth. We predict that pharmacologically targeting acetate capturing enzymes, such as acetyl-CoA synthetase 2 (ACSS2), may represent a novel targeted therapy for the tailored treatment of colorectal cancer patients.