Commonwealth Health Research Board
FY 2022/2023 Grant Award Abstracts

Michael Brown, Ph.D., University of Virginia
Risky Variants in Human Cardiovascular Disease

Project Summary: Cardiovascular disease (CVD) is the leading cause of death globally.1 A primary contributor to CVD is atherosclerosis with coronary artery disease (CAD) being the main cause of heart attack and death. Known CVD risk factors poorly predict acute events in asymptomatic individuals.2 Clinical studies of anti-inflammatory agents establish that atherosclerosis is a chronic inflammatory disease.3,4 Arterial wall lipid deposition and immune infiltration contribute to large, unstable lesions.3 Immune checkpoint proteins (ICP) regulate immune interactions. The murine glucocorticoid-induced TNFR-related (GITR) ICP drives atherosclerosis, and human GITR+ cells have been identified in unstable atherosclerotic plaques.5 Herein, we found CD56bright NK cells associated with CAD severity, and GITR variation may regulate NK responses. Our multidisciplinary team with expertise in NK cells, CVD and bioinformatics will test the novel hypothesis that variant GITR expression corresponds with human CAD and alters GITR cytoplasmic tail signaling domain expression and function in NK cells (see Figure 3).

Josh Cohen, M.D., Virginia Commonwealth University
Electrotransfer Mediated Gene Therapy Approach to Type 1 Diabetes

Project Summary: Type 1 Diabetes (T1D) effects nearly one-hundred thousand Virginians, and 2 million Americans, at a lifetime cost to the healthcare system estimated over $800B. This pilot study explores a highly innovative approach to deliver insulin and glucokinase encoding nanoplasmid DNA to skeletal muscle as a non-viral, non-integrating gene therapy and potential cure to T1D. Our laboratory has established effective and highly published protocols for gene delivery to various tissues of the body, including skin, heart, and skeletal muscle. In our CHRB work will direct these gene delivery protocols towards insulin and glucokinase in skeletal muscle to modulate blood glucose in vivo. The goal of this study is to optimize gene delivery and expression, and whether blood glucose levels can be controlled with exogenously expressed insulin and glucokinase. The results from this initial study will lead to follow-on federal funding and significant clinical advancements in T1D therapeutics.

Todd Fox, Ph.D., University of Virginia
Nervonic acid and obesity

Project Summary: Obesity in Virginian adults is currently 32% of the population. As higher fat mass is associated with dramatically increased morbidity and mortality, such as in response to COVID-19, there is an urgent need for new strategies to help people control body weight. The premise of this proposal is based on our recently published work demonstrating; 1) the fatty acid, nervonic acid, is dramatically reduced in models of obesity, and 2) dietary nervonic acid diminished weight gain with improved glucose and insulin parameters. The central hypothesis is that reduced nervonic acid plays a critical role in the development of obesity and related complications. This proposal will elucidate the underlying mechanism for reduced nervonic acid in obesity and assess nervonic acid specificity and the need to be acylated into sphingolipids for a therapeutic effect. These results will facilitate the design of new strategies to address the current need for improved weight control.

Commonwealth Health Research Board
FY 2022/2023 Grant Award Abstracts

Babette Fuss, Ph.D., Virginia Commonwealth University
The role of LPA6 receptor signaling in myelin repair

Project Summary: There are currently no neuroprotective therapies for debilitating diseases, such as Multiple Sclerosis (MS), where damage to the myelin sheath, which enwraps and protects central nervous system (CNS) nerve fibers, causes chronic nerve fiber degeneration and neurological disability. An emerging concept toward the development of novel treatment options is seen in the characterization of signals that are present in the demyelinating CNS and impede the repair capabilities of CNS myelinating cells, namely oligodendrocytes (OLGs). In this context, our novel findings suggest that the lipid signaling receptor LPA6 significantly contributes to such impediments in myelin repair. Notably, while lipid signaling has been described to be dysregulated under demyelinating conditions, its precise role in the regulation of CNS remyelination is not fully understood. Thus, in the long-term, our studies are anticipated to lead to the identification of novel therapeutic targets for stimulating myelin repair under pathologic conditions such as MS.

Rebecca Heise, Ph.D., Virginia Commonwealth University
Inhibition of cell-cell fusion as potential mechanism for treatment of covid19

Project Summary: Limited therapies are available for COVID-19, in part due to a lack of understanding of how SARSCoV-2 (SARS2) virus interacts with and affects host cells. This proposal is focused around developing a comprehensive understanding of the process by which SARS2 fuses host cells together, to form large, multi-nucleated cells, known as syncytia. SARS2 has increased syncytia formation, as compared to the original SARS virus, suggesting syncytia formation is a critical aspect of SARS2 pathogenicity. The PI (Conway) and co-I (Narayanan) have expertise in biophysics and live cell imaging and virology, respectively. The Narayanan group has found Maraviroc, an FDA-approved anti-viral, inhibits SARS2 viral replication. The Conway group has identified a potential mechanism of action, showing that Maraviroc inhibits the formation of syncytia. Data from this proposal will be critical for design of new targeted approaches to inhibit syncytia formation, which may have therapeutic value for treatment of COVID19 infection.

Bryan Hsu, Ph.D., Virginia Polytechnic Institute and State University
Self-assembling biomaterials for improved menstrual health and hygiene

Project Summary: We propose to use nondescript self-assembling biomaterials to coagulate menstrual fluid into a semi-solid, mitigating many challenges associated with traditional liquid absorption or collection strategies. We will test the efficacy of these hydrogels using in vitro models that simulate various menstrual conditions including light to heavy bleeding, frequent to infrequent hydrogel replacement, and mechanical deformation due to physical activities. In addition to coagulating menstrual fluid, these biocompatible and biodegradable hydrogels will be loaded with compounds that reduce pain, and inhibit bacterial growth, each with unique release kinetics that maximize their efficacy.

Commonwealth Health Research Board
FY 2022/2023 Grant Award Abstracts

Timothy Jarome, Ph.D., Virginia Polytechnic Institute and State University
The role of DNA 5-hydroxymethylation in the development of obesity

Project Summary: Obesity affects 40% of the U.S. population and is responsible for an estimate 300,000 deaths per year. In Virginia alone, the obesity rate in adults is around 30%, with an annual cost of over $4 billion. However, therapeutic interventions which can reverse the progression of obesity remain equivocal. The goal of this project is to identify the role of a robust, highly persistent genetic-molecular mechanism in the brain to the development of obesity. Specifically, we will test if blocking the weight gain-induced reductions in DNA 5-hydroxymethylation (5-hmC) in the hypothalamus in a cell-type specific manner prevents the development of obesity over time. Additionally, we will determine if increasing DNA 5-hmC at the major satiety gene, Pomc, in the hypothalamus can prevent obesity development. Results from this study could provide critical information needed for the development of therapeutic strategies to treat the underlying pathophysiology of obesity.

Daeha Joung, Ph.D., Virginia Commonwealth University
3D Printing Living Platform for Spinal Cord Regeneration

Project Summary: Cord Injury currently has no effective therapies that enable the restoration of disrupted signals in the impaired sites to re-establish function due to architectural and functional complexity. This project aims to develop an advanced biomanufacturing process for constructing living scaffolds using 3D printing and origami-inspired assembly that permit the use of multi-materials. The objectives of this research include: (1) develop origami-inspired folding processes to transform 3D printed plane structures into a three-dimensional scaffold, overcoming the limitations of the compatibility with a broad spectrum of biomaterials; and (2) embedded electrodes within the scaffold to deliver targeted electrical stimulation for cell growth. The integrated technology will bridge the gap between advanced biomanufacturing science and neural regeneration, ultimately promoting interdisciplinary efforts to develop life-altering clinical treatments for patients who sustain Spinal Cord Injuries in Virginia and beyond.

Jeffrey Moran, Ph.D., George Mason University
Patient-Derived Hydrogel-Based In Vitro Models of Idiopathic Pulmonary Fibrosis for Assessment of Targeted Nanoparticle Therapies

Project Summary: Idiopathic pulmonary fibrosis (IPF) is a lung disorder that kills more Americans per year than breast cancer. Its cause is poorly understood and the typical survival time is less than 5 years. IPF progression is known to depend on interactions between cells and their surrounding environment. Here, we will synthesize biomaterials that match the protein composition of real fibrotic lung tissue and use them as platforms to test new nanoparticle-based strategies to halt and possibly reverse IPF progression. Our aims are (1) synthesize decellularized hydrogels and quantify effects of changes in stiffness and pore size on disease progression in vitro; (2) test efficacy of nanoparticles, propelled by magnetic fields or ultrasound, to penetrate tissue and deliver medication to targeted locations. This work will yield insight into the effects of tissue mechanics on IPF progression and could enable lower required doses for IPF medication, reduced side effects and improved patient outcomes.

Commonwealth Health Research Board
FY 2022/2023 Grant Award Abstracts

Masahiro Sakagami, Ph.D., Virginia Commonwealth University
Local dual-action treatment of lung fibrosis: inhibiting fibroblast activation and modulating collagenolytic activity

Project Summary: Lung fibrosis causes thickened, scarred fibrotic airspaces due to aberrant extracellular matrix (ECM; collagen) accumulation. It is progressive and idiopathic, but irreversible and incurable with any drugs, resulting in respiratory failure and death in 2-5 years. AM24 is our proprietary curcumin-like derivative of melatonin. As excessive ECM accumulation in fibrotic lungs can be recognized as a net result of induced synthesis and insufficient removal of collagen, we hypothesize that AM24 uniquely possesses dual-actions of inhibiting collagen-generating fibroblast activation; and modulating collagenase and anti-collagenase imbalance, via multi-hybrid mechanisms originating from its structure origins. Hence, this 2-year project will examine AM24 for potent, mechanistically-hybrid, dual-action anti-fibrotic activities using in vitro cell-based systems (Aim 1) and an in vivo rat model of lung fibrosis (Aim 2). Successful completion will prove this dual-action strategy against "collagen dysregulation" in fibrotic lungs and offer AM24 as a novel inhaled drug for lung fibrosis treatment.

Julia Sharp, Ph.D., Eastern Virginia Medical School
Pathogenic Determinant Analysis of Community Associated Staphylococcus aureus in South Eastern Virginia

Project Summary: Staphylococcus aureus is a major cause of community and healthcare-associated infections resulting in significant illness and death worldwide. With increasing antibiotic resistance and no effective vaccine, novel anti-staphylococcal therapies are critically needed. To address this need, we propose an innovative, multifaceted approach to determine S. aureus pathogenic (disease-causing) characteristics using community associated S. aureus isolates from patients who reside in South Eastern Virginia. We will assess the potential of isolates to cause harm (virulence-factor potential) by examining bacterial DNA (genetic content) and activity (expression) of several clinically relevant virulence factors. Additionally, to further examine the host-pathogen relationship, the capacity of S. aureus isolates to bind human serum proteins (both quantity and complexity) will be evaluated. These data will permit the generation of pathogenicity profiles, cross referenced with infection type (skin/soft-tissue or blood infection) and patient locale, to benefit direct therapy interventions and highlight potential therapeutic targets.

Lisa Shollenberger, Ph.D., Old Dominion University Research Foundation
Proof-of-concept study for the development of next-generation vaccines for tick-borne intracellular diseases

Project Summary: Tick-borne diseases (TBD) are a worldwide threat to human and animal health. In the USA, Lyme disease is the most common, not the only, TBD. Other tick-borne pathogens (TBP) include Rickettsia, Ehrlichia, Anaplasma, and Francisella; Babesia, and viruses. Virginia had 8,895 reportable TBD cases from 2015-2019, one of the highest statewide incidences in the country, and tick-borne viral infection are not reportable. Development of effective vaccines for TBP is crucial, as there are currently no licensed human vaccines with most, if not all, being a humoral (antibody-based) response. Since many TBP are intracellular pathogens, a cell-mediated immunity (CMI) seems more appropriate. We hypothesize intracellular proteins, which may be conserved between multiple organisms, are appropriate candidate vaccine antigens for intracellular pathogens. Using rickettsial antigens as proof-of-concept, we will test this hypothesis through successful completion of the following aims: (1) development of the necessary immunological tools and (2) evaluation of CMI.

Commonwealth Health Research Board
FY 2022/2023 Grant Award Abstracts

Lee Solomon, Ph.D., George Mason University
An environmentally responsive peptide material capable of oxygen delivery

Project Summary: Despite an urgent need and years of study, there are no suitable blood substitutes that can be routinely used. Relying on donations is also troublesome as the blood can be contaminated with undiagnosed illnesses and is difficult to store. We propose to develop a blood substitute made from a novel peptide material, which binds heme B, the same cofactor found in human hemoglobin. For this stage of the work, we will optimize the material by changing the peptide sequence to promote stronger oxygen binding and tuning the environmental responses to be more aligned with physiological conditions. These peptides are highly modifiable and can be designed so they do not stimulate the immune system and be more stable than standard blood for long term storage. This work will serve as pilot studies for developing a next generation blood substitute that will help all Virginians suffering from hemorrhage inducing injuries.

Amy Tang, Ph.D., Eastern Virginia Medical School
Developing a prognostic companion molecular test to quantify and guide immuno-oncology (IO) therapy for triple-negative breast cancer

Project Summary: Triple-negative breast cancer (TNBC) is an aggressive subtype with high relapse rate. Recently, the FDA approved immune checkpoint blockade (ICB) therapy for high-risk early-stage; and PD-L1- positive locally recurrent, unresectable, or metastatic TNBC. The challenge is how to predict the treatment benefit of immuno-oncology (IO) therapy. To address this unmet need, we propose to evaluate SIAH as a predictive biomarker to augment PD-L1 status and pathologic response to optimize the use of IO-therapy for TNBC. • SIAHHigh/ON in TNBC tumors reflects that the EGFR/K-RAS/SIAH pathway is ON and may indicate immuno-suppression, ICB-resistance, and/or the need for additional therapies to control TNBC malignancy. • SIAHLow/OFF in TNBC tumors reflects that the EGFR/K-RAS/SIAH pathway is OFF and may indicate immuno-responsiveness, ICB-sensitivity, and good prognosis after surgery. We aim to demonstrate the clinical utility of SIAHON/OFF expression as a new prognostic biomarker to stratify patients, predict the need for and/or efficacy of neoadjuvant and/or adjuvant immunotherapy.

Zequan Yang, Ph.D., University of Virginia
Topical Neck Cooling Attenuates Acute Myocardial Infarction

Project Summary: Myocardial infarction (MI, heart attack) accounts for the vast majority of death associated with ischemic heart disease. The key to salvage the dying heart muscle is to shorten the transportation time to the hospital. However, the prehospital management to protect the heart is sadly lacking. Mild systemic hypothermia is found to be protective against MI. However, the protection is observed only when hypothermia is achieved early during the heart attack. Induction of systemic hypothermia is resource intensive and difficult to start outside hospital. The delay in initiating the hypothermia is unlikely to be solved. A therapy, that is portable and easy to apply at the onset of heart attack, may provide better heart protection. We found that topical neck cooling could attenuate MI similar as systemic hypothermia. This application will further define the mechanisms underlying the topical neck cooling and modify the device for use in big animal model.