Commonwealth Health Research Board
Abstracts for 2014/2015 Grant Awards
(July 1, 2014 to June 30, 2015)

Stephen Deutsch, M.D., Ph.D., Eastern Virginia Medical School

Identifying NMDA Receptor Interventions for the Treatment of Impaired Sociability in Autism Spectrum Disorders using an Automated High-Throughput Screening Technology

Project Summary: Patients suffering from autism spectrum disorders (ASDs) exhibit impaired sociability, which severely affects their quality of life and often precludes them from living independently. Recently, we showed for the first time in a mouse model of ASDs that sociability can be improved pharmacologically. We know that the successful drugs act on a particular receptor in the brain, and there is a great variety of promising drugs know to affect this receptor in different ways. Since testing all those drugs in a range of doses requires a high-throughput screening technique, we partnered with engineers from Old Dominion University who are developing software that allows the quantification of sociability by automatically analyzing behavioral movies. Building on this combination of medical and engineering expertise, we propose to screen all promising drugs and to identify those that most improve sociability. Appropriate analogues of these drugs could become viable medications for human administration.

Elizabeth Gilbert, Ph.D., Virginia Polytechnic Institute and State University

Using anorexic and obese chickens to identify targets for appetite regulation

Project Summary: Because 30% of adults in the Commonwealth are considered obese (CDC), Virginia is in considerable need of an effective anti-eating strategy. New perspectives on appetite may come from studying the anorexic and obese concurrently and perhaps even more so from non-mammalian models. The body weight selected lines of chickens, the only model of anorexia and obesity originating from common ancestors, existing only at Virginia Tech, have been selected for either low (LWS) or high (HWS) juvenile body weight for 55 generations and are comprised of anorexic and obese individuals. The objective of this study is to identify differentially expressed proteins between juvenile LWS and HWS in the hypothalamus, a region of the brain involved in appetite regulation. Identified peptides/proteins will be evaluated as potential pharmacological targets for manipulating appetite.

Kristian Hargadon, Ph.D., Hampden-Sydney College

The Role of Melanoma-derived Factors in Suppressing the Maturation, Activation, and T Cell Stimulatory Capacity of Dendritic Cells

Project Summary: The studies proposed in this grant application are aimed at understanding melanoma-associated suppression of dendritic cells (DC), innate immune cells that function as critical regulators of anti-tumor immune responses. Gaining mechanistic insight into the basis for melanoma-mediated suppression of DC maturation and activation and understanding the role of melanoma-altered DC in the induction of tumor-associated T cell dysfunction will enhance our understanding of tumor immune escape. Such findings have the potential to identify novel targets for interfering with melanoma-associated DC dysfunction, and they are likely to suggest immunotherapeutic strategies designed to improve the functionality of endogenous tumor-associated DC *in situ*, the efficacy of exogenous DC-based anti-tumor vaccines, and the overall quality of anti-tumor T cell-mediated immune responses.

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Rebecca Heise, Ph.D., Virginia Commonwealth University

Development of Extracellular Matrix Hydrogels for Lung Regeneration

Project Summary: Chronic Obstructive Pulmonary Disease (COPD) is the 4th leading cause of death in the United States, with at least 3,000 Virginians dying each year. Lung transplantation is the only available cure, but transplants are undesirable due to the shortage of donor lungs available, advanced age of most patients, and low survivability of lung transplant patients. Adult stem cell therapies promote regeneration of damaged lung epithelial tissue in animals through engraftment into the tissue and modulating the immune response in the lung. Injection of adult stem cells in animal lungs has fallen short because the majority of cells introduced are washed out of the lung. This proposal will develop a cell delivery system that will support adult stem cell growth in the diseased lung. The delivery matrix will also offer potential regeneration benefits. This proposal will develop a new approach to the treatment of COPD that can restore lung function.

Deborah Kelly, Ph.D., Virginia Polytechnic Institute and State University

BRCA1-directed Transcriptional Regulation in Hereditary Breast Cancer

Project Summary: Today, women diagnosed with breast cancer have a higher chance of survival than ever before especially when detected early. However, triple negative breast cancer threatens the lives of many young women in Virginia. This form of breast cancer is extremely aggressive, more likely to recur and presents major challenges for treatment. Treatment options are limited and there is currently no known cure. We will investigate the actions of a prime culprit implicated in causing the disease, the protein factor, BRCA1. We will determine, in 3D, how BRCA1 interacts with other complex proteins poised on DNA to induce cancer. Having a 3D model to understand unique protein-DNA properties will greatly contribute to the design of new drugs that interfere with cancer-causing processes. We expect this will lead to new treatment options aimed at combating triple negative breast cancer and enhancing clinical outcomes.

Michael Leopold, Ph.D., University of Richmond

Amperometric Biosensors Incorporating Nanoparticle Networks: Monitoring Sepsis using Lactate Measurement

Project Summary: Sepsis, a systemic inflammatory response triggered by infection, is the 10th leading cause of death in the U.S. with a 20% mortality rate. Identified through clinical presentation or from time-consuming laboratory blood tests, early diagnosis and monitoring of sepsis during antibiotic treatment is essential for improving patient survival from this condition. Recent clinical studies have identified lactate as a critical marker for sepsis and the ability to clear lactate from the blood as prognosticator of septic patient survival. Sensors that continuously monitor lactate in real time would represent a significant biotechnological advancement and a valuable clinical improvement for patients with sepsis. Amperometric biosensors, using enzymatic reactions to selectively detect physiological targets like lactate, can suffer from insufficient sensing performance or inadequate sensitivity. Incorporation of colloidal gold nanoparticle networks within biosensor schemes, the focus of this research proposal, may allow for improved sensing performance and miniaturization toward development of *in-vivo* devices.

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Michael Neale, Ph.D., Virginia Commonwealth University

Whole Exome Sequencing to Improve Stem Cell Transplant Outcomes

Project Summary: Stem cell transplants can be lifesaving treatment for a variety of diseases, including acute leukemia, disorders of hematopoiesis and inherited metabolic disorders. However, these transplants carry a high risk (~30%) of graft versus host disease which itself can be lethal, as can other treatment complications. This project will use Illumina hiSeq and miSeq next generation sequencing of DNA samples from 40 previously stored stem cell transplant patients and their donors. Novel assessments of specific and aggregate genomic donor-recipient differences will be used to predict transplant outcomes including survival and graft versus host disease. The HLA region, minor histocompatibility loci and other immunologically relevant genomic areas will be assessed.

Dongfeng Pan, Ph.D., University of Virginia

Tumor-targeted Delivery of Farnesylthiosalicylic Acid (FTS)

Project Summary: **Objective:** Enhancing anti-cancer efficacy of farnesylthiosalicylic acid (FTS) by targeted delivery. **Introduction:** FTS is promising candidate drug for breast cancer patients with resistant disease. However, its clinical efficacy is limited due to the poor pharmacokinetics and bioavailability. We have conjugated FTS with a small molecule tumor-targeting carrier. The conjugate exhibited improved inhibition efficacy against endocrine-resistance cancer cells compared to FTS and demonstrated highly targeted uptake into mouse xenografts. In this application we will validate its therapeutic efficacy in a preclinical setting. **Hypothesis:** Tumor-targeted delivery would enhance anti-cancer therapeutic efficacy of FTS. **Methods:** The parameters of pharmacokinetics, pharmacodynamics, and toxicity in animal model will be comprehensively studied and validated using live animal imaging and other relevant techniques. **Impact:** If succeeded, it will provide a new effective treatment for patients with relapse breast cancer from primary endocrine therapy. Furthermore, the same mechanism holds the potential for targeted delivery of other chemotherapy drugs.

Tushar Shah, M.D., M.P.H., Eastern Virginia Medical School

Role of Novel Complement inhibitor in improving neurological outcomes in an animal model of Neonatal Hypoxic Ischemic Encephalopathy

Project Summary: Hypoxic-ischemic encephalopathy (HIE) is a condition in which brain damage is caused due to birth asphyxia or oxygen deprivation around the time of birth. HIE is a major contributor to the infant mortality rate in Virginia. The complement system, a critical part of inflammatory tissue damage, plays a major role in HIE. Several clinical trials have shown that reducing body temperature (hypothermia) improves survival and neurological outcomes in infants with HIE. Our bench-top experiments suggest that hypothermia increases complement activation, likely attenuating the benefits of hypothermia. Our lab has developed a compound (Peptide inhibitor of C1, PIC1) that blocks the complement system and potentially reduces brain damage due to complement activation. Our experiments aim to test PIC1 in newborn rats and demonstrate decreased brain damage. Our long-term goal is to develop PIC1 as an intervention to decrease mortality and improve neurological outcomes in infants with HIE.

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Judith Voynow, M.D., Virginia Commonwealth University

Inhaled 2-O, 3-O desulfated heparin is a multifunctional anti-inflammatory therapy for cystic fibrosis lung disease

Project Summary: Cystic fibrosis (CF) is an inherited disease that causes abnormal airway mucus and recurrent bronchitis resulting in lung failure and death. A major cause of lung injury in CF is the high concentration in the airways of neutrophil elastase (NE), a product of white blood cells that degrades proteins. There are currently no effective anti-NE therapies to prevent the relentless progression of CF lung disease. Although heparin is an effective anti-NE and anti-inflammatory drug, it cannot be used in CF due to the risk of lung bleeding. A modified heparin, 2-O,3-O- desulfated heparin (ODSH), does not cause increased bleeding, yet maintains robust anti-NE and anti-inflammatory properties. **Therefore, we propose that ODSH will be an effective inhaled therapy to prevent progression of CF lung disease.** The CHRB proposal will generate critical preliminary data to test this hypothesis and to support preclinical toxicology for an FDA investigational New Drug application.

Laurie Wellman, Ph.D., Eastern Virginia Medical School

Oxytocin and Exposure Therapy: A Novel Approach for Treating PTSD

Project Summary: Post traumatic stress disorder (PTSD) develops in a significant percentage of the population following a psychological trauma. Core symptoms include re-experiencing the traumatic event, avoidance of traumatic cues and **sleep disturbances**. The most effective therapy for PTSD is exposure therapy; however it only works for a subset of the patients due to program incompletion, unresponsiveness, or relapse following treatment. We propose to examine the effectiveness of oxytocin (OT), a natural anti-anxiety neuropeptide, in fear conditioning (FC) of rats, a model important for understanding PTSD. Aim 1 investigates the effects of OT administered prior to or following FC on future expression of fear behaviors and normalization of sleep. Aim 2 investigates the effects of OT administered prior to or following extinction (a laboratory model of exposure therapy) on the elimination of fear behaviors and normalization of sleep. Together these studies will determine the therapeutic potential of OT for augmenting exposure therapy.