Commonwealth Health Research Board
Abstracts for 2013/2014 Grant Awards
(July 1, 2013 to June 30, 2014)

Stuart Berr, Ph.D., University of Virginia
Development of Biomarkers that Target Tumor Associated Macrophages

Project Summary: Cancer cells are not invading organisms but are self, which complicates diagnosis and treatment. Cancer cells communicate with and regulate the body's immune system to their advantage by expressing chemicals which cause white blood cells called tumor associated macrophages (TAMs) to facilitate the growth of new blood vessels and tissue that aids in tumor growth. TAMs also express chemicals that prevent other parts of the body's immune system from attacking the tumor. Others are working on creating chemical compounds that bind to cancer cells for diagnosis and/or therapy. We are working on designing and synthesizing chemicals that instead target TAMs. Successfully targeting of TAMs will allow us to better understand the role they play in cancer development and spread, and allow us to deliver a variety of payloads including radioactive elements for imaging or therapy, chemicals that can kill TAMs, or cause them to be less tumor-friendly or anti-cancer chemotherapeutics.

Michael Boyd, M.D., Carilion Medical Center
Genetic Reassessment after Induction in Advanced Non-small Cell Lung Cancer

Project Summary: Four thousand Virginians die from lung cancer each year. Much of our knowledge regarding lung cancer biology is based on molecular studies utilizing resected early staged tumors. Recently, minimally invasive biopsies from advanced lung cancers were demonstrated to provide sufficient genetic material for molecular studies. A greater understanding of the genetic abnormalities associated with advanced lung cancer could improve current therapies and outcomes. Carilion Medical Center, partnering with Virginia Tech, proposes a pilot study to confirm the presence of genetic drift in advanced non-small cell lung cancer. We will establish a specimen repository obtaining tumor tissues from patients with advanced lung cancer. Patients who develop recurrent or progressive disease and require additional biopsies will be identified. Tumor tissues from initial diagnosis and progressive disease will be compared using DNA microarray analysis. From these specimens, we intend to identify the presence of any unique genetic derangements and thus determine genetic drift.

Raymond Colello, D.Phil., Virginia Commonwealth University
Enhancing Axon Regeneration and Quality of Life Following Spinal Cord Injury

Project Summary: Nationwide over 250,000 individuals are living with spinal cord injury (SCI), with 12,000 new cases occurring each year. Locally, Richmond is home to the nation's largest SCI rehabilitation center. Patients who suffer SCI experience a diminished quality of life for a number of reasons including the loss of mobility and diminished urinary tract function. However, recent research has demonstrated that the CNS has the capacity to regenerate, thereby re-establishing lost connections and restoring some measure of function. Moreover, this regenerative capacity can be enhanced by a variety of biochemical approaches that create a more permissive environment for regeneration. Recently, our lab has shown how both bioengineering and biochemical approaches can be combined to dramatically improve axon regeneration and quality of life functions following SCI. This grant explores the cellular responses that underlie the locomotor and urinary improvements observed and aims to establish a therapeutic treatment for spinal cord injury.

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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.

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.

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.

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.