Commonwealth Health Research Board
Abstracts for 2012/2013 Grant Awards
(July 1, 2012 to June 30, 2012)

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.

Maria Belen Cassera, Ph.D., Virginia Polytechnic Institute and State University
Development of Novel Broad-Spectrum Chemotherapeutics against bacteria and protozoa

Project Summary: Drug-resistant microbes cause severe health problems in humans; new drug targets and development of potent inhibitors, with no side effects, are urgently needed to overcome this issue. Isoprenoids are chemicals present in all living organisms and are essential to a variety of biological functions. Isoprenoids are formed from two building blocks, isopentenyl diphosphate and dimethylallyl diphosphate, which are synthesized either through the mevalonate pathway or the methylerythritol phosphate (MEP) pathway. Humans exclusively use the mevalonate pathway. This is in contrast to a number of human pathogens (Chlamydia, malaria, toxoplasmosis) and biothreat agents (tularemia, plague, anthrax) that exclusively use the MEP pathway. Thus, MEP pathway enzymes are promising targets for the development of novel chemotherapeutics. This proposal focuses on the biochemical characterization of the first two enzymes of the MEP pathway from pathogens and uses high-throughput screening of chemical libraries to identify new chemical leads for development of broad-spectrum chemotherapeutics.

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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.

Robin Couch, Ph.D., George Mason University

Neuroprotection and Alzheimer's Disease: Mapping the Induction of Nerve Growth Factor

Project Summary: Alzheimer's Disease (AD) involves the progressive deterioration of cognitive and functional abilities, leading to the loss of bodily function and death. While the pathology of AD relates to the accumulation of plaques in the brain and the death of specific neurons, current therapeutics do little to slow the progress of neuronal decay. A radically different approach to the treatment/prevention of AD is known as neuroprotection, which involves the use of therapeutic agents such as nerve growth factor (NGF) to defend the neurons from death. While NGF itself is unable to penetrate the blood-brain barrier, a variety of small molecule inducers (SMIs) of endogenous NGF have been identified. However, knowledge relating to their mechanism of action is limited. To facilitate the rational development of neuroprotective drugs to treat/prevent AD, we will use reverse phase protein microarrays to identify the glial cell signal transduction pathways that become activated upon exposure to SMIs.

Alireza Hosseini, M.D., Eastern Virginia Medical School

Role of Nitric Oxide Synthase and Cytokines in the Development of Retinopathy of Prematurity

Project Summary: Retinopathy of prematurity (ROP) is an abnormal vascular development of the retina and a blinding disease of premature infants which is highly correlated with the requirement for prenatal oxygen therapy. Advances in neonatal care have increased the occurrence of ROP development which is directly related to gestational age and birth weight. Current therapies like cryotherapy, laser photocoagulation, and investigational injection of anti-angiogenic drugs into the eye, are invasive with limited efficacy and may cause severe side effects, including blindness. Although, neonatal oxygen treatment is highly correlated with the occurrence of ROP, the exact mechanism leading to ROP remains mostly unknown. This study will use new techniques and methodology to explore the possible role of oxygen in triggering cellular reactions which may have a role in pathogenesis of ROP. The results of this study may shed light into new and effective treatments for this devastating disease.

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Molly Hughes, M.D., Ph.D.
University of Virginia

Development of Novel Antimicrobial Agents for Multi-Drug Resistant Bacterial Pathogens

Project Summary: Since 1996, there has been a dramatic and alarming increase in the incidence of multi-drug resistant (MDR) Gram-negative bacteria, such as *Klebsiella pneumoniae*, causing human infections such as bloodstream infections and pneumonias. Multi-drug resistance among Gram-negative bacteria denotes resistance to three or more major classes of antibiotics. This increase in MDR Gram-negative bacteria has been recognized throughout the world and within the United States, including the Commonwealth of Virginia. Given the exceedingly few to no therapeutic options currently available, new strategies are urgently needed to fight these bacterial pathogens. We have been studying chemokines, which are proteins produced by cells of the human immune system in response to infections. Certain chemokines have demonstrated antibacterial activity against both Gram-negative bacteria (*Escherichia coli*) and Gram–positive bacteria (*Listeria monocytogenes*). Given our experience working with the chemokines, we propose to study and develop these chemokines as novel antimicrobial agents against MDR Gram-negative bacterial pathogens.

Kylene Kehn-Hall, Ph.D.
George Mason University

BTK induction by HIV: Implications for Therapeutics

Project Summary: HIV-1 is the cause of the Acquired Immunodeficiency Syndrome (AIDS), a destructive disease of the immune system. Worldwide estimates of individuals infected with HIV-1 are 40 million and increasing. The 2008 estimate indicated that there are over 20,000 people living with HIV/AIDS in Virginia. Breakthroughs in treatment have been able to delay the onset of AIDS. The existence of a latent reservoir means that the virus can never truly be eliminated. In addition, current therapies for HIV-1 (HAART) can promote resistant strains of the virus. Therefore, there is a critical need for new targets for HIV therapy, which will not develop resistance. Therapeutics targeted against non-essential host proteins hold great promise to limit resistance. Our research is aimed at understanding the therapeutic potential of targeting Bruton's Tyrosine Kinase (BTK) in HIV-1 infected cells. Studying BTK could potentially lead to new treatment options for HIV/AIDS.