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From the Commonwealth Health Research Board

The Commonwealth Health Research Board [CHRB] has awarded **$1,251,185** in grants to 13 medical and health researchers in Virginia.

Eastern Virginia Medical School
Principal Investigator: Frank Castora, Ph.D.
Grant Award: $100,000
Grant Title: *The role of differentially expressed mitochondrial energy production genes as regulators of amyloid precursor protein processing in Alzheimer's disease*
A second year of funding was awarded to support Dr. Castora and colleagues in continued study of certain abnormalities in gene expression in the brains of Alzheimer patients. The abnormally expressed genes are important for energy production and are also involved in the development of protein formations known as plaques that compromise brain cell function. An important aspect of this innovative project is the use of gene editing technology to identify targets for drugs that could delay the onset of Alzheimer's Disease and/or reduce its severity.

Virginia Polytechnic Institute and State University
Principal Investigator: Zhiyong Cheng, Ph.D.
Grant Award: $100,000
Grant Title: *An interdisciplinary approach to preventing obesity by targeting Fox01*
The obesity pandemic is a major concern in Virginia and across the nation. Dr. Cheng has shown that a protein called FoxO1 plays a critical role in the production of fat cells. He established in cellular studies that inhibition of FoxO1 activity can suppress fat cell formation, and now will extend that work to a mouse model. In addition, he plans to develop new ways to deliver the FoxO1 antagonists in vivo, using nanoparticles. This is exciting work on a promising target (FoxO1) with potentially great significance for human health.

Virginia Commonwealth University
Principal Investigator: Charles Clevenger, M.D., Ph.D.
Grant Award: $100,000
Grant Title: *HDAC6 as a Therapeutic Target in Breast Cancer*
Funding for the first year of a 2-year project was awarded to Dr. Clevenger to explore a new target for drugs to treat breast cancer. Breast cancer is a major health problem in the US. Over 1000 Virginia women die of breast cancer each year. The PI and his team have identified histone deacetylase, HDAC6, and discovered that it can remove acetyl groups from proteins and thereby act as a signaling switch. The PI and his team hypothesize that HDAC6 globally controls breast cancer gene expression and growth, by functioning as an "oncogenic node". Phase I trials in myeloma patients have shown that small molecular inhibitors of HDAC6 are safe and could be therapeutically used in breast cancer patients. The team will conduct *in vitro* studies using the advance technique of immunoprecipitation sequencing (ChIP-Seq) in breast cancer lines to identify the genome-wide relationships between HDAC6/HMGN2/H1.2 on promoter/enhancer chromatin both in terms of occupancy and co-localization. Also planned are translational *in vivo* studies in a mouse model of breast cancer.

Christopher Newport University
Principal Investigator: Kathryn Cole, Ph.D.
Grant Award: $52,369
Grant Title: ***Anticancer Drug Design: Structure and Function of New HDAC8-Depsipeptide Complexes***
Continued funding was awarded to Dr. Cole to further pursue studies on the action of two drugs already in use for the treatment of cancer. Dr. Cole and her team intend to increase the understanding of how the anti-cancer drugs, Spiruchostatin A and Xyzistatin, inhibit histone deacetylases. Histone deactylases are crucial enzymes involved in progression of many types of cancer. The team is currently engaged in molecular modeling and simulation with new analogues of the xyzistatin molecule. Dr. Cole's work may lead to new drugs for better cancer treatment.

Virginia Commonwealth University
Principal Investigator: Paul Dent, Ph.D.
Grant Award: $100,000
Grant Title: ***Novel Anti-Sarcoma Therapies***
Sarcomas, while relatively rare, are a heterogeneous group of tumors that are quite difficult to treat. The drug pazopanib is an approved therapeutic for sarcomas, and Dr. Dent has found that a class of drugs known as histone deacetylase inhibitors, including sodium valproate, increase the lethality of pazopanib in sarcoma cells. This CHRB project will use a mouse model of sarcoma tumor aimed at continuing studies of pazopanib and valproate, plus another FDA-approved inhibitor (crizotinib) to generate data that will ultimately support a Phase I clinical trial of the three-drug combination. Dr. Dent and his colleagues are productive and well-versed in the required techniques, so chances are high for success of this cutting edge basic research effort aimed at a devastating type of cancer.

Virginia Commonwealth University
Principal Investigator: Nicholas Farrell, Ph.D.
Grant Award: $100,000
Grant Title: ***Targeting Triple Negative Breast Cancer***
A second year of funding was awarded to support Dr. Farrell's continued efforts in addressing mortality associated with metastatic triple negative breast cancer. Subtypes of breast cancer are diagnosed based upon the presence or absence of three receptors: estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2). The most successful treatments for breast cancer target these receptors. If these receptors are not found in a breast cancer patient, the cancer is extremely hard to treat. Objectives for Dr. Farrell are preventing spread of the cancer tumor (metastasis) and limiting the primary tumor to a relatively localized site, thereby allowing for more effective intervention at that site. Following the hypothesis that platinum-containing drugs can be developed for their objectives, Dr. Farrell and his team are focusing on a particular drug in the class, BBR3464. This drug acts on multiple levels overcoming limitations of single-targeted drugs. It would represent a significant addition to therapy for triple negative breast cancer if new medicines are developed to simultaneously attack a range of targets. A cutting-edge aspect of this project is that the drugs sought also have the potential for personalized medicine based on genetic profiles of individual patients.

Virginia Commonwealth University
Principal Investigator: Babette Fuss, Ph.D.
Grant Award: $100,000
Grant Title: ***Regulation of myelin repair: the role of the actin cytoskeleton***
A second year of funding was awarded to Dr. Fuss for studies on stimulation of endogenous progenitor cells to develop therapies for diseases in which the central nervous system (CNS) myelin sheath is affected. The most prominent of such diseases is Multiple Sclerosis (MS), but myelin injury may also play an important role in a number of neuropsychiatric diseases. Investigations will focus on a conceptually novel molecular mechanism, namely the role of a calcium/calmodulin-dependent protein kinase IIß (CaMKIIß)-actin cytoskeleton axis, in regulating myelin repair in the CNS. Actin cytoskeleton regulatory mechanisms as part of the regulation of CNS remyelination are understudied despite known defects in such mechanisms in MS. The studies now focus on the role of Camk2b in remyelination. If successful, this project will identify novel therapeutic targets for stimulating CNS repair in MS and other conditions that involve injury to the myelin sheath.

University of Virginia
Principal Investigator: Pater Kasson, M.D., Ph.D.
Grant Award: $100,000
Grant Title: ***rapid identification of entry inhibitors and neutralizing antibodies for emerging viruses***
Zika virus infection is a critical public health problem. This proposal is for further development of a new microfluidic flow cell approach to discover antibodies and drugs that can inhibit the entry of Zika virus into cells (thus preventing infection); the improved technology should be adaptable to other viruses as well. Dr. Kasson is an expert in this area, and has already been involved in design and application of the assay to be used. His collaborators are excellent, innovation is high, and it is likely that valuable results will emerge.

University of Virginia
Principal Investigator: Li Jin, Ph.D.
Grant Award: $100,000
Grant Title: ***Could we treat acute back/leg pain with nanoparticle fullerene instead of steroid?***
Funding for the first year of a 2-year project was awarded to Dr. Jin to explore new molecules/drugs for treating low back pain. Intervertebral disc herniation is the most common cause of low back pain which, in turn, is a leading source of disability in adults. Fullerenes are forms of carbon having a large spheroidal molecule consisting of a hollow cage of atoms, of which buckminsterfullerene was the first known example. Some fullerenes, including C60, C70 and C80 have been shown to be antioxidants due to delocalization of the π-electrons over the carbon cage, which can readily react with free radicals and subsequently deliver a cascade of downstream possessions in numerous biomedical applications. The proposed research would characterize the anti-inflammatory effects of C80, a fullerene that the PI and his team has shown to have strong radical scavenging capability, anti-inflammatory effects and anti-oxidative effects. They plan to do in vitro and in vivo studies using C80 nanoparticles. If this approach is successful, it would point to fullerenes as possible new bases for anti-inflammatory drugs to treat low back pain and other chronic pain conditions.

Eastern Virginia Medical School
Principal Investigator: Albert Musto, M.D., Ph.D.
Grant Award: $100,000
Grant Title: ***Role of CD40L in Limbic Epilegtogenesis***
Funding for the first year of a 2-year proposal was awarded to Dr. Musto to pursue his hypotheses that certain inflammatory processes are central in the cause and development of temporal lobe epilepsy. There is no cure for temporal lobe epilepsy, also termed, limbic epilepsy. Temporal lobe epilepsy is the most common form of epilepsy in adults. Between 4 and 10 cases occur in every 1,000 people. Available medical treatments are not effective in controlling some limbic seizures. Early mortality and numerous related medical problems make temporal lobe epilepsy a major medical problem in the US. Numerous studies, including those of the Dr. Musto, suggest that inflammation via immune system activity contributes to LE. This proposal is based on the idea that temporal lobe epilepsy develops because immune processes alter neuronal connectivity in a region of the brain called the hippocampus. Evidence of modification of neuronal dendritic spines will be sought with special focus on the protein, CD40L, which is primarily expressed on activated immune cells, known as T cells. If successful, this project would move epilepsy research into considerations of inflammatory and immune processes and point to new therapeutic approaches.

Virginia Commonwealth University
Principal Investigator: Liya Qiao, Ph.D.
Grant Award: $100,000
Grant Title: *Role of TrkB.T1 in Bowel and Urinary Bladder Comorbidity*
This grant award will allow the investigator to explore a new neurological mechanism in the spinal cord which is, potentially, the cause for the sensation of bladder pain in patients suffering from irritable bowel syndrome. The association between bladder hypersensitivity and irritable bowel is observed in millions of patients, although the bladder is actually normal. The investigator will test whether specialized cells in the spinal cord (glial cells) are stimulated in episodes of irritable bowel and subsequently transmit pain signals to neighboring nerves, which culminates in registering them as bladder pain. The experiments will utilize sophisticated neurological and biochemical approaches. They may reveal new therapeutic targets for relieving patients from this comorbidity.

University of Virginia
Principal Investigator: Weibin Shi, Ph.D.
Grant Award: $100,000
Characterization of reticulocalbin 2 as a major gene contributing to atherosclerosis
A second year of funding was awarded to Dr. Shi and colleagues in support of their studies on atherosclerosis. Atherosclerosis is the primary cause of heart attack and stroke. Inflammatory responses initiated by oxidation of bad cholesterol (LDL) trapped in the arterial wall are a central feature of atherosclerosis. No effective medicines are available to stop the inflammatory process. Dr. Shi and the team have been using mouse strains in which a major locus for atherosclerosis has been identified on chromosome 9, Ath29. The hypothesis to be tested is that reticulocalbin 2 (Rcn2) is a gene that may contribute significantly to atherosclerosis. The PI and team have successfully constructed Rcn2 knockout mice. The next step is characterization of atherogenesis in endothelium-specific Rcn2 knockout mice. The importance of confirming Rcn2 as a major gene in atherosclerosis is that Rcn2 would be a good target for drug therapy in addressing the numerous cardiovascular consequences of atherosclerosis. Also, there is the possibility that Rcn2 can be used as a diagnostic biomarker. Successful completion of the project may reveal a novel therapeutic target for treatment of atherosclerosis.

Virginia Polytechnic Institute and State University
Principal Investigator: Daniel Slade, PhD.
Grant Award: $98,816
Grant Title: *Determining the Interplay between Human and Bacterial Proteins that drive the Onset and Progression of Colorectal Cancer*
One year of research support at $98,816 was granted to Dr. Slade to explore the causative relationship between a commonly found bacterial protein and colorectal cancer. According to 2017 statistics, colorectal cancer (CRC) is the second leading cause of cancer deaths among both men and women in the United States with more than 3000 cases in Virginia. Studies show that the common Gram-negative, oral bacterium, Fusobacterium nucleatum is overrepresented among all the bacteria linked to colorectal cancer tumors. Introducing F. nucleatum by injection or through feeding induces intestinal tumor formation and lowers the potency of chemotherapeutic drugs. More information is needed about the molecular mechanisms driving tumor formation and resistance to therapy. Using a diverse set of biological tools developed in Dr. Slade's laboratory, studies will be undertaken to identify and analyze how the molecular interplay between F. nucleatum and human proteins drives cellular invasion and cancer. By addressing how this bacterium induces tumor formation and chemoresistance, the applicants believe that the proposed studies have the potential to uncover novel strategies for treating and preventing CRC.

The Commonwealth Health Research Board (CHRB) was created by Virginia Code §32.1-162.23 to provide financial support, in the form of grants, donations, or other assistance, for research efforts that have the potential of maximizing human health benefits for the citizens of the Commonwealth. Research efforts eligible for support by the Board include traditional medical and biomedical research relating to the causes and cures of diseases as well as research related to health services and the delivery of health care. Since its inception in 1999, the CHRB has funded 215 research grants totaling almost **$17.8 million**.

The CHRB encourages collaborative research efforts among two or more institutions or organizations, gives priority to those research efforts where Board support can be leveraged to foster contributions from federal agencies or other entities, and supports both new research efforts and the expansion or continuation of existing research efforts. CHRB grant recipients - for grant awards life-to-date - have leveraged over **$35 million** in additional private and federal grant funds to further their research studies.