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Frank Castora, Ph.D., Eastern Virginia Medical School
The role of differentially expressed mitochondrial energy production genes as regulators of amyloid precursor protein processing in Alzheimer's disease

Project Summary: Alzheimer's Disease (AD) is the most common form of dementia in the elderly and within 10 years the number of Virginians with AD will climb to 160,000. Mitochondrial dysfunction is a critical component in the pathogenesis of AD where deficits in oxidative capacity and energy production have been reported. We have recently found abnormal expression of a number of genes critical to mitochondrial biogenesis and energy production in AD brains. These genes are involved in proteosomal degradation and aggregation of Aß peptides and senile plaques, hallmark features of AD. Using biochemical systems theory (BST), we have constructed a testable mathematical model for AD. We will confirm the role of these mitochondrial proteins in Aß aggregation and AD pathogenesis using CRISPR/Cas9 gene editing technology, with the goal of identifying new targets for therapeutic interventions designed to delay or modulate the onset of AD.

Zhiyong Cheng, Ph.D., Virginia Polytechnic Institute and State University
An interdisciplinary approach to preventing obesity by targeting Fox01

Project Summary: Obesity is one of the most pressing health issues in the US, and it increases the risks of cancer, type 2 diabetes and cardiovascular diseases. Virginia has 28.5% adults that are obese, associated with 9.7% diabetic population and 32.5% adult hypertension, and it leads to a healthcare cost of $1.6 billion per year. To discover novel and effective treatments for obesity and its comorbidities is of critical importance. In this project, we propose to target the FoxO1-autophagy axis to boost energy expenditure and prevent obesity, using an interdisciplinary approach that combines genetic modulation and nanomedicine, and contrasts innovative nano-carrier with the traditional method of drug administration. This project takes advantage of the unique resources at Virginia Tech and Virginia Commonwealth University through cross-institutional collaboration. Success of this project may discover new therapeutic or preventive options for obesity.

Charles Clevenger, M.D., Ph.D., Virginia Commonwealth University
HDAC6 as a Therapeutic Target in Breast Cancer

Project Summary: We recently identified a growth regulatory role in breast cancer for the histone deacetylase, HDAC6. HDAC6 functions as a "signaling switch" for cancer by removing acetyl groups from proteins. We discovered that HDAC6, acting through the complex of HGMN2/H1.2/Stat5, regulates the growth and progression of breast cancer. Through these actions, we hypothesize that HDAC6 is controlling breast cancer gene expression and growth at a global level, functioning as an "oncogenic node". These findings are significant in that small molecular inhibitors of HDAC6, have proven safety in Phase I trials (in myeloma patients), and therefore can be rapidly translated to breast cancer patients. To test our hypotheses, we propose two specific aims to assess the nuclear function of HDAC6 in breast cancer:
Aim #1. **To assess HDAC6 regulation of global gene expression in breast cancer.**
Aim #2. **To translate the therapeutic potential of HDAC6 inhibition into mouse models of mammary cancer.**

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Kathryn Cole, Ph.D., Christopher Newport University

Anticancer Drug Design: Structure and Function of New HDAC8-Depsipeptide Complexes

Project Summary: Histone deacetylases (HDACs) play a critical role in the regulation of many biological processes, including cell differentiation, proliferation, senescence, and apoptosis. Aberrant HDAC activity has been implicated in a number of diseases, most notably cancer, making these enzymes validated targets for drug design. Indeed, four HDAC inhibitors (HDACi) have been FDA approved for the treatment of cancer. Depsipeptides are a new class of HDACi. These molecules bind to the catalytic zinc ion and make extensive binding interactions with the mouth of the enzyme active site, making them the most potent HDACi known to date. Spiruchostatin A and its synthetic derivative, Xyzistatin, are both analogs of one of the FDA approved HDACi. The research proposed herein investigates HDAC8 inhibition by Spiruchostatin A and Xyzistatin. We propose to measure HDAC8 inhibition and determine the structures of the HDAC8-inhibitor complexes to elucidate specific binding interactions and to develop more potent, second generation inhibitors.

Paul Dent, Ph.D., Virginia Commonwealth University

Novel anti-sarcoma therapies

Project Summary: Votrient (pazopanib) is approved for the treatment of sarcoma. We discovered that the seizure medication Depakote (sodium valproate) synergized with pazopanib to kill sarcoma cells on a plastic dish and when the cells were growing as a tumor. Cells that had been exposed to [pazopanib + valproate] had evolved and activated an enzyme called c-MET, which on a plastic dish made the cells chemotherapy resistant. **Aim 1. Determine whether inhibition of c-MET promotes [pazopanib + valproate] lethality against sarcoma tumors.** Treatment of sarcoma cells with valproate and more so [pazopanib + valproate] rapidly reduced the levels of proteins called PD-L1, IDO-1 and ODC that block anti-tumor immune responses, and increased levels of the class I MHC protein MHCA, which enhances anti-tumor immune responses. **Aim 2. Determine using mouse sarcoma tumors the impact of [pazopanib + valproate] has on the anti-tumor response of anti-PD-1 and of anti-CTLA4 checkpoint inhibitor immunotherapies**.

Nicholas Farrell, Ph.D., Virginia Commonwealth University

Targeting Triple Negative Breast Cancer

Project Summary: This proposal aims to meet the overarching challenge of eliminating the mortality associated with metastatic triple negative breast cancer. This achievement will also meet the secondary overarching challenge to revolutionize treatment regimens by developing safe and effective interventions. A major goal of cancer research is to prevent metastasis and limit the primary tumor to a relatively localized site, allowing for more effective intervention at that site. The effectiveness of chemotherapy is limited by metastasis when the tumor spreads away from the primary site of occurrence, sometimes years later. The new treatment conceptualized is based on drugs that can act on multiple levels overcoming limitations of as single-targeted drugs. Development of new medicines which may simultaneously attack a range of targets, and with potential for personalized medicine based on genetic profile, would represent a significant addition to the anti-cancer armamentarium as adjuvant therapy in triple negative breast cancer.

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Babette Fuss, Ph.D., Virginia Commonwealth University
Regulation of myelin repair: the role of the actin cytoskeleton

Project Summary: Stimulation of endogenous progenitor cells represents a promising but yet unavailable therapeutic strategy 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. Our studies proposed here investigate 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. These studies are pioneering in the sense that actin cytoskeleton regulatory mechanisms as part of the regulation of CNS remyelination are a highly understudied area, despite known defects in such mechanisms in MS. In the long-term, we anticipate these studies to lead to the identification of novel therapeutic targets for stimulating CNS repair under pathologic conditions that involve injury to the myelin sheath.

Peter Kasson, M.D., Ph.D., University of Virginia
Rapid identification of entry inhibitors and neutralizing antibodies for emerging viruses

Project Summary: Zika virus is an emerging health threat in the Americas, causing a febrile illness with severe neurological after-effects and birth defects. Virginia has mosquitos capable of transmitting Zika and similar viruses and had over 100 cases of Zika in 2016. Early evidence suggests that some antibodies to Zika can be protective while others may actually increase the severity of infection. This proposal develops a means to discover antibodies and drugs that inhibit Zika entry in a fashion that is readily adaptable to other emerging viruses. We will accomplish this via an assay using fluorescence microscopy in microfluidic flow cells to measure viral entry. This capability will help bolster the public health defense in Virginia and elsewhere against emerging viruses by allowing rapid testing of potential antibodies and antiviral drugs.

Li Jin., Ph.D., University of Virginia
Could we treat acute back/leg pain with nanoparticle fullerene instead of steroid?

Project Summary: Low back/leg pain is the single leading cause of disability worldwide. The use of fluoroscopy-guided lumbar epidural injections of steroids to reduce local inflammatory response induced by disc herniation has increased dramatically. However, side effects of epidural steroid injection have been reported widely. Nanoparticle C80 has potent anti-inflammatory and anti-oxidative stress effects. We hypothesized that local administration of C80 relieves the back/leg pain and retard disc degeneration. Due to the long-lasting activity of C80 and its excellent cell membrane-penetrating abilities, we anticipate that nanoparticles C80 replace steroids for acute back/leg pain. The proposed three-aim study will delineate the beneficial effects of C80 on back/leg pain both *in vitro* and *in vivo*. The preliminary work strongly suggests that predicted outcomes are highly feasible. The success of this proposal is ensured by a strong multidisciplinary collaboration among Drs. Jin (biologist, UVA), Dorn (nanofullerene expert, VT) and Li (a spine surgeon, UVA).

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Alberto Musto, M.D., Ph.D., Eastern Virginia Medical School
Role of CD40L in Limbic Epileptogenesis

Project Summary: Temporal lobe epilepsy (TLE) or limbic epilepsy, the most common forms of epilepsy in adults, has no cure or effective treatment in a subset of patients. CD40 ligand (CD40L), small protein involved in immune and inflammatory process is upregulated after seizures. The overall objective is to define if CD40L interaction with its receptor CD40 participates in an aberrant neuronal circuitry organization during development of epilepsy or epileptogenesis. Therefore, blocking CD40L-CD40 interaction should limit seizures and neuronal damage, improving survival rate and prevent TLE.

Liya Qiao, Ph.D., Virginia Commonwealth University
Role of TrB.T1 in Bowel and Urinary Bladder Comorbidity

Project Summary: The pain-sensing neurons in the sensory ganglia are surrounded by satellite glial cells (SGCs) and in the spinal cord by astrocytes, which form glial networks, and receive and pass pain signals from one type of neurons (e.g. those that sense pain of the colon) to another (e.g. those that sense pain of the urinary bladder), causing comorbidity of the bowel and the urinary bladder. TrkB.T1 is the sole high affinity receptor in SGCs and astrocytes for brain-derived neurotrophic factor (BDNF), a critical pain-related molecule in the occurrence of bowel and urinary bladder comorbidity. However, deletion of BDNF is lethal and cannot be used as an intervention target. We aim to use various novel genetic tools to provide evidence that TrkB.T1 is involved in bowel and urinary bladder comorbidity (Aim 1), and TrkB.T1 is a safe and unique therapeutic target in treatment of bowel and urinary bladder comorbidity (Aim 2).

Weibin Shi, Ph.D., University of Virginia
Characterization of reticulocalbin 2 as a major gene contributing to atherosclerosis

Project Summary: Atherosclerosis is the primary cause of heart attack and stroke. Inflammatory responses initiated by oxidation of LDL (bad cholesterol) trapped in the arterial wall are a central feature of atherosclerosis, but no effective medicines are available to intervene the inflammatory process due to lack of appropriate targets. Using mouse strains, we identified a major locus, Ath29, on chromosome 9 for atherosclerosis. Combined genetic and genome-wide gene expression analysis pinned Rcn2 down as a promising candidate for Ath29. RNA interference uncovered a crucial role for Rcn2 in both basal and oxidized lipid-induced inflammatory gene production in arterial wall cells. **Objective:** Test the hypothesis that Rcn2 is a major gene contributing to atherosclerosis. **Approach:** We will make and characterize arterial cell-specific knockout mice to define the role of Rcn2 in atherosclerosis and arterial inflammatory responses. **Impact:** Successful completion of this aim may derive a novel therapeutic target for treatment of atherosclerosis.

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Daniel Slade, Ph.D., Virginia Polytechnic Institute and State University

Determining the Interplay between Human and Bacterial Proteins that drive the Onset and Progression of Colorectal Cancer

Project Summary: Colorectal cancer (CRC) is the leading cause of cancer death among both men and women in the United States. In Virginia alone, more than 3000 cases per year are reported with an annual cost > $180 million. It was recently discovered that the Gram-negative, oral bacterium *Fusobacterium nucleatum* induces intestinal tumor formation, and the presence of *F. nucleatum* lowers the potency of the chemotherapeutic drugs during the treatment of CRC. While these findings provide evidence for a significant role for this bacterium in the onset and progression of disease, we know very little about the proteins and molecular mechanisms driving these pathologies. By addressing how this bacterium induces tumor formation and chemoresistance, this proposal has the potential to uncover novel strategies for treating and preventing CRC.