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Farrokh Alemi, Ph.D., George Mason University
Optimizing Antidepressant Selection through Artificial Intelligence

Project Summary: The long term goal of this study is to improve management of depressed patients in primary care. Robert Wood Johnson Foundation has funded the principal investigator to analyze outcomes for depressed patients taking antidepressant. The foundation has funded the analysis of data on 115 million lives, at QualLabs, under the supervision of Alemi. No funds are available for activities at the university. The current request will supplement the existing foundation-funded effort and enable the creation of the first Artificial Intelligence decision aid for prescription of antidepressants. The aid is composed of two parts: (1) an emphatic, conversational interview to assess the patient's medical history and (2) a report to the patient and the patient's clinician of the antidepressant most likely to benefit the patient.

Bahareh Behkam, Ph.D., Virginia Polytechnic Institute and State University
Mechanobiology of Implant Infection: Effect of Surface Roughness on the Attachment Density and Phenotype of Adherent Staphylococcus aureus

Project Summary: The increasing demand for orthopedic implants in our aging society, coupled with a dramatic increase in the emergence of antibiotic-resistant bacterial strains has made implant infection control progressively challenging and costly. Bacterial adhesion and biofilm formation on implants play important roles in infection and treatment resistance. It has been demonstrated by us and others that nanoscale surface features significantly affect microbial adhesion and viability; however, the physical and biological underpinnings of microbe-nanostructure interactions remain largely unknown. We propose to nanofabricate topographical features of well-defined sizes and spacing on titanium implants and investigate the effect of the nanostructures on the attachment density and biological activity of Staphylococcus aureus, the most common etiological agent for orthopedic infections. Through understanding the mechanisms by which the physical properties of engineered surfaces regulate adherent bacteria behavior, this proposal has the potential to uncover novel non-toxic antimicrobial strategies for mitigating medical implant infection.

Matthew Buczynski, Ph.D., Virginia Polytechnic Institute and State University
Evaluation of a 12/15-LM receptor as a target for Non-Opioid Pain Therapeutics

Project Summary: The opioid crisis has reached epidemic proportions in the United States, and in 2016 Governor McAuliffe declared opioid addiction in the Commonwealth as a Public Health Emergency [1]. Rural western VA (where Virginia Tech is located) reports some of the highest per capita opioid abuse in the country. Thus, non-opioid therapeutic alternatives to NSAIDs (Nonsteroidal Anti-inflammatory Drugs, e.g. ibuprofen) for the effective management of chronic pain are essential to limiting opioid overuse. Our published studies identified a novel class of signals (12/15-lipoxygenase metabolites, 12/15-LMs) that contribute directly to (NSAID)-insensitive nociceptive behaviors in multiple pre-clinical pain models, and our preliminary results identified a novel receptor for 12/15-LMs. In this proposal, we plan to characterize the 12/15-LM receptor, and screen potential lead compounds that block receptor activity. Ultimately, our goal is to enable drug discovery efforts for novel analgesics with minimal abuse potential and mitigate risks of opiate misuse, diversion and addiction.

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Paul Fisher, MPhil, Ph.D., Virginia Commonwealth University
Rational Design of Cancer Invasion and Metastasis Inhibitors

Project Summary: Approximately 90% of patient deaths from solid cancers result from metastasis. Melanoma differentiation associated gene-9 (*mda-9*) is a key genomic element in diverse cancers that controls invasion and metastasis. We developed a first generation novel pharmacological inhibitor of MDA-9, PDZ1i that profoundly suppresses cancer cell spread, invasion and metastasis in a broad-spectrum of human cancers in preclinical animal models. Our central goal, is to develop effective pharmacological *in vivo* inhibitors of cancer migration/invasion/metastasis. We will apply rationally-designed medicinal chemistry approaches to produce the next generation PDZ1i (NG-PDZ1i) and PDZ2i with further enhanced anti-metastatic properties. To ensure achieving this endpoint we will use two innovative strategies we have developed, i.e., semi-high throughput screening assays in zebrafish and invasion assays using cultured mammalian tumor cells. Developing NG-PDZ1i and PDZ2i will provide significant societal health benefits and enhance the economy of VA through growth of a biotechnology company, InVaMet Therapeutics.

Brent French, Ph.D., University of Virginia
Bioengineering of Cardiac Regeneration In Situ after Myocardial Infarction

Project Summary: Heart failure currently afflicts some 5.7 million Americans, and by 2030 this number will increase by 46%. The single most common cause of heart failure is heart attack (or myocardial infarction) which results in the irreversible loss of cardiac muscle. Current statistics show that ~790,000 people in the US have heart attacks each year. Of those, about 114,000 will ultimately die from heart failure. The overarching goal of this project is to combine recent advances in cardiology, radiology and gene therapy to demonstrate that cardiomyocytes can be genetically-reprogrammed to divide and replace the heart muscle lost during heart attack. This is important because the adult heart has essentially no capacity to repair itself after a heart attack. Instead, injured cardiomyocytes are replaced by scar tissue to prevent the heart from rupturing. If successful, this research will show that gene therapy can regenerate muscle tissue after heart attack instead of scar.

Aurora Esquela Kerscher, Ph.D., Eastern Virginia Medical School
Molecular dissection of a microRNA cluster network of aggressiveness

Project Summary: Prostate cancer (PCa) is the most prevalent form of cancer in Virginian males. Our state's PCa mortality rate is ranked 8th in the nation. This proposal will develop more effective theranostic tools for this disease, focusing on the microRNA (miRNA) class of small noncoding RNAs. MiRNA dysregulation is a common feature of PCa but little is known how they functionally interact as a cancer network to promote disease progression. We will investigate this problem by studying the miR-888 cluster, which consists of seven miRNA genes mapping close together on human chromosome X within a hereditary PCa locus. We found that the miR-888 cluster is elevated in patients with aggressive PCa and induces proliferation, invasion, and tumor formation. Our integrated translational research team (EVMS, University of Virginia) will use high throughput CRISPR gene editing, proteomics, nanostring technology and antimiR reagents to molecularly dissect the miR-888 cluster and validate its clinical potential.

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Kyle Lampe, Ph.D., University of Virginia
Self-assembling, shear-tinning peptide hydrogels to support cell transplantation and host cell interaction after ischemic stroke

Project Summary: Stroke is the third leading cause of death in the US and 20% of stroke survivors are so significantly disabled that they cannot walk without help. Despite broad research, stroke and other disorders of the brain and spinal cord continue to be the leading cause of disability nationwide. No treatment exists to rebuild neural tissue destroyed by ischemic stroke and the subsequent cell death. We propose a new engineered biogel to transplant neural stem cells (NSCs), and encourage growth of host NSCs and vascular cells into the infarct site. These materials are designed to be injectable and cell compatible, and thus may improve NSC transplantation survival. Establishing this collaboration will support future development, especially early insight to biogel interventions in a rat model of ischemic stroke. The aims will provide important materials development and characterization and pre-clinical data toward supporting cell growth and decreasing or reversing stroke-induced brain damage.

James Landers, Ph.D., University of Virginia
Diagnostic Assay for On-Site Detection of Bordatella pertussis

Project Summary: *Bordetella pertussis*, the causative agent of whooping cough, infects millions of individuals worldwide each year and continues to be the world's leading cause of vaccine preventable deaths. In recent decades, there has been an alarming resurgence of reported pertussis cases. A major step to address this problem is for *B. pertussis* to be detected rapidly during a suspected outbreak, enabling initiation of treatment, limitation of transmission and reduction in mortality. However, current methods require patient samples to be sent to centralized laboratories for analysis and results are typically not available in time to support epidemiologic intervention. Instead, physicians and healthcare officials use presumptive antibiotic treatment until diagnostic results are available, thereby putting many individuals at risk unnecessarily. To address this challenge, we are developing a portable microfluidic device, "lab-on-a-CD", to screen for the presence of *B. pertussis* DNA and allow for robust identification of infection in 20 min or less.

Nagaraja Nagre, Ph.D., Eastern Virginia Medical School
Exploring the potential role of cannabinoid receptor type-2 activation in protection against bacterial pneumonia-induced lung injury

Project Summary: Bacterial pneumonia is a major risk factor for developing acute lung injury (ALI). Although mechanical ventilation remains the last resort of treatment, it carries risks of lung cell injury, high mortality, and morbidities. *Pseudomonas aeruginosa* is an opportunistic pathogen causing a wide range of acute and chronic infections and is a major cause for Ventilator-Associated Pneumonia (VAP). The ineffectiveness of conventional antibiotics therapy among severe pneumonia-induced lung injury patients appeals for novel options of treatment. One such candidate is Cannabinoid receptor-2 (CB2R) that is predominantly expressed in immune cells. Synthetic agonists like endocannabinoids (that do not generate undesired psychotic effects) can be used to activate these CB2Rs leading to the display of anti-inflammatory functions. Considering the unique stance of CB2R as a potential novel therapy for bacterial pneumonia, the hypothesis that CB2R activation can ameliorates bacterial pneumonia induced lung inflammatory/injury (using a well-validated mouse model) will be tested in this project.

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Swati Palit Deb, Ph.D., Virginia Commonwealth University
Targeting mutant p53-dependent checkpoints of genome duplication in lung cancer

Project Summary: The American Cancer Society estimated number of new lung cancer cases this year alone is 234,030 in the US, and 5,860 in Virginia, of which at least 60% of patients will not survive, suggesting extremely poor efficacy of current lung cancer treatment. Gain-of-function (GOF) mutations of tumor suppressor p53 are very frequent (up to 70%) in lung cancer and establish resistance to chemo- or radiotherapy and are essential for oncogenesis. Accordingly, the tumorigenic ability of human lung cancer cells lines is drastically reduced or eliminated when endogenous mutant p53 is disabled. **In a recently published study (highlighted by the Journal of Clinical Investigation),** we demonstrated that GOFp53 activates checkpoint signaling to establish its oncogenic activities**.** Here we propose to determine the mechanism by which GOFp53 activates checkpoint signaling to establish dependency in lung cancer cells and evaluate the therapeutic efficacy of GOFp53-induced checkpoint signaling inhibitors, which has not been explored.

Bhaumik Patel, M.D., McGuire Research Institute
Development of a Selective Non-Saccharide Glycosaminoglycan Mimetic for Colon Cancer

Project Summary Complete cure of cancer is never achieved for most advanced colorectal cancer, in part, due to the inability of the standard chemotherapy and other targeted drugs in eradicating the 'seeds of cancer', also called cancer stem cells (CSCs). We have demonstrated, for the first time that specific short sequence of heparin (HSO6) selectively eliminates CSCs. But, HSO6 cannot be a candidate drug as it is very difficult and expensive to purify it. However, we have succeeded in synthesizing a non-sugar mimetic of HSO6 – G2.2 which is easy to make, homogenous, and rather inexpensive. Using primary human CSCs, innovative animal models, and advanced in vitro methods to study stem cells, we will determine the efficacy and toxicity of G2.2 as well as its potent analogs against colon CSCs in conjunction with FDA approved colon cancer therapies. This, in our opinion, is a major step towards achieving complete cancer cure.

Alicia Pickrell, Ph.D., Virginia Polytechnic Institute and State University
STING-Dependent Type 1 Interferon Response in TBI

Project Summary: Traumatic brain injury (TBI) is the most commonly acquired central nervous system (CNS) injury affecting both civilian and military populations in the United States. This highly complex, heterogeneous epidemic results in excessive morbidity and long-term disability for an estimated 5.3 million Americans with an annual economic cost of $37.8 billion. In Virginia (VA), over 2% of the population suffer from disabilities related to TBI, and an estimated 28,000 Virginians sustain a TBI annually. Inflammation in the brain after the mechanical insult contributes to neurodegeneration affecting functional outcomes for patients. In our published and preliminary data, we profiled a novel immune response in a preclinical mouse model of TBI. TBI-injured mice showed an abnormal upregulation of Type I interferons. In this proposal, we plan to characterize this novel interferon pathway after TBI to decipher whether targeting interferon signaling therapeutically reduces inflammation and neurodegeneration in the brain after injury.

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Jason Reed, Ph.D., Virginia Commonwealth University
A new approach for detecting IGH translocations in hematologic malignancies

Project Summary: Blood cancer represents a large group of different malignancies and represents roughly 10% of all cancers diagnosed in the United States each year. The complexity and implications for treatment, of blood cancer diagnosis create a critical need for molecular methods which can be applied in less specialized medical settings such as community hospitals. To address this need, we will employ very simple 'DNA barcoding' approach to detect chromosome rearrangements in blood cancers. This method will be as accurate, but much quicker and substantially less costly than, all existing alternatives. This technology can significantly improve outcomes for patients in underserved populations.

Steven Shell, Ph.D., University of Virginia's College at Wise
Mass Spectrometry Analysis of the Human XPA-XPC Complex

Project Summary: Many chemotherapeutics work by inducing DNA damage in cancer cells. Therefore, understanding the molecular mechanisms of DNA repair is vital to pharmaceutical development. One such process is the Nucleotide Excision Repair pathway. NER relies on a series of protein-protein complexes to repair DNA. Two proteins, XPC and XPA, act early in the human NER pathway. We hypothesize that XPA forms a direct physical complex with XPC necessary for establishing an efficient NER response. We propose using mass spectrometry footprinting to identify the molecular surfaces on each protein responsible for mediating the interaction. Chemical labeling will be used to identify all surface-exposed lysine residues on each protein and the protein complex. Residues protected from modification in the complex will be mapped onto structural models for each protein. Computational docking will be used to create a model of the complex. These results will provide targets for future functional studies in human cells.

Martin Wu, Ph.D., University of Virginia
Are persister cells culprits of recurrent Clostridium difficile infections?

Project Summary: *Clostridium difficile* infection (CDI) causes mild to life-threatening diarrhea. It poses a major healthcare burden to the global population primarily affecting individuals treated with antibiotics. The biggest challenge facing CDI is the high rate of treatment failure or recurrence, which has increased remarkably in the past two decades. Persister cells (dormant or slow-growing bacteria) are known to survive antibiotic treatment. However, whether they are a major cause of recurrent CDI remains unclear. We hypothesize that persister cells play an important role in recurrent CDI. Specifically, we aim to 1) determine whether the presence and abundance of persister cells are significant risk factors for CDI recurrence, 2) determine the genetic basis of persistence by sequencing genomes of the persister cells. This study will be the first to quantitatively determine whether persister cells are significant risk factors for recurrent CDI and therefore has the potential to shift the paradigm in therapeutic strategies.

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Chongzhi Zang, Ph.D., University of Virginia
Aberrant CTCF binding as an epigenetic signature of cancer

Project Summary: CTCF is a protein that can function as a chromatin insulator and facilitates chromatin looping. Disruption of individual CTCF binding sites in the human genome have been reported in several cancers that associate with altered chromatin structure and dysregulation of genes in the chromatin domains. Our preliminary studies show that cancer-specific CTCF binding events are common in many cancers, and the level of aberrant CTCF binding in each cancer type is correlated with clinical outcome. We hypothesize that CTCF binding aberration is an epigenetic signature of cancer. In this project, we propose to use novel integrative computational genomics approaches to systematically characterize aberrant CTCF binding events in the genome in several human cancer systems and their function in gene regulation.