2020-21 Research Fellowship Grants and Young Clinician Investigator Awards

Ahmad Alhourani, MD
University of Louisville

Award: Academy of Neurological Surgeons 2020-21 Research Fellowship Grant
Project Title: Dissecting the role of the subthalamic nucleus in inhibitory control

Inhibitory control is a critical element of human cognition, making it possible to suppress or prevent undesired behaviors. Inhibitory control deficits are a core feature of neurodegenerative (e.g., Parkinson's disease, Huntington's disease) and neuropsychiatric diseases that generate tremendous economic burdens and disrupt quality of life.

The Subthalamic nucleus, a key node in the cortical-striatal circuitry that is involved in inhibitory control, is thought to delay or stop an unwanted motor plan. However, the precise cortical mechanisms and timing characteristics that drive the STN inhibitory signals remain unclear. Understanding how these pathways differentially contribute to inhibitory control is crucial for guiding emerging neuromodulatory therapies for neurodegenerative and neuropsychiatric diseases. An emerging hypothesis posits that Prefrontal Cortex (PFC) activity modulates STN activity to generate early global inhibitory signal to halt all ongoing action plans to afford more time to respond followed by a more targeted inhibitory signal projecting to the basal ganglia to selectively suppress the conflicting action impulse

We employ simultaneous recordings from the PFC, striatum, and STN from movement disorder patients undergoing deep brain stimulation while performing cognitive tasks to determine the temporal and spatial characteristics of inhibitory control signaling using connectivity analysis and event-based stimulation.

Mohammed Alshareef, MD
Medical University of South Carolina

Award: AANS/CNS Section on Pediatric Neurological Surgery & NREF 2020-21 Research Fellowship Grant
Project Title: The Role of Complement in Secondary Injury after Neonatal Germinal Matrix Hemorrhage

Germinal matrix hemorrhage (GMH) is a disease of infancy that results in sudden bleeding within vital brain regions. This process often times occurs in neonates born prematurely. Ultimately, GMH results in persistent inflammation that can lead to hydrocephalus and scarring of the brain tissue, known as periventricular leukomalacia (PVL). There are currently no treatments for this disease process.

The current research focuses on the effect of the complement system on the inflammatory process that follows GMH. We build upon research performed in traumatic brain injury and stroke, in which complement activation is known to propagate the deleterious effects of inflammation. Thus, we have developed a unique GMH mouse model that mimics the disease process in humans. We utilize a unique drug developed in our lab, CR2-Crry, to inhibit the complement system at the site of injury. We expect to find a significant reduction in inflammation, hydrocephalus, and PVL in mice treated with the complement inhibitor. We also anticipate a significant improvement in cognitive outcomes following treatment.

This is a highly translatable study with a large potential for further clinical investigation of neonatal GMH using a novel targeted complement inhibitor.

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Matei A. Banu, MD
Columbia University

Award: AANS/CNS Section on Tumors & NREF 2020-21 Research Fellowship Grant
Project Title: Leveraging metabolic vulnerabilities of cell populations in the glioma microenvironment to trigger ferroptotic cell death and immune response in GBM

Glioblastoma (GBM), the most common brain tumor, remains universally fatal. Standard chemotherapy and radiation provide a minimal survival benefit. Novel treatment strategies, such as targeted therapies and immunotherapy have also had disappointing results. Complex cellular architecture and constant changes in molecular wiring pose a seemingly insurmountable challenge for effective treatment in GBM.

Here, we propose a different treatment paradigm: combination therapies targeting specific vulnerabilities in distinct tumor cell populations. We have identified two major tumor cell populations in the GBM microenvironment, each with its own therapeutic "Achilles' heel". A major subset of tumor cells resembles early progenitors, building blocks of the brain with rapid growth, susceptible to standard chemotherapy agents. A second population of tumor cells hiding at the tumor margins resembles astrocytes, slow growing supportive cells in the brain and therefore highly resistant to chemotherapy or radiation. These dormant astrocyte-like tumor cells, putative culprits of tumor recurrence, rely on a fat-based rather than a sugar-based diet. Notably, non-tumor cells suppressing the immune response in GBM appear to follow a similar fat-based diet.

We propose therapeutically leveraging this vulnerability by blocking the mechanisms that protect astrocytes from self destruction through lipid peroxides, a dangerous byproduct of fat metabolism. To this end, we will use a class of drugs designed by our collaborators to induce a novel form of lipid peroxide and iron-based cell death, termed ferroptosis. Furthermore, by disrupting the chatter between the astrocyte-like tumor cells and immune suppressive cells, we hope to induce a cytokine storm in the immune cold GBM environment, triggering an effective immune response with long lasting effects.

Therefore, in this study, we will test a novel therapeutic strategy in GBM, combining chemotherapy to target rapidly proliferating tumor cells with ferroptosis drugs to target dormant tumor cells as well as immunosuppressive cells.

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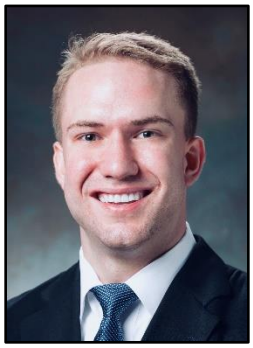
Jacob F. Baranoski, MD, MHS
St. Joseph's Hospital/Barrow



Award: L. Nelson "Nick" Hopkins/NREF 2020-21 Research Fellowship Grant jointly sponsored by Arvind Ahuja, MD, FAANS, and the AANS/CNS Cerebrovascular Section
Project Title: Effects of dietary phytoestrogens on aneurysm wall inflammation and rates of aneurysmal rupture

Up to 7% of people have an intracranial aneurysm and 30,000 patients suffer a hemorrhage due to a ruptured aneurysm annually in the U.S. Therefore, the discovery of pharmacologic treatments that can protect against aneurysm formation or decrease the risk of aneurysm rupture is of considerable interest. Recently, estrogen supplementation has been shown to decrease the risk of aneurysm formation and subsequent rupture in a mouse model. This is of particular clinical significance, as post-menopausal women are at an increased risk for aneurysm rupture. Unfortunately, systemic estrogen hormone replacement is associated with adverse clinical outcomes primarily due to its off-target effects and is therefore not a clinically feasible strategy for protection against aneurysm rupture. We need a pharmacologic therapy that can selectively target the aneurysm without the systemic side effects.

We are increasingly learning about the influence that dietary intake and the gut microbiome have on inflammation and disease states. We know that inflammation within the blood vessel wall plays a role in aneurysm formation and rupture. The goal of this project is to determine if a specific plant-based, diet-derived compound called equol can decrease the rate of aneurysm formation and subsequent rupture while limiting off target side effects. Equol is a compound that is similar to estrogen but importantly has tissue and receptor specificity. We hypothesize that supplementation with equol will decrease the incidence of aneurysm formation and rupture by limiting the amount of inflammation within the arterial wall.

Stanley Bazarek, MD, PhD
Brigham & Women's Hospital / Massachusetts General Hospital / Harvard University

Award: NREF/Medtronic 2020-2021 Research Fellowship Grant
Project Title: Transplantation of Human Induced Pluripotent Stem Cell-Derived Spinal Motor Neurons to Restore Function following Peripheral Nerve or Spinal Cord Injury

Motor function may be lost following traumatic injury to the spinal cord or peripheral nerves. Nerve transfers sacrifice a functional nerve under voluntary control to restore a more critical function and has emerged as a successful surgical intervention to restore upper extremity function. Nerve transfers are often time-dependent due to degeneration of the injured nerve and target muscle.

We propose that transplantation of stem cell-derived spinal motor neurons into the distal, injured nerve may preserve neuro-muscular viability, thus expanding nerve repair options, including those for the lower extremities and bladder control. Furthermore, addition of a gene that enables the transplanted neuron to be activated by a laser (optogenetics), would enable a system that could be controlled directly from brain signals (brain-machine interface). Therefore, the proposed pre-clinical study directly addresses a demand of developing cellular therapy for nervous system repair with anticipated outcomes to help advance the field of reconstructive neurosurgery.

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Victoria E. Clark, MD, PhD
Massachusetts General Hospital

Award: Andrew T. Parsa 2020-21 Research Fellowship Grant
Project Title: Characterizing Recurrent RNA Polymerase II Meningioma Driver Mutations

Meningiomas are the most common primary brain and spinal tumor, accounting for over one third of all intracranial and spinal neoplasms in adults. Recurrent mutations in the dock domain of RNA polymerase II, which plays a central role in gene regulation by transcribing DNA into messenger RNA, have been identified to drive 6% of benign meningiomas. This is the first time that mutations in RNA polymerase II have been reported in human disease, and direct mutation of Pol II represents a distinct pathway for tumors to form.

The experiments proposed to characterize the transcriptional impact of these mutations have the potential to expand the current therapeutic options for patients with *POLR2A* mutant meningiomas and to reveal the function of the dock domain of RNA polymerase II, one of the most essential proteins for life.

Laureen D. Hachem, MD
Toronto Western Hospital

Award: Academy of Neurological Surgeons/NREF 2020-21 Research Fellowship Grant
Project Title: Elucidating the mechanisms of glutamate-mediated activation of adult spinal cord neural stem/progenitor cells to reveal therapeutic targets for spinal cord injury

Stem cell-based therapies have shown promise in promoting regeneration after spinal cord injury, however, clinical translation remains limited by poor cell survival and minimal functional connectivity. A population of neural stem/progenitor cells (NSPCs) reside in the ependymal zone of the adult spinal cord and hold the capacity to regenerate all three cells of the neural lineage – neurons, oligodendrocytes and astrocytes. Currently, the mechanisms that activate this population of stem cells to divide and form mature neuronal cells remains unknown.

Recently, we demonstrated that the excitatory neurotransmitter glutamate increases adult spinal cord NSPC survival and proliferation via the AMPA subtype of glutamate receptors. Our study will now define, for the first time, the mechanisms involved in glutamate-mediated signalling in rodent and human spinal cord NSPCs. Unlocking this mechanism holds the potential to enhance endogenous and transplanted NSPC neurogenesis as well as functional connectivity after spinal cord injury.

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Jennifer Hong, MD
Dartmouth-Hitchcock Medical Center

Award: Bagan Family Foundation/NREF 2020-21 Young Clinician Investigator Award
Project Title: Axonal reprogramming to accelerate nerve regeneration

Peripheral nerve injuries (PNI) are common and can lead to permanent disability. A major limitation in our ability to treat these injuries is the slow rate of nerve regeneration in humans. In order investigate new therapeutic approaches for patients with PNI, I propose to develop and test new gene-therapy approaches to treating nerve injuries by re-programming nerves to grow more quickly using new gene-editing technology.

I will use a mouse model of nerve injury to find viruses that can infect the peripheral nervous system and speed nerve regeneration. I will also test whether these viruses can work in humans by studying their function in cells from the peripheral nervous system donated by patients and organ donors. This work will establish feasibility for new therapeutic approaches to rapidly heal devastating nerve injuries, giving new hope to patients with PNI.

Ramin A. Morshed, MD
University of California, San Francisco

Award: AANS/CNS Section on Tumors & NREF 2020-21 Research Fellowship Grant
Project Title: Identification of genes mediating brain-tropism in a syngeneic model of metastatic breast cancer

Breast cancer is the most common malignancy in women in the United States, and brain metastases in these patients are associated with poor prognosis. Immunoediting is a critical component of metastatic tumor cell elimination, and tumor clones that develop immune-escape mechanisms are associated with progression and metastatic dissemination.

This project aims to identify immunomodulatory tumor-intrinsic gene expression changes in breast cancer brain metastatic cells that promote brain tropism and account for the immunosuppressive microenvironment seen in these tumors.

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Cody Lee Nesvick, MD
Mayo Clinic

Award: Academy of Neurological Surgeons/NREF 2020-21 Research Fellowship Grant
Project Title: Reversal Through Revertance: Targeting Pathogenic Mutations in Pediatric Brain Tumors with Gene Editing

Diffuse midline glioma (DMG) and atypical teratoid rhabdoid tumor (ATRT) are rare but lethal brain cancers of childhood and infancy. In recent years, there has been a surge in basic research on the underlying genetic causes of these tumors, but this has not yet translated into efficacious therapy. DMG and ATRT are unique amongst cancers in that they contain few genetic changes and are believed to cause cancer through *epigenetic* modifications, or altering how DNA is read by the cell. Our laboratory uses molecular techniques to restore normal function of mutated genes in DMG and ATRT cells.

By studying the downstream effects of gene restoration on the epigenome and cell survival, we aim to provide new insights that will enhance our ability to develop novel, efficacious therapy for these tumors.

Chad A. Tuchek, MD
University of Kansas Medical Center

Award: AANS/CNS Section on Neurotrauma & Critical Care/NREF 2020-21 Research Fellowship Grant
Project Title: Evaluation of Novel Polymeric Substrates for Direct Extradural Application of Therapies Following Traumatic Brain Injury: An Innovative Approach to a Difficult Problem

Traumatic brain injury (TBI) is the leading cause of disability in adults under the age of 40. We propose to modernize traumatic brain injury treatment through a completely new treatment paradigm using novel hydrogels to deliver medications directly onto the surface following TBI. It is through the use of our novel hydrogels that we hope to provide targeted medications to reduce swelling and permanent injury in the traumatically injured brain.