2021-22 Research Fellowship Grants & Young Clinician Investigator Awards

Oluwaseun O. Akinduro, MD, *Mayo Clinic*
Award: 2021-22 NREF & AANS/CNS Section on Tumors Research Fellowship Grant
Sponsor: Alfredo Quinones-Hinojosa, MD, FAANS
Project Title: Targeting Chordoma Therapy Resistance Through the YAP Pathway

Chordomas are the most common primary malignant tumors of the spine and are poorly responsive to radiation. There are no FDA approved drugs with the ability to inhibit growth and/or sensitize chordoma to radiation.

In this proposal, we hope to better our understand of the mechanism behind radio-resistance in chordoma, and the role by which the brachyury-Yes associated protein (YAP) regulatory axis supports this resistance. We will assess the efficacy of the drug Verteporfin in sensitization of chordoma to radiation via inhibition of the YAP regulatory axis using our novel verteporfin-loaded microparticles for intra-tumoral treatment. We will use our patient-derived chordoma cell lines, a subcutaneous chordoma mouse model, and our novel biodegradable verteporfin-loaded microparticles to develop an understanding of chordoma treatment resistance.

We hope to use this understanding and translate this therapy into treatment options for patients with this debilitating cancer and very limited management options.

Ahmed J. Awad, MD, *Medical College of Wisconsin*
Award: 2021-22 NREF & American Society of Stereotactic and Functional Neurosurgery (ASSFN) Research Fellowship Grant
Sponsor: Marieke Gilmartin, PhD
Project Title: The Contribution of Prefrontal Cortical-Thalamic Circuits to Fear Memory and Extinction: Potential New Targets for Deep Brain Stimulation

This proposal will examine neural activity in a "cognitive-emotional" brain circuit during fear learning in male and female rats to identify novel patterns of brain activity in each sex that help promote adaptive fear behavior and which may be dysregulated in pathological fear disorders such as PTSD.

Daniel Eichberg, MD, *University of Miami*
Award: 2021-22 NREF & StacheStrong Research Fellowship Grant on behalf of the AANS/CNS Section on Tumors
Sponsor: Michael Ivan, MD, FAANS and Nagi Ayad, PhD
Project Title: Investigating the Role of CD97/ADGRE5 Receptor in Glioblastoma Invasion and its Mechanism of Action in the Brain

Glioblastoma (GBM) has a uniformly fatal prognosis due to aggressive invasion. The mechanism underlying GBM's invasive behavior is unknown. CD97 is an adhesion G-protein coupled receptor implicated in tumor invasiveness in many cancers. However, the mechanism of CD97 function in GBM is unknown. To investigate the correlation between CD97 and GBM invasion, we established primary glioma stem cells (GSCs) from patient tumors. We found that higher CD97 protein levels correlate with higher *in vitro* invasion rates and more invasive patient MRI patterns. Moreover, CD97 knockdown decreases GSC invasion rates *in vitro*, and over-expression increases invasion rates. These results suggest that CD97 potentially represents a novel prognostic marker for GBM invasiveness, and a potentially attractive drug target for inhibiting GSC invasion. In this study, we will confirm our *in vitro* results in a mouse model and investigate the CD97 mechanism of action in GBM, potentially enabling drug discovery targeting GBM invasion.

Matthew Garrett, MD, PhD, *University of Cincinnati*
Award: 2021-22 B*CURED & NREF Young Clinician Investigator Award
Sponsor: Richard Lu
Project Title: Targeting the malignant epigenome of IDH1 mutant gliomas

Diffuse intrinsic pontine glioma (DIPG) is a universally lethal brain cancer found in young children. This tumor is created by mutations that affect the way the DNA molecule is folded and packaged. This misfolding leads to the expression of pathologic genes which subsequently drive growth. In an attempt to find compounds that might reverse this mis-folding, we performed a drug screen of multiple compounds known to affect the way DNA is folded and arranged. We identified a compound chaetocin that was uniquely effective at slowing DIPG cells. In this study, we propose to further discover the mechanism by which chaetocin slows growth in DIPG cells and determine whether this novel compound works effectively with HDAC inhibition and/or radiation.

Katherine G. Holste, MD, *University of Michigan*
Award: 2021-22 NREF & AANS/CNS Section on Pediatric Neurological Surgery Research Fellowship Grant
Sponsor: Guohua Xi, MD, PhD
Project Title: The role of complement in pediatric intraventricular hemorrhage and development of posthemorrhagic hydrocephalus

Neonatal Intraventricular Hemorrhage (IVH) occurs when the fragile and immature blood vessels within the neonatal brain rupture and bleed into the nearby spinal-fluid-filled spaces. One third of patients with high grade IVH will go on to develop posthemorrhagic hydrocephalus (PHH). Hydrocephalus damages the brain tissue itself leading to cognitive delay, seizures, cerebral palsy and, if left untreated, death. The mainstay of treatment of PHH is diversion of spinal fluid using permanently implanted shunts which carry with them a risk of malfunction, infection and failure.

The goal of this study is to better understand the pathophysiology of PHH, looking specifically at inflammation within the brain due to the complement cascade. The complement cascade is a collection of proteins which help direct the body's immune system, usually to address bacteria or dead cells, but in the setting of IVH, attack the blood clot. Iron-containing products are then able to leak out and cause injury to nearby neurons. The nearby inflammation caused by complement activation may also play a role in the development of PHH. In this study we will be examining the role of complement in development of PHH after IVH and subsequently examining whether inhibition of complement improves neurologic and functional outcomes after IVH.

Benjamin R. Johnston MD, PhD, *Brigham & Women's Hospital*
Award: 2021-22 NREF & Medtronic Research Fellowship Grant
Sponsor: Justin Brown, MD, FAANS
Project Title: Optogenetic Motor Neuron Transplantation to Restore Bladder Contraction

Spinal cord and peripheral nerve injuries present many challenges for recovery. Control of bladder function is important for both patient independence and for limiting infections and kidney injury. The bladder and associated urethral sphincters are innervated by several types of neurons requiring coordination to void appropriately. Contraction is carried out by the detrusor muscle with corresponding relaxation of the urethral sphincters. Our goal is to provide an alternative source of neurons that can be controlled to initiate detrusor contraction. This will involve the development an implantable group of harvested motor neurons that are given a special protein that is responsive to a certain wavelength of light. When the light is applied to the neurons, they will activate the detrusor and the bladder will contract. This project will hopefully demonstrate the value of transplanting controllable motor neurons to the muscle of interest rather than therapies that attempt to regenerate neurons from the central nervous system.

Michael B. Keough, MD, PhD, *Stanford University*
Award: 2021-22 NREF & Andrew T. Parsa Research Fellowship Grant
Sponsor: Michelle Monje, MD, PhD
Project Title: Targeting neuron-glioma circuit dynamics as a novel treatment for high-grade glioma

A recent discovery in cell culture experiments has shown that glioma tumor cells communicate with normal brain cells in a similar manner that brain cells talk to one another, and this process may be involved in the progression of tumor growth in patients with glioma. These findings need to be proven in animal model experiments before they can be brought forth to human trials. Michael and his colleagues will use a new live imaging microscope to watch communication between normal brain cells and glioma tumor cells in mice with implanted glioma tumors, in real time. They will study a new drug that blocks communication between brain cells and glioma cells to see if this slows down tumor growth. These experiments will hopefully show a new approach to treating patients with glioma in the future.

Alexander Ksendzovsky, MD, PhD, *University of Maryland*
Award: 2021-22 NREF & Academy of Neurological Surgeons Young Clinician Investigator Award
Sponsor: Peter Crino, MD, PhD
Project Title: LDHA enzyme may form the link between metabolism and epilepsy

Thirty percent of epilepsy patients continue to have seizures despite medical therapy, which is due to a lack of understanding of the molecular mechanisms underlying epileptogenesis. Recently, there has been evidence suggesting that differences in the way neurons metabolize sugar may contribute to epileptogenesis. Our previous work showed that neurons adapt to frequent seizures by changing the way they metabolize glucose. We showed these changes in human epileptic surgical specimens and in culture models of epilepsy. Given these previous findings, the proposed study will explore these metabolic changes' (LDHA enzyme) role in the pathogenesis of epilepsy. Overall, this study will help to better understand how changes in neuronal metabolism are associated with epilepsy. These data will lead to new diagnostic and treatment strategies and offer new hope for patients with this life altering condition.

Nealen Gordon Laxpati, MD, PhD, *Emory University*
Award: 2021-22 NREF & Bagan Family Foundation Research Fellowship Grant
Sponsor: Robert E. Gross, MD, PhD, FAANS
Project Title: Optogenetic Neuromodulation of the Septohippocampal Axis for the Treatment of Epilepsy

The goal of this project is to modulate hippocampal seizure activity with genetically targeted light-based control of neurons in the medial septum.

Mark Alexander MacLean, MD, MSc, *Dalhousie University*
Award: 2021-22 NREF & Academy of Neurological Surgeons Research Fellowship Grant
Sponsor: Alon Friedman, MD, PhD
Project Title: Exploring Mechanisms Underlying Mild Traumatic Brain Injury-Related Microvasculopathy

Research Problem: Traumatic brain injury (TBI) is a leading cause of death and disability. Translation of laboratory TBI research findings to the clinical setting remains challenging. Mechanisms underlying mild TBI remain unclear and require further study.

Scientific Importance: Understanding the relationship between neurons and the blood-brain barrier (BBB) following mild TBI may facilitate an improved ability to monitor, prevent, and treat acquired brain injuries.

Study Design and Objectives: This study will be carried out using an established rodent model of mild TBI. After inducing mild TBI, we will monitor neuronal electrical activity and relate this to rodent neurological function. The relationship between neuronal activity and BBB function will be determined via imaging the rodent brain using a novel type of magnetic resonance imaging. We will examine the type of chemicals released by neurons after they are injured and the impact this has on BBB function. Targeted therapies will be tested to improve neuronal and BBB function.
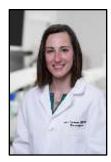
Geoffrey W. Peitz, MD, *University of Texas-San Antonio*
Award: 2021-22 NREF & Academy of Neurological Surgeons Research Fellowship Grant
Sponsor: Naomi Sayre
Project Title: Closed-loop sodium administration system for treatment of cerebral edema and intracranial hypertension: System development and proof-of-concept evaluation in a rat model

Keeping patients' sodium levels in the proper range is an important part of treatment for people with **brain injuries**. Under- or over-correcting sodium levels can be dangerous, especially for injured brains. With the research grant we will develop an improved system to precisely adjust sodium levels in the blood, and then we will test the system in rats. If successful, the method could be translated to sodium management in humans.

Anja I. Srienc, MD, PhD, *Washington University*
Award: 2021-22 NREF & L. Nelson "Nick" Hopkins Research Fellowship Grant jointly sponsored by Arvind Ahuja, MD, FAANS, and the AANS/CNS Cerebrovascular Section
Sponsor: Joseph P. Culver, PhD
Project Title: Characterizing Changes in Functional Connectivity After Aneurysmal Subarachnoid Hemorrhage Using Bedside Diffuse Optical Tomography

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating condition with the highest morbidity and mortality of any type of stroke. Patients who survive long enough to be admitted to a hospital usually experience a clinical course fraught with serious, and sometimes life-threatening, neurological complications. However, detecting neurological deterioration at the bedside relies on serial neurological exams and can be challenging in critically ill patients. Having a continuous method of monitoring neurologic function would be an important clinical advancement that would catch deterioration earlier, allowing for rapid intervention and could improve functional outcomes.

Diffuse optical tomography (DOT) is a noninvasive imaging technique that can be used to analyze spontaneous brain activity at rest and detect disruptions in functional networks. I will use this method to monitor aSAH patients to test whether network disruptions correlate with (i) severity of aSAH, (ii) periods of neurological decline, and (iii) neurological function at the time of discharge from the hospital. The real-time and longitudinal information about neurological status provided by DOT could be highly useful to help guide care and rehabilitation strategies after severe neurological injury.

Justin Zihan Wang, MD, BSc, *University of Toronto*
Award: 2021-22 NREF & Southeastern Brain Tumor Foundation (SBTF) Research Fellowship Grant on behalf of the AANS/CNS Section on Tumors
Sponsor: Gelareh Zadeh, MD, PhD, FAANS, FRCSC
Project Title: Establishing the utility of plasma-based liquid biopsies in meningiomas using cell-free methylated DNA immunoprecipitation with deep sequencing

Contemporary management of brain tumors is contingent upon invasively obtaining a tissue diagnosis through surgery. A "liquid biopsy" to sample the tumor genome from patient plasma can bypass risks of an operation while providing personalized prognostic information. We propose use of a novel technique: cell-free methylated DNA immunoprecipitation with deep sequencing (cfMeDIPseq) for the diagnosis and prognostication of meningiomas, the most common primary brain tumor in adults. We will perform cfMeDIP-seq on plasma samples and use differentially methylated regions comparing high- and low-risk meningiomas to train a machine-learning model to predict recurrence risk using plasma signatures. Model performance will be evaluated and validated in an independent cohort. Success in this proposal will represent a paradigm shift in meningioma treatment by providing clinicians and patients with information that could dramatically alter management, follow-up, and surgical planning through a simple blood test.

Jacob Stewart Young, MD, *University of California, San Francisco*
Award: 2021-22 NREF & StacheStrong Research Fellowship Grant on behalf of the AANS/CNS Section on Tumors
Sponsor: Manish K. Aghi, MD, PhD, FAANS
Project Title: In Vivo Gene Screening and Transcriptome Editing with Retroviral-Delivered CRISPR-Cas for the Treatment of Glioblastoma

Immunotherapy has revolutionized treatment for many malignancies, but unfortunately these agents have not been effective for glioblastoma patients. This project aims to deliver genome-editing technology specifically to glioblastoma cells in a durable and adaptable fashion to overcome the intrinsic immunosuppression found in the tumor microenvironment and render glioblastoma susceptible to powerful immune-activating therapies.