

Research Fellowship Grants & Young Clinician Investigator Awards - 2019-20 Academic Year



Christian Bowers, MD, Westchester Medical Center Foundation
Award: Academy of Neurological Surgeons 2019-20 Young Clinician Investigator Award

Project Title: eICU Virtual Clinician Corrects the Discrepancies between Ordered, Charted, and Observed RASS Scores in Mechanically Ventilated ICU Patients while Resolving Day/Night RASS Discordance

Critically-ill patients are occasionally unable to breathe on their own safely. Therefore, many ICU patients have been intubated and are receiving mechanical ventilation on a respirator. The combination of their injury and the ventilator frequently require sedating medications to ensure patient comfort. However, overly sedating patients with these medications can lead to multiple complications, including additional days spent on the ventilator and pneumonias. Physicians order a specific level of sedation but the nurses have control of the medication rate that is constantly being administered through an IV drip. We also believe that patients are overly sedated overnight.

This project is to use the eICU, an electronic or "telehealth" ICU, support to ensure that patients are at the appropriate level of sedation. These eICU clinicians will randomly spot-check the sedation level by requesting the nurse examine the patients at random times while the eICU watches with the camera and ensures that the sedation level is at the ordered level. This will ensure that patients are not overstated and will eliminate any excessive overnight sedation. We believe patients will have better outcomes as a result of this sedation level correction.



Benjamin T. Himes, MD, Mayo Clinic

Award: Andrew T. Parsa 2019-20 Research Fellowship Grant

Project Title: Extracellular vesicle-mediated immunosuppression in glioblastoma

We seek to understand the **dysfunction of the immune system** exhibited in patients suffering from glioblastoma, an aggressive incurable brain tumor. Suppressing the immune system is one means by which tumors can grow, and understanding the mechanisms of tumor-mediated immunosuppression is critical to developing new therapies to effectively treat glioblastoma. We plan to study the formation of immunosuppressive monocytes—immune cells that take on immunosuppressive behavior in the context of cancer—and how glioblastoma tumors cause these cells to develop. One mechanism we are exploring is the shedding of extracellular vesicles—small membrane-bound particles that can carry proteins and nucleic acids that can carry signals between cells—by tumor cells, and the influence of specific proteins carried in these vesicles on the formation of immunosuppressive monocytes. We are also studying methods for inhibiting the interaction of these tumor-derived vesicles with monocytes as a therapeutic target to treat immunosuppression in glioblastoma.



Christina Jackson, MD, Johns Hopkins University

Award: B*CURED/NREF 2019-20 Research Fellowship Grant

Project Title: The changing neoantigen landscape and associated immune response during immune checkpoint blockade in recurrent glioblastoma: a pathway to personalized tumor immunotherapy

Glioblastoma (GBM) is the most common primary brain tumor in adults with approximately 13,000 new cases diagnosed each year and a dismal median survival of 15 months. Despite aggressive surgical resection, radiation, and chemotherapy, tumor recurrence is inevitable, and patients will uniformly succumb to their disease. This has made the development of novel therapies of paramount importance. Immune checkpoint inhibitors

have emerged as a promising strategy to enhance a patient's own immune system to facilitate improved anti-tumor response. It has been shown to have dramatic improvements in survival in a number of non-GBM cancers. Despite this, its effectiveness in treating GBM has thus far been less dramatic.

This may be due to (1) a lack of predictive metrics to determine which patients will better respond to immune checkpoint therapy, (2) acquired resistance during treatment rendering immunotherapy ineffective, or (3) a lack of effective immunotherapy targets. We will investigate the dynamic changes in tumor mutations and immune response of patients with GBM during immune checkpoint inhibitor therapy to help overcome these barriers and to identify patients who would preferentially benefit from immune checkpoint blockade in order to maximize treatment options. These efforts will improve our understanding of fundamental central nervous system immunobiology, potentially impact the current treatment paradigm of GBM, and allow for the development of novel personalized immune-based therapies that could improve survival in patients with GBM.



Darrin J. Lee, MD, PhD, University of Southern California

Award: Academy of Neurological Surgeons/NREF 2019-20 Young Clinician Investigator Award

Project Title: Septohippocampal stimulation for cognitive restoration and seizure reduction in epilepsy

Epilepsy is a severe, debilitating neurological condition that affects approximately 1% of the population. One of the most common co-morbidities of epilepsy is cognitive dysfunction. In this study, we will evaluate the potential of deep brain stimulation to reduce seizure activity and improve cognition. Using electrophysiological, behavioral and

histological measures, we will study the underlying disease process and potential for a new treatment paradigm.



Athar N. Malik, MD, PhD, Massachusetts General Hospital

Award: AANS/CNS Section on Neurotrauma & Critical Care & NREF 2019-20 Research Fellowship Grant

Project Title: Development and characterization of a mouse model of midbrain compression to explore neural circuits underlying coma and consciousness

Brain injuries that compress an important part of the brain called the midbrain can cause loss of consciousness and coma. This can be seen in various settings including bleeding, stroke, tumor, and infection. We don't understand exactly why midbrain compression causes loss of consciousness, what determines whether or not an injured brain will

recover, and what processes allow recovery to take place. To try to answer these questions, I will model the process of midbrain compression in laboratory mice. By performing careful and controlled experiments, I will be able to study this type of brain injury and the subsequent recovery. Improving our understanding of this type of brain injury will lead to the development of treatments for patients who suffer from disorders of consciousness and coma.



Farshad Nassiri, MD, University of Toronto

Award: AANS/CNS Section on Tumors & NREF 2019-20 Research Fellowship Grant

Project Title: Establishing the prognostic implications of heterogeneity in meningioma using single-cell sequencing

Meningiomas are the most common primary brain tumor in adults. A subset of these tumors are very aggressive and grow back quickly despite aggressive surgery and radiation therapy. Diversity in cellular make-up of tumors has been linked to aggressiveness and has not previously been investigated in meningioma. In this proposal, we will use novel state-of-the-art genetic techniques to study the cellular composition of tumors at a single-cell resolution.



Taemin Oh, MD, University of California, San Francisco

Award: AANS/CNS Section on Pediatric Neurological Surgery & NREF 2019-20 Research Fellowship Grant

Project Title: Defining Mechanisms of Immune Cell Depletion in Group 3 Medulloblastoma

Medulloblastoma (MB) is the most common malignant brain tumor in children. Gold standard therapy of maximum safe surgical resection, radiation, and chemotherapy have resulted in modest improvements in patient survival. Nevertheless, this tumor still accounts for approximately 15% of all deaths from childhood cancer. Furthermore, gold standard therapy often incurs significant costs to patient quality of life, and thus

promising alternative or adjunct treatment modalities are in hot demand. Immunotherapy – a therapeutic modality that emphasizes using the patient's own immune system to attack tumor cells – is one such promising treatment method. However, multiple studies have shown that MB tumors lack enough surrounding immune cells to activate this response. The goal of this proposal is to identify the root cause of this paucity, and explore methods of potentially reversing this lack of immune response.



Bhuvic Patel, MD, Washington University

Award: Academy of Neurological Surgeons/NREF 2019-20 Research Fellowship Grant

Project Title: Identifying Biomarkers and Mechanisms of Radiation Resistance in Grade II Meningiomas

Meningiomas are a common brain tumor with a prevalence of 170,000 in the United States. World Health Organization (WHO) grade II meningiomas (G2M) constitute approximately 25% of meningiomas and are associated with an aggressive clinical course with frequent recurrence and poor survivorship. These lesions are increasingly being treated with surgery and/or radiation. Prior work by Dr. Kim's group showed that cell death within

the tumor predicts tumor resistance to radiation. We will perform genetic sequencing of these radiation resistant G2Ms and induce the genetic changes we find in meningioma cells which we will expose to radiation in the lab. The results of this project will allow us to develop genetic markers of radiation resistance, understand the underlying mechanism, and identify potential therapeutic targets.



Jennifer Sokolowski, MD, PhD, University of Virginia

Award: L. Nelson "Nick" Hopkins NREF 2019-20 Research Fellowship Grant jointly sponsored by Arvind Ahuja, MD, FAANS, and the AANS/CNS Cerebrovascular Section

Project Title: Role of the meninges and meningeal lymphatic system in the immune response after ischemic stroke

Acute cerebral ischemia not only involves an initial insult but also delayed secondary injury that may be worsened by a damaging inflammatory reaction. Most studies examining this have focused on the response in the brain parenchyma; as of yet, no one has taken a detailed look at the role of the meninges. The meninges is in a prime position

to mediate transport of antigens, debris, immune cells and cytokines to and from the infarct zone which may perpetuate detrimental inflammation and exacerbate injury. This study will examine the response of the meninges and the meningeal lymphatics after acute ischemic stroke and assess whether modulation of this response holds promise as an adjunct treatment to reduce secondary injury after stroke.



John R. Williams, MD, University of Washington

Award: Bagan Family Foundation & NREF 2019-20 Research Fellowship Grant

Project Title: Examination of brainstem lesions on CT following Severe TBI for prognostication of outcome

Traumatic brain injury (TBI) affects millions of Americans annually. In 2010, there were \$76 billion dollars-worth of costs associated with it. Diffuse axonal injury (DAI) is a type of severe TBI where a large amount of energy passes through the brain, causing microscopic damage to the connections between brain cells. In some patient's, this damage is so wide-spread, it can cause comas that can last for days to weeks to even the rest of a patient's life. It is difficult to predict which patients with DAI will wake up and return to a relatively normal lifestyle and which patients will be in a coma or coma-like stat indefinitely. Using a large database called TRACK-TBI, our goal is to analyze brain imaging from patients with DAI in their first week of hospitalization to see if there are any patterns that will allow us to predict which patients wake up and which patient's do not. With this information, we can help guide families and providers faced with difficult decisions regarding medical care after these injuries. We may also be able to use this information to cross reference other models of how the brain achieves consciousness in general to better understand the brain regions and pathways that allow us to wake up each morning and engage in the cognitive processes like thought, speech and movement that make us human.

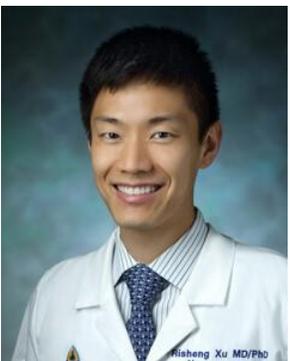


Thomas J. Wilson, MD, Stanford University

Award: Medtronic 2019-20 Young Clinician Investigator Award

Project Title: Deep Machine Learning and Convolutional Neural Networks for the Evaluation and Classification of Peripheral Nerve Tumors

With conventional imaging techniques and clinical assessment, differentiating between benign and malignant **nerve tumors**, identifying tumor subtype, and predicting growing versus non-growing tumors have proven difficult. These are very important distinctions in determining appropriate management. Utilizing artificial intelligence, we believe we can recognize patterns not previously identified and that we can extract information not obvious via traditional imaging interpretation. In this way, the proposed project seeks to better characterize nerve tumors utilizing artificial intelligence, which has the potential to reduce misdiagnosis and to allow better upfront management of these tumors.



Risheng Xu, MD, PhD, Johns Hopkins University

Award: AANS/CNS Section on Pain & NREF 2019-20 Research Fellowship Grant

Project Title: BVR and NRF2 as potential regulators of oxidative stress and pain in trigeminal neuralgia

Trigeminal neuralgia (TN) is a devastating but potentially treatable facial pain syndrome afflicting 1 per 10,000 people. To date, the molecular mechanisms underlying trigeminal neuralgia remain obscure. We hypothesize oxidative stress to be a major driver of pain in TN. Using genetically modified mice and patient CSF samples, we hope to better understand the role of oxidative stress in causing TN pain. This may allow for novel adjunctive therapies in the treatment of facial pain.