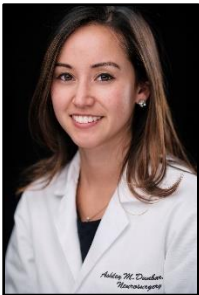


2025-26 NREF Research Fellowship Grants & Young Clinician Investigator Awards – Project Descriptions



Rebecca Du, MD, Northwestern University
Project Title: TIM3 as a Therapeutic Target for Chordomas

Chordomas are locally aggressive axial skeleton (skull base, mobile spine, and sacrum) tumors. With no effective pharmacotherapies and relative resistance to radiotherapy, the standard of care for chordomas is en bloc resection when anatomical constraints allow. However, even with negative margins, chordomas can locally recur and metastasize, portending a poor prognosis due to limited salvage therapy options. Our preliminary data found T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) as the most promising immunotherapeutic target for chordoma treatment. TIM-3 is highly expressed by myeloid cells in chordomas and likely plays a key role in exhaustion of tumor infiltrating cytotoxic T-cells. Our hypothesis is that TIM-3 controls myeloid-cell mediated immunosuppression in chordomas, and TIM-3 blockade will reprogram myeloid cells to mount an anti-tumor cytotoxic immune response. Through this study, we aim to validate the immunosuppressive TIM-3 axis in chordomas and determine that TIM-3 blockade promotes anti-tumor immunity against chordomas.



Ashley M. Dunbar, MD, Washington University in Saint Louis
Project Title: Non-invasive vagus nerve stimulation and intraventricular hemorrhage of prematurity

Intraventricular hemorrhage (IVH) of prematurity affects a significant portion of premature babies and often results in severe neurodevelopmental outcomes. There is a critical need for research on this topic as no interventions aimed at treatment of IVH exist. IVH arises from the instability of fragile cerebral vessels and results in pathologic inflammation that contributes to the severity of hemorrhage and subsequent brain injury. Studies have shown that vagal nerve stimulation (VNS) can attenuate the cerebral and systemic immune response, and this modulation has been associated with improved clinical outcomes. Given this relationship, we propose investigating the effect of VNS on inflammation in an IVH rodent model. Our hypothesis is that VNS will significantly reduce levels of inflammatory cytokines and result in decreased rates of post-hemorrhagic hydrocephalus and relative improvement in behavioral functioning. This will provide important preliminary data for a future clinical trial testing VNS in premature infants with IVH.



Jennifer L. Quon, MD, MHS, The Hospital for Sick Children; University of Toronto
Project Title: Machine learning for prediction and delineation of pediatric arteriovenous malformation recurrence after surgery

Brain arteriovenous malformations (AVMs) are abnormal tangles of blood vessels that connect arteries and veins in the brain. In children, AVMs carry a high risk of bleeding, which can lead to serious complications or even death. Because of this, finding effective treatments is crucial. However, even after surgery to completely remove an AVM, there's still a high chance it could regrow in pediatric patients. The goal of this study is to develop a machine learning model that can predict the likelihood of AVM regrowth after surgery by analyzing pre-surgery images. The model would also help identify the specific areas of the brain most at risk for regrowth. By using this tool, surgeons could perform more targeted surgeries, conduct additional monitoring with imaging, and focus on studying brain tissue in the high-risk areas.



Zachary A. Sorrentino, MD, University of Florida

Project Title: Endovascular immune-modulatory therapy for treatment of subarachnoid hemorrhage associated cerebral vasospasm and other neurological disorders

Rupture of a brain aneurysm is a devastating event leading to diffuse brain bleeding, and the first step in treatment is controlling this bleeding with neurosurgical treatment of the aneurysm. In patients who survive the initial rupture, one of the main challenges in treatment is preventing strokes due to “vasospasm”, which is a condition where brain blood vessels constrict due to various factors including inflammation caused by brain bleeding after the aneurysm rupture. Anti-inflammatory therapies have demonstrated promise in animal models to prevent vasospasm, and herein we plan to deliver powerful anti-inflammatory therapies through a targeted endovascular approach to temporarily deplete the main immune cells of the brain, microglia, in the region of aneurysm rupture to prevent the severe inflammation we believe underlies vasospasm. We are testing this approach in mouse models of aneurysm rupture with plans for translation to human studies.

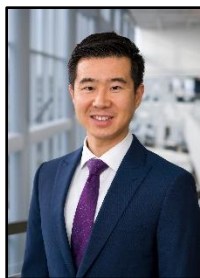


Samantha E. Spellicy, MD, PhD, Duke University

Project Title: IL-1 β -mediated stimulation of the adrenergic systemic and immune polarization in a mouse model of stroke

Ischemic stroke is a leading cause of death and long-term disability worldwide, affecting approximately 12 million people each year. Part of the morbidity and mortality of stroke is related to the post-stroke inflammatory response. Early on, brain immune cells called *microglia* become activated. Although the exact mechanisms are not fully understood, this activation appears to stimulate the sympathetic nervous system (“fight or flight” response), which then amplifies inflammation throughout the body.

Our study aims to better understand how inflammation spreads from the brain to the rest of the body after a stroke. We are particularly interested in a molecule called *interleukin-1 beta* (IL-1 β), which we believe plays a key role in this process. We will investigate how blocking IL-1 β affects the hypothalamus (a part of the brain involved in regulating the nervous and immune systems), as well as its impact on immune cell activity and immune organ function.



Matthew Z. Sun, MD, UT Southwestern Medical Center

Project Title: Investigating the Immunomodulatory Effects of Radiation on Targeted Meningioma Immunotherapy

High-grade meningiomas are aggressive brain tumors with poor prognosis, and are usually treated with surgery followed by radiation, without immunotherapy options. While radiation helps control tumors, it may also suppress the immune system and reduce the effectiveness of new cancer immunotherapies. This project investigates whether radiation triggers these effects in meningiomas. Previous work showed that specially engineered immune cells (TCR-T cells) can recognize and kill meningioma cells by targeting a tumor marker NY-ESO-1. This study will examine whether radiation increases immune-suppressing signals and NY-ESO-1. By studying patient tumor samples and lab-grown tumor models, we will test if radiation makes TCR-T therapy less effective and whether adding immune checkpoint blockers can restore its benefit. The goal is to better understand how radiation changes the tumor’s immune environment and to design combination treatments that work more effectively against aggressive meningiomas.



Xiaonan (Richard) Sun, MD, PhD, Dartmouth Hitchcock Medical Center

Project Title: Cortico-subthalamic population code in the representation of cognitive computations

Electrical modulation of brain tissue through deep brain stimulation (DBS) surgery is highly effective in relieving the symptoms of neurological disorders such as Parkinson’s disease, often resulting in significant improvements in quality of life. Limitations of DBS include loss of efficacy over time, partial resolution of symptoms, and cognitive and psychiatric side effects. To address this, one promising approach leverages the recording of brain signals to simultaneously guide adjustment of stimulation. Current DBS technologies lack the ability to fully resolve the richness of the signals in therapeutic brain regions such as the subthalamic nucleus (STN). Mechanistically, it is unclear how large populations of single neurons collectively orchestrate complex motor and cognitive behaviors. This work seeks to gain insight into the neural coding principles of the STN and its associated brain networks through large-scale, high-resolution electrophysiology in rodents trained to solve complex cognitive behaviors.