2024-25 NREF Research Fellowship Grants & Young Clinician Investigator Awards

NREF
NEUROSURGERY RESEARCH & EDUCATION FOUNDATION

Kathryn Kearns MD, The Rector and Visitors of the University of Virginia
Award: 2024-25 NREF & AANS/CNS Cerebrovascular Section Research Fellowship Grant
Project Title: Preventing Aneurysm Rupture: Therapeutic Mitigation of Immune Crosstalk
Sponsor: Petr Tvrdik, Ph.D

Moyamoya disease (MD) is characterized by progressive stenosis of intracranial arteries leading to reduction of brain perfusion. As the disease worsens, patients can experience ischemic strokes resulting in neurological deficits. Surgical treatments for MD include placing healthy muscle tissue or blood vessels over the ischemic brain to promote formation of new blood vessels to increase perfusion. However, this process can take several months, during which time patients remain at risk of ischemic stroke. VEGF is a protein produced by the body that promotes formation of new blood vessels. We will examine the possibility that introducing additional VEGF to MD patients undergoing revascularization surgeries may produce faster, more robust blood vessel formation at the surgical site, affording earlier and more significant clinical benefit. We plan to trial implantable protein matrices loaded with slow-release VEGF, focused-ultrasound sonication, and viral delivery of VEGF genes to allow focal VEGF administration to the surgical site.

Brandon P. Lucke-Wold, MD, PhD, University of Florida
Award: 2024-25 NREF & AANS/CNS Cerebrovascular Section Research Fellowship Grant
Project Title: Preventing Aneurysm Rupture: Therapeutic Mitigation of Immune Crosstalk
Sponsor: Brian L. Hoh, MD, FAANS, FACS, FAHA, MBA

Subarachnoid hemorrhage frequently occurs after a rupture of a brain aneurysm. Outcomes can be poor due to the devastating course that follows rupture. Recent data has shown that peripheral immune cells interact with central immune cells called microglia. This project is looking at the interaction between these cells types as a therapeutic target to understand why aneurysms grow, rupture, and cause an inflammatory deluge. The information gleaned will be pivotal in providing improved treatments. In particular, the endocannabinoid receptors on microglia offer to be a key component to immune crosstalk. The translational focus is geared towards the advancement of first in human trials.

Chloe Gui, **MD,** Mayo Clinic
Award: 2024-25 NREF & AANS/CNS Section on Disorders of the Spine and Peripheral Nerves Sanford J. Larson Research Fellowship Grant
Project Title: Lineage tracing in malignant peripheral nerve sheath tumors and plexiform neurofibromas to assess tumoral heterogeneity and mechanisms of MEK inhibitor resistance
Sponsor: Gelareh Mohammad Zadeh, MD, PhD, FAANS, FRCS

Plexiform neurofibromas (PNs) and malignant peripheral nerve sheath tumors (MPNSTs) are peripheral nerve sheath tumors that arise spontaneously or in association with Neurofibromatosis Type 1 (NF1), a tumor predisposition syndrome. PNs can cause significant morbidity and may transform into MPNSTs, aggressive cancers that represent the leading cause of death in NF1. Preclinical studies have demonstrated the effectiveness of MEK inhibitors such as selumetinib in PNs and MPNSTs. Selumetinib has recently been approved for symptomatic inoperable pediatric PNs and causes partial shrinkage. Drug resistance, however, remains a challenge, and we hypothesize that

clusters of cell subpopulation have or acquire genetic mechanisms that lead to treatment resistance. In this project, we identify, track, and characterize selumetinib-resistant cell subpopulations throughout in vitro and in vivo treatment.

Riccardo Serra, MD, University of Maryland - Baltimore
Award: 2024-25 NREF & AANS/CNS Section on Pediatric Neurological Surgery Research Fellowship Grant
Project Title: Intercellular Junctions Modulate Paracellular Flow after Intraventricular Hemorrhage
Sponsor: J Marc Simard, MD, PhD, FAANS

Intraventricular hemorrhage (IVH) - a complication of intracranial bleeds and trauma - is associated with post-hemorrhagic hydrocephalus (PHH), worse outcomes, death. While post-IVH inflammation promotes CSF secretion via expression of ion channels, the movement of proteins and cells has not been characterized. Intercellular junctions regulate passage along the paracellular route, sealing this space to create the Blood-CSF Barrier (BCSFB). From preliminary data, generalized breakdown of junctions is seen in the first hours after IVH. TLR4-dependent junctional damage could therefore determine paracellular passage of particles and cells across the choroidal epithelium, driving PHH and inflammation. Knockout animals will be used to study the disruption of junctions. Microscopic changes in claudins, cadherins, and downstream mediators will be defined. IRAK4 inhibition and TLR4 knockout will confirm its role in junctional phosphorylation and disruption. The movement of tracers across the BCSFB will define epithelial leakiness and opening of the paracellular route after junctional breakdown.

Adip G. Bhargav, MD, University of Kansas Medical Center
Award: 2024-25 NREF & AANS/CNS Section on Tumors Research Fellowship Grant
Project Title: Enhancing CAR-T Cell Therapy by Reprogramming Tumor-associated Macrophages using a Novel Nanosponge against GBM
Sponsor: David Akhavan, MD. PhD

Glioblastoma (GBM) is the most common primary malignant brain tumor for which no curative treatments are available. Recent advances in immunotherapy and an improved understanding of the GBM microenvironment has led to promising translational efforts. Specifically, chimeric antigen receptor T (CAR-T) cell therapy is a form of immunotherapy demonstrating disease-modifying activity in early clinical trials; however, challenges remain in maximizing the efficacy of this therapy by overcoming the tumor's ability to suppress a strong anti-tumor immune response. This study aims to design and investigate a novel selective, drug-loaded nanosponge therapeutic agent that can be simultaneously administered with targeted CAR-T cell therapy to reprogram the suppressive players in the tumor microenvironment and improve the potency of the CAR-T cell therapy. Through this study, we aim to develop new strategies to enhance CAR-T cell therapy for GBM and gain important insights into the mechanisms of treatment failure and resistance to immune effector cell-based therapy.

Malia McAvoy, MD, University of Washington
Award: 2024-25 Academy of Neurological Surgeons Research Fellowship Grant
Project Title: A Novel Tyrosine Kinase Inhibitor Coated Flow Diverting Stent as a Drug Delivery System for Intracranial Aneuysms
Sponsor: Michael R. Levitt, MD, FAANS

The technology we use to treat brain aneurysms has rapidly changed and now we have minimally invasive techniques to deliver devices to aneurysms using a catheter through the arteries. The devices we use to treat these aneurysms all aim to slow down blood flow in the brain. The next step for treating brain aneurysms is to create treatments that not only stop blood flow but also tackle the main genetic causes of aneurysms. To make this happen,

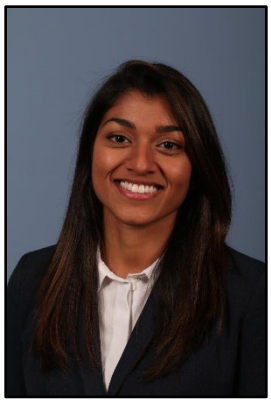
we suggest using a method like how we treat cancer, involving targeted medications. Our idea is to make a stent coated with drugs delivering specific treatments to the aneurysm. A stent coated with a drug in a stable form would allow for treatment of the aneurysm for many years. This would halt brain aneurysm growth due to blood flow and deal with the root causes at the same time.
Today, minimally invasive techniques to treat brain aneurysms have centered on reducing blood flow to prevent further growth. Our new novel device innovates on this technique by incorporating chemotherapy to not only stop blood flow but also tackle the main genetic causes of aneurysms. This device enables targeted delivery of drugs locally to the aneurysm thanks to a breakthrough coating technique that enables a stent to treat an aneurysm for many years. Through this targeted approach, patients can avoid the harmful side-effects of chemotherapy while treating the root causes of the aneurysm.

Panagiotis Mastorakos, MD, PhD, University of Texas Southwestern Medical Center
Award: 2023-24 NREF & Academy of Neurological Surgeons Young Clinician Investigator Award
Project Title: IL6/JAK/STAT pathway activation drives microglia-mediated angiogenesis after stroke
Sponsor: Bradley C. Lega, MD, FAANS

The factors that influence recovery trajectories after stroke are largely unknown. However, recent findings suggest that the innate immune response plays a pivotal role in repair and recovery following both ischemic and hemorrhagic strokes. We now aim to expand our understanding of repair mechanisms in human tissue samples from patients requiring decompressive hemicraniectomy for stroke. We will identify innate immune cell populations within stroke tissue, with a specific focus on defining the repair-associated microglia population phenotypes, previously identified in rodent models. Additionally, we seek to delve into the molecular pathways involved in stroke recovery, particularly focusing on the the IL6/JAK/STAT/VEGFA pathway. Characterization of this pathway can offer new avenues for intervention to facilitate successful cerebrovascular repair and functional recovery.

Andrew T. Hale, **MD, PhD**, University of Alabama at Birmingham
Award: 2024-25 NREF & Academy of Neurological Surgeons Research Fellowship Grant
Project Title: Cerebral organoids as a model of genetic and acquired hydrocephalus
Sponsors: Graham Fieggen, BSc, MBChB., MSc, FCS, MD, and Mubeen Goolam, PhD

Hydrocephalus (HC), a disorder of abnormal cerebrospinal fluid homeostasis leading to increased intracranial pressure, is amongst the most common indications for children's brain surgery world-wide. However, development of effective pharmacologic therapies has been impeded by a lack of detailed molecular mechanistic and genetic understanding of the disease. Recently, induced pluripotent stem cells (iPSC)-derived cerebral organoids - which form anatomically and genetically representative brain structures in a dish– have been used as a tool to elucidate mechanisms of neurologic disease. As a NREF/Academy Research Grant Awardee, I will create the first cerebral organoid models of genetic and acquired HC in partnership with scientists and neurosurgeons at the University Cape Town Neuroscience Institute (UCTNI), MRC Laboratory of Molecular Biology, University of Cambridge, UK (Madeline Lancaster) and Massachusetts General Hospital, Harvard Medical School (Kristopher T. Kahle), focusing on deriving models representative of African ancestries where the burden of HC is highest.



Arushi Tripathy, MD, University of Michigan
Award: 2024-25 NREF & Andrew T. Parsa Research Fellowship Grant
Project Title: Defining spatial transcriptional mediators of DNA repair in glioblastoma as a mechanism of treatment resistance
Sponsor: Daniel Wahl, MD, PhD

Glioblastoma is an incurable primary brain cancer. Nearly every tumor comes back after standard treatment with radiation and chemotherapy, with most patients surviving an average of only 15 months. The majority of glioblastomas recur within the treatment field and multiple additional chemotherapy drugs have failed to improve outcomes in clinical trials. Therefore, it is critical to understand what causes resistance to therapy.
The glioblastoma tumor microenvironment is heterogeneous, with unique spatial niches that harbor recurrence-initiating cells. Recurrent glioblastomas are better at repairing treatment-induced DNA damage. Our previous studies found that the THY1 cell surface receptor mediates resistance to treatment. Now we aim to understand how THY1 does this, in a spatially-dependent manner and by mediating glioblastoma cells' response to DNA damage. Identifying these key regional factors involved in treatment resistance will guide development of targeted drugs that could greatly improve patient survival.

Shehryar R. Sheikh, MD, MPH, Cleveland Clinic
Award: 2024-25 NREF & Bagan Family Foundation Research Fellowship Grant
Project Title: An EEG-based Predictive Biomarker of Seizure Outcome after Epilepsy Surgery
Sponsor: Carl Saab, PhD

30-50% of patients who undergo resection for drug resistant epilepsy (DRE) fail to achieve sustained seizure freedom. To address this patient selection problem, accurate computational models to predict patient outcomes could be instrumental. Existing models are of limited clinical utility due to modest accuracy (~60-70%) or reliance on complex data inputs that are not part of routine care. Crucially, these models do not take into account the baseline preoperative brain network features of a patient's epilepsy. This is a critical gap as data from intracranial stereo-EEG studies and functional neuroimaging suggest that preoperative network features correlate with postoperative seizure outcome. We are using preoperative scalp EEG from epilepsy surgery patients to develop brain network models which can then be fed into a cutting-edge machine learning pipeline in order to develop predictors of post-operative seizure outcome. Our approach has the potential to identify a scalp-EEG derived predictive biomarker of responsiveness to resection in DRE.

Benjamin T. Himes, MD, Montefiore Medical Center/Albert Einstein College of Medicine
Award: 2024-25 B*CURED & NREF Young Clinician Investigator Award
Project Title: The role of B7-H3 in glioblastoma extracellular vesicles in tumor-mediated immune suppression
Sponsor: XingXing Zang, PhD

Glioblastoma (GBM) patients are profoundly immune suppressed, which has prevented the development of effective immunotherapies in GBM, but the mechanisms of this immune suppression are poorly understood. Tumor-derived extracellular vesicles (EVs) are multimodal signaling molecules shed in large quantities by GBM cells, and express a diverse array of immune-modulating molecules that have the potential to influence both local and systemic immune suppression. B7-H3 is an understudied immune checkpoint protein that evidence suggests may be a critical immunomodulatory protein in GBM. This work will study the role of B7-H3 in the immunomodulatory signaling of GBM-EVs, especially in the formation of important immunosuppressive myeloid cells, which are critical mediators of immune suppression. These studies have the potential to open novel therapeutic avenues for reversing systemic immune suppression in GBM, a critical factor in the development of effective immunotherapies for this deadly tumor.
