

2023-24 NREF Research Fellowship Grants & Young Clinician Investigator Awards



Charuta G. Furey, MD, Barrow Neurological Institute

Award: 2023-24 NREF & SBTf Research Fellowship Grant on behalf of the AANS/CNS Section on Tumors

Project Title: Characterizing glioma evolution through longitudinal cerebrospinal fluid liquid biopsy in a Phase 0/2 clinical trial of niraparib for newly-diagnosed glioblastoma

Sponsor: Nader Sanai, MD, FAANS

Effective drug development in glioblastoma requires visualization of tumor evolution in response to experimental therapy. Today, genomic and transcriptomic mechanisms of tumor resistance remain undetected in clinical trials due to the morbidity associated with surgical tissue collection. This study proposes a new method of liquid biopsy using an intracavitary reservoir for serial, outpatient cerebrospinal fluid collection. This minimally invasive technique facilitates prospectively tracking circulating tumor DNA and glioblastoma cells during a prospective clinical trial of niraparib, a PARP1/2 inhibitor that represses DNA damage repair. The results will provide valuable translational insights into transcriptomic and genomic glioma evolution in response to selective pressure from PARP1/2 inhibition, including putative glioblastoma resistance mechanisms and treatment-related cell state changes that can be leveraged to create better combination therapies.



Vivek Sean Gupta, MD, Washington University in St. Louis School of Medicine

Award: 2023-24 NREF & AANS/CNS Section on Pediatric Neurological Surgery Research Fellowship Grant

Project Title: Microstructural Injury to the Brainstem and Spinal Cord Determines Outcomes in Chiari Malformation and Syringomyelia

Sponsor: David Limbrick, MD, PhD, FAANS

Chiari I Malformation is a common pediatric neurosurgical condition with a wide array of clinical presentations. Although Chiari I Malformation is traditionally diagnosed using a single radiographic image, there is evidence to suggest that it involves a hyperdynamic pathophysiologic state. We currently lack quantitative tools to effectively stratify patients along the spectrum of clinical presentation, assess histologic changes within neurologic tissue, and predict response to therapy. Diffusion Basis Spectrum Imaging (DBSI) is a tool that can analyze MRI images to assess changes in neural tissue such as axonal loss, myelination patterns, and inflammation and edema. This project aims to determine whether DBSI metrics of the brainstem and cervical spinal cord in Chiari I Malformation and the associated condition syringomyelia accurately reflect neurologic impairments, functional outcomes, and response to therapy in patients with these conditions.



Natasha T. L. Ironside, MD, University of Virginia

Award: 2023-24 Academy of Neurological Surgeons Research Fellowship Grant

Project Title: Predicting Hematoma Expansion in Spontaneous Intracerebral Hemorrhage

Sponsors: Gustavo Kunde Rohde, PhD and Min Park, MD, FAANS

Spontaneous intracerebral hemorrhage is a stroke caused by bleeding into the brain tissue. Not only does it have high rates of death and disability, but there is currently no effective treatment that improves outcomes for spontaneous intracerebral hemorrhage patients. After the initial bleed, increased bleeding, or hematoma expansion, occurs in one third of patients. This is associated with worse outcomes. An ability to predict hematoma expansion might allow for it to be prevented with surgical or medical therapies. Using an innovative artificial intelligence method, "optimal mass transportation", we aim to develop an automatic and

efficient tool to predict hematoma expansion from the brain scans of spontaneous intracerebral hemorrhage patients. We intend to study the relationships between the bleed location, image features, expansion, and neurological outcome. We hope to identify the patients who can most benefit from treatments to prevent hematoma expansion.



Elena Kurudza, MD, University of Utah

Award: 2023-24 NREF & Andrew T. Parsa Research Fellowship Grant

Project Title: Utilizing Chimeric Antigen Receptor Macrophages (CAR-M) to promote tumor phagocytosis and repolarization of the tumor microenvironment in Glioblastoma

Sponsor: Minna Roh-Johnson, PhD

Chimeric antigen receptor (CAR) technology works by engineering the patient's own immune cells to target and kill cancer cells that would otherwise evade the patient's immune system. While this technology has proven to be successful in treating a number of blood cancers through the use of CAR-T cells, the success of CAR-T cells has been limited in the treatment of solid tumors, such as glioblastoma. We believe the tumor microenvironment is key. While T cells do not efficiently infiltrate solid tumors, macrophages are known to infiltrate solid tumors. Additionally, macrophages play a key role in regulating the tumor microenvironment. They can

alter the microenvironment from an immunosuppressive, tumor promoting state to more of an inflammatory, anti-tumor state. The goal of this project is to create CAR Macrophages that target glioblastoma cells, and promote tumor death while additionally reprogramming the tumor microenvironment in order to develop a novel treatment for glioblastoma.



Ryan M. Naylor, MD, Mayo Clinic

Award: 2023-24 NREF & Academy of Neurological Surgeons Research Fellowship Grant

Project Title: Diagnostic and Therapeutic Implications of KRAS Mutations in Brain Arteriovenous Malformations

Sponsor: David J. Daniels, MD, PhD, FAANS

Brain arteriovenous malformations (bAVMs) predispose patients to intracranial hemorrhage and can be cured by microsurgical resection. Patients with asymptomatic or inoperable bAVMs are often referred for stereotactic radiosurgery (SRS), which is associated with a prolonged latency period and persistent hemorrhage risk before obliteration. The major barrier to improving outcomes for bAVM patients undergoing SRS has been a lack of insight into the pathogenesis of bAVMs. However, with the recent discovery that a substantial majority of

bAVMs harbor activating *KRAS* mutations, the stage is set for major translational breakthroughs. Here, we describe our strategy for enhancing the surveillance and treatment for patients with *KRAS* mutant bAVMs undergoing SRS. In Aim 1, we will examine the feasibility of liquid biopsy for bAVM *KRAS* genotyping. In Aim 2, we will investigate a novel role for immune checkpoints in *KRAS* mutant bAVMs. Results from this proposal could have immediate translational implications.



Peyton L. Nisson, MD, Barrow Neurological Institute

Award: 2023-24 NREF & Bagan Family Foundation Research Fellowship Grant

Project Title: Vascular-Endothelial-Growth-Factor A and Angiogenesis Role in the Growth and Rupture of Intracranial Aneurysms. The Missing Link in a Complex Pathophysiologic Process in Females

Sponsor: Tomoki Hashimoto

The hormone Vascular-Endothelial-Growth-Factor (VEGF) may play a central role in the development of brain aneurysms. An important question that led to this investigation has been the search for understanding why women have a much larger incidence and rate of rupture of brain aneurysms compared to men. Though several studies have pointed to the hormone estrogen and other anatomical differences, they still do not fully explain the differences seen between sexes. However, there is evidence suggesting the uterus may produce VEGF at excess amounts as the body enters menopause. This hormone is considered the most potent factor in the development of new blood vessels and recently has been implicated in the development of aneurysms. Using a mice model, we are exploring its effects by amplifying the production of VEGF, blocking it, and or removing the uterus, which might one day provide the foundation for developing new therapies to treat aneurysms.



Jonathon J. Parker MD, PhD, Mayo Clinic Arizona

Award: 2023-24 NREF & Academy of Neurological Surgeons Young Clinician Investigator Award

Project Title: Short Fiber Stimulation to Suppress Epileptiform Activity in Human Neocortical Epilepsy

Sponsor: Greg Worrell, MD, PhD

Device-based neurostimulation is increasingly used to treat neocortical onset epilepsy resistant to medication. This is an appealing approach as it less destructive than surgical resection, with the potential to rehabilitate epileptic cortex. Currently we are unable to predict the ideal brain location to apply stimulation for individual patients. As part of standard clinical care, depth electrodes are temporarily implanted in the brain of epilepsy patients to map seizure onset regions. Through these electrodes our lab will perform low-frequency stimulation targeted to the white matter adjacent to a seizure zone. We hypothesize that direct white matter stimulation will be more effective than gray matter stimulation to suppress abnormal electrical patterns observed in epileptic cortex. This study will provide valuable clinical insights to inform the targeting of future regional neuromodulation approaches to treat medication refractory epilepsy.



Kunal Patel, MD, UCLA

Award: 2023-24 NREF & Gladiator Project Young Clinician Investigator Award on behalf of the AANS/CNS Section on Tumors

Project Title: Visualization, Quantitation, and Targeting of Infiltrating Glioblastoma Cells with pH Sensitive Amine Chemical Exchange Saturation Transfer Magnetic Resonance Imaging

Sponsors: Harley Kornblum, MD, PhD and Benjamin Ellingson, PhD

Glioblastoma is the most common form of primary brain cancer and has extremely poor survival outcomes. Standard of care surgical resections are image guided surgeries using magnetic resonance imaging (MRI) with contrast. However, this fails to visualize infiltrating tumor cells beyond the contrast enhancing bulk of tumor. We have developed a pH sensitive MRI technique called amine chemical exchange saturation transfer (CEST) MRI. In this proposal, we will prospectively study the ability for CEST MRI to visualize infiltrating tumor cells during surgery and identify on a molecular level what are the biological underpinnings for abnormalities in pH in these areas of tumor.



Jeffrey I. Traylor, MD, UT Southwestern Medical Center

Award: 2023-24 NREF & AANS/CNS Section on Tumors Research Fellowship Grant

Project Title: Investigating acquired resistance to DHODH inhibition in IDH mutant glioma

Sponsor: Samuel McBrayer, PhD

The goal of this project is to define mechanisms of resistance to BAY 2402234. Our group has previously identified de novo pyrimidine synthesis as a targetable vulnerability induced by IDH oncogenes in glioma. We showed that an inhibitor (BAY 2402234) of one pyrimidine synthesis enzyme, DHODH, displays activity against IDH-mutant glioma; these data provide rationale for a clinical trial slated to begin next year. In mouse models, we observed acquired resistance to BAY 2402234 and now seek to define the molecular mechanisms underlying this phenotype. We identified two enzymes upregulated in resistant IDH-mutant glioma cells: DHRS2 and CPS1. If successful, my research will reveal a new biochemical pathway for de novo pyrimidine synthesis in IDH-mutant glioma. These findings will also define the mechanism of acquired resistance to BAY 2402234 and nominate new therapeutic targets that can be engaged to increase the durability of BAY 2402234 antitumor efficacy in IDH-mutant glioma.
