2022-23 NREF Research Fellowship Grants and Young Clinician Investigator Awards

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NEUROSURGERY RESEARCH & EDUCATION FOUNDATION

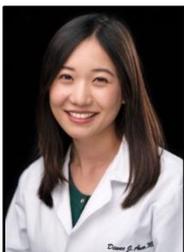**Nitin Agarwal, MD**, Washington University School of Medicine
Award: NREF & Academy of Neurological Surgeons Young Clinician Investigator Award
Project Title: Predicting Spinal Cord Injury Prognosis Using a Novel Non-Invasive Biomarker
Sponsor: Wilson Z. Ray MD, FAANS

Spinal cord injury (SCI) is an extremely important public health problem. Every year, approximately 17,500 patients experience spinal cord injuries in the United States, leading to substantial morbidity and decreases in patient quality of life. A major shortcoming limiting efforts to improve current therapeutic models in SCI is the lack of verifiable data regarding biomarkers and their correlation with acute neurological injury and prognosis. While current fluid-based biomarkers offer a promising measure to the diagnosis and prognostication of SCI outcomes, they reflect multiple systemic processes and do not necessarily represent the local or regional changes to neurologic tissues to accurately predict outcomes and identify mechanistic based treatments. Non-invasive imaging approaches offer a potential solution to reveal the SCI specific structural and functional damage to neural tissue needed to predict outcomes and identify treatments.

In preclinical studies, we have developed and demonstrated the potential value of a novel imaging approach, called diffusion basis spectrum imaging (DBSI). Here we plan to translate our promising approach to clinical populations to improve diagnosis, optimize treatment selection, and better predict clinical outcomes for survivors of acute SCI. In this proposal, we aim to determine the utility of DBSI as a non-invasive biomarker for SCI. We hypothesize that pathologies in patients with SCI can be accurately assessed by DBSI and that DBSI-defined abnormalities correlate with neurological and functional impairments. Identifying a non-invasive, quantitative biomarker of neuropathology and neurological impairment will provide important insights into the pathological mechanisms underlying neurological phenotypes in SCI.

Diane Aum, MD, Washington University in St. Louis
Award: NREF & Henry G. Schwartz Research Fellowship Grant
Project Title: Determinants of Cognitive Outcome through Functional Resting State and White Matter Connectivity in Pediatric Patients with Posterior Fossa Tumors
Sponsor: Eric Leuthardt, MD, FAANS

Pediatric brain tumors are the most common solid tumors of childhood and account for nearly half of all pediatric oncology diagnoses. Many survivors frequently face life-long debilitating, cognitive deficits, which represent the greatest barrier to full independence in their adult lives. This project will study the impact of disruption of resting state functional connectivity and anatomical white matter connectivity on neurocognitive disability in this patient population. We plan to assess resting state functional connectivity using cortical and subcortical regions of interest and assess anatomical white matter connectivity using diffusion tensor imaging analysis. There has been growing interest in in cerebellar function, as many emerging studies have implicated cerebellar connectivity in neuropsychological disorders. This study could help elucidate the functional effects of the cerebellum on other regions of the brain, by identifying radiomic biomarkers as prognosticators for neurocognitive outcome.

Gabriel Friedman, MD, Massachusetts Institute of Technology
Award: NREF & Academy of Neurological Surgeons Research Fellowship Grant
Project Title: Recapitulating proprioceptive function via biological actuation in a neural prosthetic model
Sponsor: Hugh Herr, PhD

Neural prosthetic systems are devices that interface with the nervous system to restore function in the setting of spinal cord injury, stroke, motor paralysis, amputation, and other causes of neurological disability. Existing devices can decode signals from the brain and produce movement in the extremities, but sensory feedback in these systems is still quite limited. Proprioception is the sensation of limb position and is important for movement planning, but has yet to be integrated into existing neural prosthetic systems.

In this project, I will explore using a novel construct called the proprioceptive mechanoneural interface (PMI). This interface can modulate afferent proprioceptive signals going back into the nervous system through stimulation of muscle tissue paired with a biological actuator. Ultimately, I will assess whether this PMI construct is able to improve gait dynamics in the rodent model. If successful, this project will be a critical step in incorporating naturalistic proprioceptive function into next-generation neural prosthetic systems.

Christopher S. Graffeo, MD, University of Oklahoma
Award: NREF & Albert L. Rhoton Young Clinician Investigator Award
Project Title: Skull Basics: Novel Tools for Simulation & Education in Complex Cranial Surgery
Sponsor: Ian F. Dunn, MD, FAANS

Christopher S. Graffeo's research interest, Skull Basics, is focused on the development, testing, and dissemination of novel tools for complex cranial education that incorporate new technologies such as virtual/augmented reality, 3D printing, and advanced simulation systems.

In the innovative spirit of Professor Rhoton's neuroanatomy corpus, Skull Basics describe a novel approach to building, testing, and distributing tools for advancing simulation and education for complex cranial surgery, with the goal of accelerating knowledge acquisition among trainees, advancing neurosurgical pedagogy, and improving patient safety.

Trevor Hardigan, MD, PhD, Mount Sinai Health System
Award: Academy of Neurological Surgeons Research Fellowship Grant
Project Title: The role of IL-3 in the regulation of post-stroke inflammation
Sponsor: Filip K. Swirski, PhD

Ischemic stroke remains a devastating health issue worldwide despite recent therapeutic advances including mechanical thrombectomy. It is the second leading cause of death worldwide and leaves up to 80% of survivors with a permanent neurological disability. The recovery from stroke is dependent on a multitude of factors, and it has become increasingly clear that inflammation and the immune system play a critical role in this process. Understanding the dynamic inflammatory response after ischemic stroke has the potential to transform the standard of care for these patients. We have shown that diseases like stroke affect the generation of different immune cells and the number of these cells circulating in the blood. We have also shown how a specific inflammatory factor called interleukin-3 regulates these processes in other diseases. We will show in the study how interleukin-3 is involved in post-stroke inflammation and recovery.

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Peter J. Madsen, MD, Children's Hospital of Philadelphia
Award: NREF & AANS/CNS Section on Pediatric Neurosurgery Young Clinician Investigator Award
Project Title: Development of CAR-T cells against claudin-6 in atypical teratoid/rhabdoid tumor
Sponsor: Adam C. Resnick, PhD

Atypical teratoid/rhabdoid tumor (ATRT) is a highly aggressive brain tumor that tends to affect young children. There are very limited treatment options for these children and the five-year survival rate is less than 40%. This research sets out to test a chimeric antigen receptor (CAR) T cell therapy that uses an engineered T cell capable of binding to a specific protein on the surface of ATRT cells and initiating targeted tumor cell killing. Success of this work will form the basis of a clinical trial of CAR-T cell therapy in children with ATRT.

Angela M. Richardson, MD, PhD, Indiana University
Award: NREF & AANS/CNS Section on Tumors Young Clinician Investigator Award
Project Title: Tumor selective retroviral replicating vectors for the treatment of leptomeningeal medulloblastoma
Sponsor: Karen E. Pollok, PhD

This grant will investigate the use of a viral vector to infect tumor cells and implant a "suicide gene". This gene (cytosine deaminase) is then able to converted a benign oral medication (5-fluorocytosine) into a toxic chemotherapy drug (5-flurouracil) within the tumor cells. Medulloblastoma is a the most common solid brain tumor in children, and preliminary data suggests that this viral vector along with prodrug is capable of spreading through, and killing, tumor cells. This grant investigates the use of this viral vector technology in the most lethal form of medulloblastoma, leptomeningeal spread, where tumors occur throughout the entire brain and spine in a mouse model of disease.

Ashish Shah, MD, University of Miami
Award: NREF & Andrew T. Parsa Young Clinician Investigator Award
Project Title: Epigenetic potentiation of immune checkpoint inhibition through endogenous retroviral immune responses
Sponsor: Maria Figueroa

Glioblastoma is a uniformly fatal disease afflicting over 12,000 new patients yearly with a poor prognosis despite maximal safe resection and chemoradiation Therefore, novel treatment modalities must be explored to improve outcomes for patients suffering from this disease. Although immunotherapies have demonstrated positive outcomes in some cancers, recent immunotherapy trials have failed to demonstrate success in glioblastoma. We are using a novel approach to elicit anti-tumor immune responses in glioblastoma through reactivation of endogenous retroviral elements (viral mimicry). We hope to use viral mimicry to improve responses to immunotherapy in glioblastoma patients, and ultimately translate these findings to clinical trials.

Genaro R. Villa, MD, PhD, Brigham and Women's Hospital
Award: NREF & StacheStrong Research Fellowship Grant on behalf of the AANS/CNS Section on Tumors
Project Title: Assessing Tumor-Associated Macrophage Plasticity Regulation by HNRNPH1 to Augment Adaptive Antitumor Responses in Glioblastoma
Sponsor: E. Antonio Chiocca, MD PhD FAANS

Immunotherapy has not shown significant improvement in survival in patients with Glioblastoma (GBM), in part due to the immunosuppressive tumor microenvironment (TME). Identifying molecular pathways that contribute to immune suppression in GBM cells and the TME may provide a synergistic therapeutic approach to immunotherapy. Tumor-associated macrophages (TAMs) contribute to immunotherapy resistance in GBM. However, the pathways regulating glioblastoma TAM polarization to an anti- and pro-tumor state are not well understood. We propose the heterogeneous nuclear ribonucleoprotein H1 (HNRNPH1) is a key regulator of interferong signaling in GBM and TAM polarization. HNRNPH1 knockdown upregulates interferon-stimulated gene expression in GBM cells, rendering them sensitive to immunotherapy and, importantly, reprograms macrophages to an anti-tumor state. Through a high-dimensional multi-omics approach, we will identify the pathway by which HNRNPH1 regulates TAM polarization, correlate this to GBM patient outcome, and identify HNRNPH1 as a target and biomarker providing a therapeutic approach augment adaptive antitumor responses.

Mark William Youngblood, MD, Northwestern University
Award: 2022-23 NREF & Southeastern Brain Tumor Foundation (SBTF) Research Fellowship Grant on behalf of the AANS/CNS Section on Tumors
Project Title: Molecular Markers of Meningioma Growth Arrest after HDAC Inhibition
Sponsor: Craig Horbinski, MD, PhD

The molecular events that cause meningioma formation and progression are increasingly well-understood, however effective chemotherapies remain elusive. Previous studies have shown that histone deacetylase inhibitors (HDACi) may hold promise, however additional pre-clinical tests are needed before this medication can be trialed in humans. In the present study, we will identify molecular biomarkers that predict response of meningioma patients to HDACi. Tumor cells from responsive and resistant patients will be compared to determine key distinguishing features, and in a similar fashion, cells will be compared before and after treatment to determine potential mechanisms of this drug. The results will lay essential groundwork for future clinical trials, providing key markers for prospective patient stratification, identification of potential synergistic co-therapies, and pathways of resistance.

John K. Yue, MD, University of California, San Francisco
Award: NREF & Bagan Family Foundation Research Fellowship Grant
Project Title: Improving Traumatic Brain Injury Stratification and Prognosis through Big Data Harmonization and Machine Learning
Sponsor: Geoffrey T. Manley, MD, PhD, FAANS

While understanding of the molecular and cellular mechanisms of traumatic brain injury (TBI) has improved over the past 30 years, these advances have not translated into a successful Phase 3 clinical trial. Barriers include innate heterogeneity of TBI, outdated classification systems, and the complex natural history of recovery, which pose challenges to accurate risk stratification. This proposal aims to harmonize and analyze the deeply-phenotyped data of large multicenter prospective studies (combined N $\sim$ 10,000) to bridge these key evidence gaps. Harmonized data will be interrogated using dynamic prediction models and machine learning techniques to better predict heterogeneous outcomes after TBI, and identify factors associated with trajectories of recovery. The fitted models will aid in creating novel precision medicine classifications of TBI patients, and identify who would most benefit from emerging treatment trials.