2021 Medical Student Summer Research Fellowships – Awardee Abstracts

Oluwaseyi Adeuyan, The Neurological Institute at NYP/Columbia University Irving Medical Center
Project Title: Targeting GPX4 for the Induction of Ferroptosis in GBM

Despite aggressive therapy, glioblastoma (GBM) invariably recurs. A slowly proliferating subpopulation of glioma cells, resistant to conventional chemotherapy and radiation, is the likely culprit. These dormant cells have been shown to predominantly undergo lipid peroxidation instead of glycolysis, the main energy source in rapidly proliferating tumor cells[1]. Ferroptosis, an iron-driven, nonapoptotic form of cell death, is driven by lipid peroxidation and may therefore provide a promising therapeutic avenue in conjunction with standard chemotherapy. GPX4 is a lipid repair enzyme and key regulator in the ferroptosis pathway[2]. By testing GPX4 inhibitors and the TOP2A inhibitor Etoposide *in vivo* using a murine glioma model as well as in *ex vivo* human slice cultures, we may be able to analyze their differential effects on discrete glioma cell subpopulations. In order to predict treatment response, we also propose identifying potential biomarkers of responders to ferroptosis.

Jonathan Bao, Albany Medical College
Project Title: The effect of low intensity pulsed focused ultrasound on neuronal activity in pain processing regions of the brain

Chronic pain affects millions of Americans, but effective, non-invasive treatments are limited. Our lab has utilized external low intensity pulsed focused ultrasound (liFUS) to treat chronic neuropathic pain in animal models without histological damage or tachyphylaxis. However, the mechanism of action remains unknown. Previously, we demonstrated electrophysiological changes downstream of the dorsal root ganglion (DRG) treatment site following liFUS. Here, we hypothesize that liFUS treatment of the L5 DRG acutely alters brain neuronal activity in a rat model of chronic neuropathic pain. Electrophysiological recordings will be performed in the primary somatosensory cortex and anterior cingulate cortex before and after liFUS administration. Preliminary results have indicated that liFUS significantly increases neuronal firing in the primary somatosensory cortex. Increased neuronal activity has been associated with pain relief through activation of inhibitory pain pathways. We believe these increases may account for the long-term behavioral effects induced by a 3-minute liFUS treatment.

Megan Bauman, Mayo Clinic
Project Title: Inhibition of IDO-1 in Glioma-Derived Extracellular Vesicles

Indoleamine 2,3-dioxygenase (IDO-1) is an enzyme overexpressed in glioblastomas (GBM) and catalyzes the conversion of tryptophan to kynurenine, which has been implicated in tumor evasion. Kynurenine is also overexpressed in extracellular vesicles (EVs) released from GBMs. EVs have been shown to induce immunosuppression by increasing differentiation of myeloid-derived suppressor cells (MDSCs), thereby downregulating T-cell proliferation. Therefore, the inhibition of IDO-1 may serve as a target to limit the immunosuppressive effects of EVs. We will apply the IDO-1 inhibitors to differentiated, patient-derived, GBM cell lines. The levels of tryptophan and kynurenine in the extracted EVs will allow us to determine whether IDO-1 inhibition eliminates the metabolic bias towards kynurenine. Additionally, we will apply these EVs to monocytes and T-cells to determine their effects on MDSC expansion and T-cell proliferation. We anticipate IDO-1 inhibition in EVs will cause decreased kynurenine, which in turn will decrease MDSC expansion and increase T cell proliferation.

Troy Patrick Carnwath, University of Cincinnati
Project Title: HDAC1 maintains repression of HoxB13 and drives malignant growth of IDH1 mutant gliomas

Mutations in the IDH1 gene lead to the synthesis of 2-hydroxyglutarate, an oncometabolite implicated tumorigenesis via inhibition of demethylation enzymes.[1] Aberrant, hypermethylated chromatin leads to the inactivation of crucial tumor suppressor genes.[2,3] Therapeutic efforts to inhibit IDH1 have failed;[4] however, a recent drug screen suggests that histone deacetylases (HDAC) are viable targets in IDH1-mutant gliomas. Our goal is to employ a CRISPR/Cas9 lentiviral knockout system to eliminate HDAC1 in patient-derived IDH1-mutant glioma cell lines in order to examine the effects on gene expression and histone methylation. We will conduct RNA-seq and H3K27ac/H3K27me3 ChiP-seq to quantify alterations in chromatin architecture and observe changes in cell growth. We expect to see a 2-fold decrease in methylation peaks and a 2-fold increase in gene expression at tumor suppressor loci as well as decreased proliferation in HDAC1 KO cell lines. Insights into the molecular mechanisms underlying IDH1-mutant pathophysiology will lead to novel therapeutic strategies.

1. Xu, W. *et al.* Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. *Cancer Cell* **19**, 17–30 (2011).
2. Turcan, S. *et al.* IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature* **483**, 479–483 (2012).
3. Ohm, J. E. *et al.* A stem cell-like chromatin pattern may predispose tumor suppressor genes to DNA hypermethylation and heritable silencing. *Nat. Genet.* **39**, 237–242 (2007).
4. Tateishi, K. *et al.* Extreme Vulnerability of IDH1 Mutant Cancers to NAD+ Depletion. *Cancer Cell* **28**, 773–784 (2015).

Eric Chalif, BS, University of California, San Francisco
Project Title: A Comparative Analysis of the Immunological Microenvironment Between Murine Glioma Models and Human Glioblastoma

The Aghi Lab has recently demonstrated that certain Glioblastoma (GBM) subtypes which report higher levels of such immunologic markers as cytolytic activity score and immune checkpoint gene score are also associated with a poorer prognosis. These subtypes may particularly benefit from multi-faceted immunotherapies, given their already elevated tumor CD8+ T cell levels. However, we currently lack an understanding of which targets are ideal in these “immune reactive” tumors, as well as an understanding of which mice are ideal translational models. To address this, we will perform a cross-species comparative analysis between human GBM and a comprehensive panel of six mouse models. We hypothesize that similar immunologic subtypes of GBM will be found in murine GBM models as those found in human GBM. We anticipate that our results will successfully align mouse models of GBM with their human immunological subtype counterparts, in addition to revealing multiple, rational targets for personalized immunotherapy.

Tara Dalton, Duke University
Project Title: The role of UDP-glucose-6-dehydrogenase (UGDH) in CNS metastases of hormonally responsive breast cancer

Background - Up to 30% of breast cancer patients develop metastatic disease to the central nervous system (CNS), and despite advances in screening and treatment, the incidence and morbidity of CNS metastases remains high. Evidence also demonstrates that the metastasis free-interval is a strong prognostic factor affecting the overall survival of breast cancer patients. The literature has implicated dysregulation of the protein UDP-Glucose-6-dehydrogenase (UGDH) in the spread of metastatic disease including stabilization of EMT-associated transcription factors and cell migration. In vivo, it has been demonstrated that UGDH genetic knockdown significantly reduces metastasis in murine models of breast cancer metastases.

Methods - We plan to conduct a series of murine experiments investigating the tumor growth of ER+ and ER- in wild-type and UGDH knockdown breast cancer cell lines.

Hypothesis - Mice receiving implantation of UGDH knockdown breast cancer cells will experience decreased tumor growth when compared to those receiving wild-type breast cancer cells.

Rachel Gologorsky, NYU Langone Health
Project Title: A Deep Learning Approach to Preoperative Lateralization of Pituitary Microadenomas

Preoperative localization of adrenocorticotropic hormone (ACTH)-secreting pituitary microadenomas remains a diagnostic challenge. Although pituitary MRI is the most common diagnostic study for pituitary tumors, negative MRIs occur in up to 50% of patients with biochemically confirmed Cushing's disease and surgical failure approaches 50% in this group. Inferior petrosal sinus sampling (IPSS) was developed to lateralize ACTH-secreting adenomas. Unfortunately, IPSS is invasive and has a lateralization accuracy of 69%. There is a critical need to improve preoperative localization in order to optimize the safety, accuracy, and efficacy of surgical treatment. We hypothesize that deep convolutional neural networks trained on institutionally curated pituitary adenoma MRIs and public brain MRI datasets will allow for automated detection and localization of ACTH-secreting microadenomas. In addition to the clinical contribution, we aim to contribute a methodological template for automated detection and localization of complex skull base lesions.

Sung Min (Jane) Han, MS, Keck School of Medicine of the University of Southern California
Project Title: Regulation of GBM's invasive capacity by inhibiting LH02727

Glioblastoma multiforme (GBM) is the most common malignant tumor of the central nervous system. There has been limited progress in patient outcomes because of GBM's insidious cortical invasion beyond visible tumor boundaries. To address this, our lab conducted a functional CRISPR screen of U87 and identified a novel long noncoding RNA (lncRNA) candidate, LH02727, which, upon knockdown (KD) showed significant reduction during *in vitro* GBM invasion. Following lncRNA KD, RNAseq showed that matrix metalloproteinase-3 (MMP-3) was the most significantly downregulated gene. We will build upon these findings by confirming if LH02727 KD modulates MMP-3 protein expression and if MMP-3 KD can effectively inhibit cell invasion *in vitro.* Then, we will assess the effect of LH02727 KD on tumor invasion into surrounding parenchyma *in vivo.* By characterizing the mechanism of LH02727, the prospective application of this lncRNA as a diagnostic and therapeutic target can be further explored.

Marita Ann John, Texas A&M College of Medicine
Project Title: Verbascoside antagonism of CD44 to improve post-traumatic outcomes

Traumatic brain injury (TBI) occurs in over 2.7 million Americans annually and there are no approved therapies to improve the often-devastating post-traumatic outcomes. TBI has a major immunological component related to CD74. Innate immune signaling of CD74 is initiated by binding of macrophage migration inhibitory factor (MIF) with co stimulatory CD44. Previous studies showed CD74 deletion produced neuroprotection, whereas MIF antagonism ameliorated astrocyte activation, but did not provide neuroprotection. Therefore, it is possible that the CD44 signaling component mediates the neuroprotective effects of CD74 deletion. Verbascoside (VB) antagonizes CD44 via dimerization which decreases the release of the CD44 intracellular domain and suppresses the expression of CD44. VB is antioxidant and anti-inflammatory in addition to its wound-healing and neuroprotective properties. We hypothesize that antagonizing CD44 with VB will be neuroprotective, anti-inflammatory and improve posttraumatic outcomes in a mouse TBI model.

Aditi Kulkarni, University of Minnesota
Project Title: Defining the role of LYST and lysosome function in chordoma tumorigenesis

Chordoma is a rare and malignant tumor that originates from notochord remnants. One hallmark of chordoma is the presence of physaliferous lysosome vacuoles, whose function are unknown. Additionally, mutation of LYST, a lysosome traffic regulator, occurs in 10% of chordoma patients. This project seeks to establish a mechanistic explanation for chordoma tumorigenesis of patients with LYST mutations. Our specific aims will test the hypothesis that chordoma tumor progression can be predicted by LYST-dependent lysosome trafficking in notochord cells. During this project, we will track lysosome function after LYST activation and inactivation in iPSC-derived notochord cells. Further, we will establish a genomic profile of developing mesodermal notochord cells, including LYST expression. We anticipate that this work will begin elucidating a mechanism of LYST mutation in chordoma tumorigenesis. Moreover, by robustly defining subsets chordoma genomic profiles, this project sets the foundation for a better understanding of chordoma progression and development of future therapies.

Bennett R. Levy, GW School of Medicine and Health Sciences / University of Buffalo
Project Title: A novel method for pain control in post operative spine surgery using a Q-Pump

Opioid usage has been a long standing epidemic within the United States with 450,000 deaths secondary to opioid use from 1995 to 2018. With a 10% increase in synthetic opioid use from 2017 to 2018 many providers are looking at alternative post-operative pain regimens such as ketamine infusions intraoperatively. After large scoliosis correction operations patient rely heavily on narcotics for pain control, preliminary data suggests that there is significant decrease in narcotic use in patients who receive On-Q pain pump subfascially after surgery. We aim to further study and compare if the use of these local anesthetic pumps improve not only pain control, but physical activity, and overall quality of life post operatively when a compared to patients whose pain control is not supplemented with the ON-Q pain pump.

Katherine Link, BS, NYU Langone
Project Title: Deep Learning Classification of Progression vs. Pseudoprogression of Brain Metastases Using Temporal MRI and Multi-Modal Dependencies

Brain metastases are the most common type of intracranial tumor, however it is often difficult to determine using imaging whether tumors are exhibiting true disease progression or post-treatment pseudoprogression. We propose a novel deep learning architecture to automatically determine progression status on a per-tumor basis across longitudinal imaging. The architecture will first segment metastases on T1 post-contrast MRI scans using a U-Net model trained on existing Gamma Knife segmentations. A cropped image of the tumor and contextual clinical data will then be fused into a multi-modal embedding and inputted into a recurrent neural network, which will output progression status of each tumor and will be compared to the tumor status determined from radiological reports at future time points. Successful validation of this model will enable improved identification of disease progression and thus earlier appropriate treatment and reduced unnecessary procedures, substantially improving neurosurgical management and outcomes of patients with brain metastases.

Alice Liu, Dartmouth-Hitchcock Medical Center
Project Title: A mouse model for AAV-mediated gene therapy in the PNS

Pten (phosphatase and tensin homolog) is a key regulator of neuronal development. Pten knockout in mouse sciatic nerve injury models has been shown to increase peripheral nerve outgrowth and speed recovery. Because current methods for Pten reduction cannot be replicated in humans, we must create new tools for gene-based modulation of the human PNS in order to develop PTEN-based peripheral nerve injury therapies. Adeno-Associated Virus (AAV)-mediated gene editing can provide an effective means to modulate PTEN in the PNS. I hypothesize that specific AAV serotypes display tropism for the PNS that will facilitate directed delivery of shRNA targeting Pten in regenerating neurons. Using an animal model for nerve regeneration, I will utilize viral-mediated gene therapy approaches to conditionally inactive Pten in peripheral nerves. I will assess AAV infection rates in mice, analyze live-imaged primary neuron cultures, and conduct behavioral analyses in mice to assess sciatic nerve function.

Ian Mandybur, The Ohio State University Wexner Medical Center
Project Title: Correlation of VWF levels and clinical stroke outcomes: can VWF inhibition improve thrombolytic efficacy?

Introduction - Inhibition of Von Willebrand Factor has shown promise limiting thrombosis. DTRI-031 is an RNA aptamer that inhibits VWF and has a reversible antidote.

Hypothesis - VWF levels in clots of LVO AIS patients correlate to circulating VWF, stroke severity and functional outcomes. DTRI-031 will result in superior thrombolysis in whole blood from LVO AIS patients.

Methods - Thrombus from patients undergoing mechanical thrombectomy will be scanned with a Zeiss-Axio-Scan using Orbit-Image analysis for quantification of platelets, RBCs, fibrinogen, and VWF. Circulating VWF levels will be determined using ELISA. Kinetics of clot maturation and thrombolysis by DTRI-031 will be determined using Halo Assays.

Data Analysis - Clot formation, maturation and thrombolysis will be recorded by a spectrophotometer at 510nm every minute to create a kinetic graph including maximum degradation, activation time, and maximum clot lysis rate for each treatment.

Danielle McAuliffe, Lewis Katz School of Medicine at Temple University / National Institutes of Health
Project Title: Predicting seizure trajectories using Interictal Epileptiform Discharge Patterns and Functional Connectivity to Different Propagation Zones

Epilepsy is a common neurological disorder, characterized by multiple attacks of seizure activity. Irregular and hyper cortical synchrony is thought to contribute to the mechanisms of seizures spread and is reflected by Interictal Epileptiform Discharges (IEDs), which can be recorded by implanted electrodes. The purpose of this project is to characterize how seizure onset zones form communities and interact differently with close seizure spread zones vs distant seizure spread zones. Interictal Epileptiform Discharges (IEDs) occur in consistent patterns within the seizure onset zone (SOZ) and precede the spread of interictal discharges to propagation zones, which predict seizure trajectories. Spread of epileptiform activity to local vs distant communities can be predicted by the strength and frequency of coherence between these communities and the SOZ. Statistical comparison will investigate differences between leading IED sequence propagation to local vs long range communities and frequency dependent coherence differences between communities.

Patrick Ng, BS, BA, Massachusetts General Hospital
Project Title: Human Neurophysiological Investigation of the Temporal Lobe in Memory Formation and Stability

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The single-neuronal and population activities of the human brain that underlie memory retrieval remain largely unknown. Here, we will use high-resolution multi-electrode microarrays implanted in the lateral associative temporal areas of study participants undergoing intracranial neurophysiology for standard epilepsy monitoring to study the neuronal activity patterns that are specific and unique to retrieved memories. Neuronal recordings will be conducted while participants perform structured tasks that will test hetero-associative (i.e. recollection) and auto-associative (i.e. recognition) memory processes. Spiking patterns related to retrieved memories will be analyzed with new computational techniques that have been shown to reliably infer first-, second-, and higher-order spatiotemporal network structures from stochastic spiking data. We anticipate that hetero-associative and auto-associative retrieval will elicit unique and specific higher-order neuronal activity patterns.

Anthony Piscopo, BS, University of Iowa
Project Title: Minimally Invasive Recording of the Gyrus Rectus During Embolization of Cerebral Aneurysm

Background - The Woven EndoBridge (WEB) Aneurysm Embolization System is an approved device for obliterating cerebral aneurysms and is capable of conducting electrical signals. Before deployment, its insertion wire can be connected to record from the distal wire mesh end. This transarterial approach allows recording of deep structures previously unexplored and inaccessible, such as the gyrus rectus which may have implications regarding decision-making and emotion.

Methods - Recordings will take place during awake endovascular treatment of anterior communicating artery aneurysms in 10 patients. The WEB device will be deployed, and recordings will be collected while the subject is shown stimulating questions and pictures for 10 minutes. We will compare WEB recordings to scalp electrodes.

Hypothesis - We hypothesize that electrical brain activity can be successfully recorded from the WEB device implanted in cerebral arteries. It is anticipated that signals may be detected from areas of emotion and decision-making, such as the gyrus rectus.

Je Yeong Sone, BA, University of Chicago Medicine and Biological Sciences
Project Title: Mechanistic microRNAs as Biomarkers of Cavernous Angiomas with Symptomatic Hemorrhage (CASH)

Cavernous angiomas (CAs) with symptomatic hemorrhage (CASH) have a ten-fold increase in the risk of rebleed in the subsequent five years after an initial hemorrhage, highlighting the need to accurately diagnose CASH. We hypothesize that differentially expressed (DE) plasma microRNAs with putative gene targets within the published CA transcriptome may be used as diagnostic CASH biomarkers. Plasma microRNome of 20 CASH, 20 non-CASH, and 10 non-CA control subjects matched by demographic propensity scores were sequenced and analyzed. Plasma levels of the top 5 DE microRNAs selected based on fold-change (p<0.05, false discovery rate-corrected) and putative targets in the CA transcriptome will be measured using real-time quantitative PCR (qPCR). The qPCR levels will be assessed individually and as the best weighted combination to determine their diagnostic associations with CASH. In conclusion, DE plasma microRNAs may provide novel insights into the hemorrhagic activity of CASH and help diagnosis for CASH patients.

Yohannes Tsehay, Johns Hopkins University School of Medicine
Project Title: Effect of Low-intensity Focused Ultrasound on Rats with Spinal Cord Injury

Spinal cord injury (SCI) is a devastating condition that affects about 17,000 individuals every year in the US with approximately a quarter million people living with the ramifications of the initial trauma. After the initial mechanical injury, SCI has a secondary phase where the spinal cord continues to sustain further injury due to ischemia, excitotoxicity, immune-mediated damage, mitochondrial dysfunction, apoptosis, and oxidative stress. Even with our current medical and surgical interventions, patients continue to experience poor outcomes. In traumatic brain injury animal studies, low-intensity focused ultrasound (LIFU) has been shown to improve perfusion. The efficacy of LIFU in SCI animal studies has yet to be determined. We hypothesize that LIFU treatment will increase blood perfusion to the spinal cord at the injury site. We will apply ultrasound imaging, laser speckle contrast imaging, and electrophysiology to characterize the effects of LIFU stimulation of the spinal cord in a rodent SCI model.

Alexandra J. White, Cleveland Clinic Lerner Research Institute
Project Title: Effect of Behaviorally Triggered Closed-Loop Stimulation of the Lateral Cerebellar Nucleus on Motor Recovery in a Rodent Model of Ischemic Stroke

I am honored to working under the mentorship of Kenneth Baker, PhD, a specialist in electrophysiology, and Andre Machado, MD PhD, a neurosurgeon-scientist. The lab has proposed deep brain stimulation of the cerebellum as a strategy for motor rehabilitation after stroke to the contralateral cerebral cortex. They previously demonstrated that chronic stimulation of the cerebellum in rats leads to enhanced motor recovery after stroke. My project will build on past findings to evaluate the effectiveness of behaviorally triggered cerebellar neurostimulation on motor recovery in a rodent model of stroke, with the goal of laying the groundwork for a novel approach to neurostimulation in stroke recovery. This summer, I will spend my time familiarizing myself with surgical techniques for stroke induction and electrode implantation and training animals on the behavioral task that will be used as a metric of motor recovery, accompanied by weekly meetings with my mentors to assess my progress.

Bradley Wilhelmy, The University of Maryland School of Medicine
Project Title: An evaluation of drug-induced hypothermia plus glibenclamide for improving neurological function in a rat model of traumatic spinal cord injury

Spinal cord injury (SCI) is a devastating event defined by a primary and secondary injury, the latter of which expands for several hours following the initial trauma and is a crucial determinant of recovery. Hypothermia has shown benefit in treating neurological trauma; however, traditional cooling methods carry practical limitations. Drug-induced hypothermia using dihydrocapsaicin (DHC) ameliorates many of these limitations and is actively being investigated as a therapy for SCI. Similarly, ongoing research has demonstrated the ability of glibenclamide to limit SCI lesion expansion. A synergistic combination of these treatments proved highly effective in animal models of cerebral ischemia. We aim to demonstrate a similar benefit in a clinically relevant model of SCI. We hypothesize that glibenclamide will reduce lesion expansion, thereby allowing hypothermia to be more effective. This work, using two human-safe treatments with potential for pre-hospital administration, has immediate relevance to patients suffering from such debilitating injuries.

Daniel Yang Zhang, Rush Medical College
Project Title: Minimizing Brain Shift in Deep Brain Stimulation Improves Lead Placement and Therapeutic Outcomes

Brain shift due to pneumocephalus is a cause of lead placement error in Deep Brain Stimulation (DBS) surgery. Current standard technique involves placement of burr hole and opening the dura for cranial access. This project seeks to evaluate a cranial access method that prevents pneumocephalus and thus brain shift during DBS surgery. Patients undergoing DBS surgery at the investigators' center will be randomized 1:1 to have the procedure performed with traditional technique or pneumocephalus prevention technique (PPT). The primary aim of this study is to measure efficacy of PPT in reducing brain shift and pneumocephalus compared to the standard procedure. We anticipate PPT will substantially reduce brain shift compared to traditional cranial access techniques. Furthermore, we predict reduction of brain shift will reduce surgery duration, number of passes required for electrode implantation and adverse events as well as improving therapeutic outcomes.