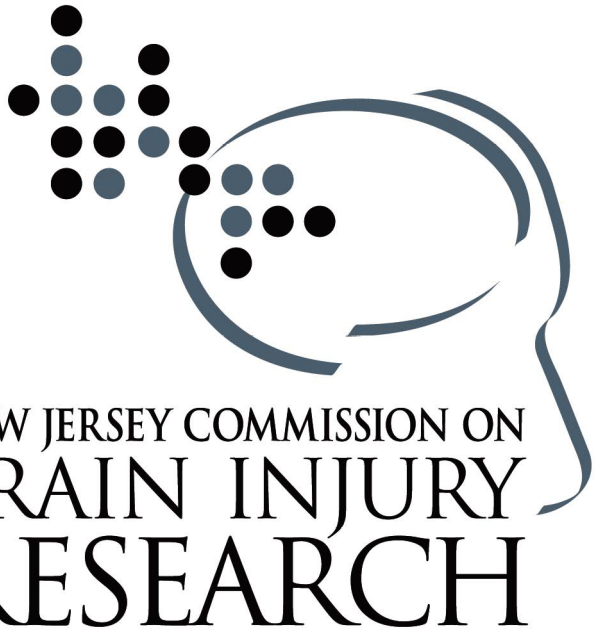

DIRECTORY OF GRANT AWARDS
2025 GRANT CYCLE
MARCH 2025

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

2025 MEMBERSHIP INFORMATION

Richard Boergers, Ph.D., ATC, Chairperson
Carolyn Daniels, D.H.Sc., M.Ed.
Sharon Cross

COMMISSION PERSONNEL

Mary Ray, Administrator
Tunisia Sye, Fiscal Manager

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

This data was compiled in compliance with the New Jersey Commission on Brain Injury Research's statutory mandate, N.J.S.A. 52:9EE-1“ …to compile a directory of brain injury research being conducted in the State.”

The information contained within this directory is not all-inclusive. The research projects and researchers listed in this directory are all based in the State of New Jersey and have applied to and received funding during the fiscal year 2025 grant cycle. The research projects are not categorized or listed in any order.

This directory is not a complete listing of all scientific research being performed within the State of New Jersey due to the proprietary nature of the research being conducted at various institutions throughout the State. In addition, institutions are not obligated to share their research information with the New Jersey Commission on Brain Injury Research.

Please feel free to contact the New Jersey Commission on Brain Injury Research at P.O. Box 360, 25 South Stockton Street, Trenton, New Jersey, 08625. The Commission's office can be reached by telephone at 609-913-5010, by fax at 609-943-4213, or by e-mail at NJCBIR@doh.nj.gov.

For information on the New Jersey Commission on Brain Injury Research's grant award process, grant applications and deadlines, please see: www.state.nj.us/health/njcbir.

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG001
Xiaobo Li, Ph.D.
New Jersey Institute of Technology
$540,000

Project Title: *Big data-based brain predictors of attention deficits and other psychopathological trajectories in youth with childhood TBI*

This study will utilize multi-construct RDoC framework and apply advanced deep learning and parametric approaches in longitudinal big data from the ACBD Study, to identify and establish robust neural predictors for TBI-related attention deficits and other psychopathological trajectories from childhood to early adolescence.

Attention deficits, such as problems in focusing and hyperactivity/impulsivity, are among the most common cognitive consequences observed in more than 35% of children within two years of their TBI. Such problems can persist into late adolescence and have been linked to the onset of severe mental and behavioral impairments. Without having established neurobiological standards, treatments and interventions of these problems in children with TBI have been based on subjective observations from clinicians and have resulted in suboptimal efficacy. Our research team has focused on understanding the neurobiological substrates of TBI-related attention deficits in children. Our recent imaging studies found that TBI-related attention deficits in children have close relationships with systems-level structural and functional brain abnormalities associated with frontal, parietal, temporal, and occipital lobes, with the altered regional topological properties in parietal and temporal regions significantly linking to elevated inattentive symptoms in children with TBI-related attention deficits. By using the advanced semi-supervised deep learning technique in a relatively larger sample, we further validated that abnormal structural and functional network topological properties associated with left prefrontal, parietal, and occipital cortices significantly predict attention deficits in children with TBI. Although results of these studies are informative about the treatment target for TBI-related attention problems, the relatively small sample sizes of these studies limit the reliability and reproducibility of the findings.

Based on our strong preliminary results, this proposed project will use both advanced deep learning and parametric approaches to test the hypothesis that neural networks subserving the NIH Research Domain Criteria (RDoC) constructs of response inhibition (RI) and attention (ATT), together with the ATT- and RI-related cognitive deficits, contribute to the shifting presentation and severity of attention deficits and other psychopathology from childhood to early adolescence in children with TBI. The longitudinal dataset from the Adolescent Brain Cognitive Development (ABCD) Study will be used to test this overall hypothesis. The ABCD Study acquires fMRI data during processes of ATT, RI, and resting-state, as well as substantial phenotypic measures of ATT and RI through our-of-scanner paradigms in a large community

sample of children from their 9-10 years of age and are repeating these measures through adulthood. Roughly 455 children in the ABCD Study baseline pool reported histories of TBI, allowing us to conduct big data-based and longitudinal investigations that significantly guarantee the power and reproducibility of the proposed studies. This project will develop a mechanistic model of the psycho-biological factors that promote TBI-related attention deficits and other psychopathology at different ages. Success of the proposed research will provide valid biomarkers to facilitate the development of tailored diagnostic, treatment and intervention strategies in affected children.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG005
Ying Xu, M.D., Ph.D.
Rutgers Biomedical and Health Sciences
$515,623

Project Title: *Novel Mitochondrial Phosphodiesterase-2A Selective Inhibitors and Traumatic Brain Injury Induced Dementia*

This proposal aims to validate PDE2A, particularly the mitochondrial PDE2A isoform, as a mediator of mitochondrial fission and fusion dynamic dysfunction, neurodegeneration, and cognitive deficits after traumatic brain injury (TBI), and develop and validate novel mitochondria-specific inhibitors targeting PDE2A to improve TBI-induced dementia using cell and mouse models of Alzheimer's disease (AD).

Traumatic brain injury (TBI) is a significant risk factor for dementia, particularly among adults aged 65 and older, who are most likely to experience TBI. Individuals with a history of mild TBI increase the risk of developing Alzheimer's disease (AD) related dementia (ADRD) by 17%. This may be due to an increased accumulation of ß-amyloid and oxidative stress in the brain, which are linked to mitochondrial dysfunction. Mitochondrial dysfunction is recognized as an early pathological feature in TBI-induced ADRD. Recent studies suggest that both the amyloid precursor protein (APP) and Aß are localized to mitochondria. Regulation of mitochondrial dysfunction could be a promising therapeutic approach for rescuing TBI and preventing progression to AD. An enzyme called phosphodiesterase 2A (PDE2A) is an essential regulator of two intracellular signaling molecules, cAMP and cGMP, which are important for cognition. PDE2A isoform 2 (PDE2A2) is localized at the mitochondria, where it is involved in mitochondrial dynamic equilibrium by regulation of local cAMP and cGMP signaling. Dysregulation of PDE2A2 signaling within mitochondria after TBI contributes to the development of AD. To date, the development of PDE2A inhibitors has not progressed, mainly due to their toxicity and poor tolerability. Targeting the mitochondrial PDE2A2 isoform instead of the cytosolic PDE2A1 and PDE2A3 isoforms would greatly reduce toxicity and side effects. Thus, in this proposal, we will develop novel mitochondria-targeting PDE2A2 inhibitors with high affinity and selectivity. We will determine if inhibition of mitochondrial PDE2A in mice after TBI slows or halts their progression to ADRD. The proposed work will determine if mitochondrial PDE2A2 contributes to memory impairments caused by TBI, and if mitochondria-specific PDE2A inhibitors could be a new class of drugs for treating TBI and progression to ADRD.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG013
Bruce A. Citron, Ph.D.
Veterans Biomedical Research Institute
$540,000

Project Title: *Hippocampal effects of repetitive closed head traumatic brain injuries*

To advance the development of effective therapy we will investigate modulation of cell specific regulatory changes in the hippocampal region of the brain that result from repetitive traumatic brain injury and treatment.

Approximately 200,000 New Jersey residents are presently suffering from consequences related to traumatic brain injury (TBI) and 13,500 more are diagnosed with TBI each year. TBI is also the greatest environmental risk factor for developing Parkinson's disease later in life. Due to the variability of TBI and wide variety of cell types present in the brain, the exact mechanisms that drive brain cells to degenerate after a TBI remain unknown, especially at longer times after injury and in particularly sensitive brain regions involved in learning and memory. Recent advances in single cell sequencing have provided the capability to determine the genetic expression changes, after repetitive TBI, unique to specific types of neurons and supporting brain cells (glia). This technique will enable identification of cell specific genetic changes after repetitive TBI and treatment. This in turn will yield a better understanding of the fundamental changes in each cell type following a TBI and help develop more effective treatments. This investigation begins by focusing on the hippocampus region of the brain that governs the formation of new memories, spatial navigation and emotions. Damage to the hippocampus is responsible for both short-term and long-term neuropsychiatric disorders following a TBI such as impaired memory, PTSD, and depression. Genes activated by the treatments under test can be protective after TBI. The goal is to quantify the expression of changes and the influence of different genes in each of the brain cell types present in the hippocampus following repetitive TBI and treatment. This will result in a better understanding of the underlying causes of functional loss in the brain and how to correct it.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG015
KiBum Lee, Ph.D.
Rutgers, The State University
$540,000

Project Title: *Harvesting Opioid Receptor Antagonist-derived Extracellular Vesicles (EVs) from Neural Stem Cells (NSCs) to Enhance Neuronal Differentiation Following TBI*

This project aims to investigate the neuroregenerative potential of extracellular vesicles derived from opioid receptor antagonist treatment, utilizing metabolomic and transcriptomic approaches to identify neurogenic therapies and therapeutic targets, ultimately contributing to the development of more effective treatments for traumatic brain injury (TBI) and improving patient outcomes.

This research project aims to develop and evaluate new therapeutic strategies for enhancing recovery from brain injuries. By leveraging advanced transcriptomic and metabolomic techniques, we seek to identify new therapeutic moieties capable of modulating key biological pathways involved in Neural Stem Cells (NSCs) to replace dysfunctional neurons following injury. Our approach integrates nanotechnology, chemical biology, and neuroscience to address the complex challenges of neurotrauma, ultimately aiming to provide more effective treatment options.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG016
Steven W. Levison, Ph.D.
Rutgers Biomedical and Health Sciences
$537,628

Project Title: *LIF nanoparticles to prevent delayed neurodegeneration after mTBI*

The goal of this proposal is to perform preclinical studies to test the feasibility of administering leukemia inhibitory factor either in soluble form or within nanoparticles during the chronic stage of recovery to prevent axonal degeneration, gliosis and to improve neurological function.

Concussions are prevalent among young adults due to sports-related injuries, car accidents and from injuries sustained in the military. It has been estimated that 12,000 to 15,000 New Jersey residents suffer brain injuries from traumatic events each year. For those survivors, the medical and non-medical costs have been estimated to be $152,000 to $196,000 respectively. Progress is being made in developing neuroprotective strategies to reduce acute brain injury; however, there is an unmet need for therapeutics that can be delivered during the chronic period of recovery which can restore neurological function by preventing delayed axonal injury and by promoting re- myelination. Work in my lab over the past decade has established that a naturally produced injury signal known as leukemia inhibitory factor (aka LIF) dampens the degree of brain injury, whether administered either acutely or after a significant delay. Therefore, the goal of this application is to test the therapeutic benefits of delivering nose drops containing LIF either in an un-encapsulated formulation or encapsulated with nanoparticles. Completing these studies will answer several key questions about the long-term efficacy of delayed intranasal LIF treatment on preventing axonal injury, promoting myelination and preserving neurological functional after mild TBI. Our preliminary data support the feasibility of these studies which, when translated into clinical trials could enable individuals who have sustained a head injury to live more independent and productive lives.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG017
Sona Patel, Ph.D.
Seton Hall University
$404,362

Project Title: *Comprehensive Monitoring of Cognitive, Sleep, Emotional, and Speech Disruptions in Concussion Recovery*

Using a within- and between-subjects design, we aim to examine how impairments in cognitive-linguistic speech integrity, cognitive flexibility, sleep quality, and emotional control and reactivity manifest and interact during concussion recovery.

There is growing awareness about the immediate and long-term risks to neurological health caused by sports-related concussion. In response, there are increasing calls for more sensitive and comprehensive symptom monitoring. The most recent Consensus Statement on Concussion in Sport calls directly for the use of more sensitive measures of cognition and emotional status post-concussion. However, current clinical methods of assessment fail to capture the array of impairments that develop in the post-concussion period. More sensitive comprehensive assessments have not been adopted as the standard of care due to costs and the lack of clarity regarding the severity of changes in speech, cognitive, sleep, and emotional performance.

Our previous research has shown that in various neurological conditions, speech is a robust indicator of dysfunction that conveys emotional, physiological, cognitive, and motor information. The goal of this research is to rigorously examine changes across a comprehensive range of symptom domains throughout concussion recovery and to determine the relatedness and recovery patterns associated. Specifically, we will explore how impairments in cognitive flexibility, speech errors, sleep quality, and emotional regulation interact and influence each other, potentially exacerbating or alleviating symptom severity and duration.

Using a within- and between-subjects design, we will compare the evolution of symptoms in Division I athletes who have sustained concussions with an athlete control group, providing a detailed analysis of how these impairments manifest and evolve in both groups. Understanding how interrelated symptoms evolve and the influence of this on concussion recovery is critical for the future development of targeted diagnostic and therapeutic recommendations, including tailored guidelines for domain-specific and multi-domain interventions, as well as preventative measures to reduce the risk of secondary injury in young athletes. Identifying existing patterns in symptom presence and evolution during concussion recovery will result in a direct impact on the standard of care and improve the safety, health, and rehabilitation outcomes of student-athletes in New Jersey who sustain a concussion.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG022
Jessica Loweth, Ph.D.
Rowan University
$540,000

Project Title: *Investigating the neuromolecular mechanism linking repetitive mild traumatic brain injury and oxycodone craving*

Using rodent models of repetitive mild traumatic brain injury and drug craving and relapse vulnerability, this proposal investigates mechanisms through which repetitive mild TBI alters the reward circuitry to impact oxycodone craving.

Research over the past two decades has revealed that mild traumatic brain injuries like concussions can alter reward processing and addiction liability. Individuals with a TBI are particularly at risk for misusing prescription opioids like oxycodone used to treat injury-induced pain. This chronic use and misuse of prescription opioids increases in individuals that have experienced mild repeated traumatic brain injuries (rmTBI), like professional athletes and military personnel. This is a serious problem because we now know that most individuals initiate compulsive opioid misuse with prescription opioids like oxycodone before transitioning to illicit opioids like heroin or fentanyl. As a result, prescription opioid misuse has significantly contributed to the current opioid epidemic, in which we have observed more than a threefold increase in opioid-related overdose deaths over the past decade alone. Therefore, understanding the impact of risk factors like rmTBI on oxycodone use and misuse is necessary to reduce overall opioid addiction risk. A critical component driving continued oxycodone use are drug-associated cues that elicit intense drug cravings and promote drug use even after periods of prolonged abstinence. While evidence indicates that prior rmTBI exposure produces changes within the brain that impact oxycodone seeking or craving, how rmTBI and oxycodone exposure interact at the neuronal level to impact craving is unknown. Identifying mechanisms through which rmTBI alters the reward circuitry to impact compulsive drug taking and seeking behavior is necessary in order to develop effective therapeutic treatments to both reduce pain and prevent prescription opioid misuse post-injury. Using molecular and behavioral pharmacology approaches in rodent models of rmTBI and substance use disorders, the proposed studies will advance our understanding of how rmTBI impacts oxycodone craving and relapse vulnerability.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR25IRG024
Simiao Niu, Ph.D.
Rutgers, The State University
$540,000

Project Title: *Battery-free Wearable Motion Sensors for Assessing Locomotor Behavior and Rehabilitation after Traumatic Brain Injury*

The projects employ battery-free wearable motion sensors (accelerometer and gyroscope) to monitor mice's activities following TBI, and subsequently develop an algorithm that utilizes the collected motion data to automatically generate a neurological severity score to assess rehabilitation of traumatic brain injury.

Human traumatic brain injury (TBI) is the leading cause of death and disability in children and young adults in the United States. TBI is defined as a blow to the head that disrupts brain function and results in temporary or permanent neurological damage including loss of memory, cognitive function, and motor function, and results in temporary or permanent neurological damage including loss of memory, cognitive function, and motor function. Currently, there is no effective treatment for TBI since little can be done to reverse the tissue damage caused by trauma. It is estimated that 5.3 million individuals in the United States are living with disabilities from TBI. TBI is responsible for approximately 282,000 emergency room visits and 56,000 deaths annually. The annual economic burden of direct and indirect costs for TBI in the United States alone is estimated around $50 billion annually. Consequently, patients with TBI often require long-term rehabilitation and comprehensive support, encompassing cognitive rehabilitation, physical therapy, occupational therapy, speech and language therapy, psychological assistance, and family support, leading to substantial healthcare burdens. Despite numerous available preclinical studies on TBI intervention in animal research, a technology gap persists in continuously, autonomously, and accurately evaluating the intervention's locomotor and neurological behavioral outcomes, and thus, the TBI rehabilitation status in animal research, as locomotion and brain functionalities are closely interconnected. Normal locomotion is a key biomarker that reflects normal brain functionality and robust TBI rehabilitation status. Currently, methods for assessing motor and neurobehavioral outcomes in animal research mainly include the Neurological Severity Score (NSS), which evaluates neurological function in animal models by assessing the performance when animals perform various behavioral tasks related to motor abilities, reflexes, and responses to external stimuli. However, the generation of NSS is far from ideal since its evaluation heavily relies on the observers' subjective judgments and thus causes potential human bias. Additionally, the NSS requires operators to manually bring the mice to perform various tasks, lacking autonomous measures. Consequently, due to the difficulty in NSS generation, researchers face challenges in selecting the most suitable clinical interventions, slowing down the development process of new TBI therapies. Thus, there is a critical need to create a cost-effective, continuous, autonomous, data-efficient, and wearable monitoring tool capable of evaluating the motor and neurobehavioral behavior and effectiveness of clinical interventions for TBI animal models. Such a tool could pave the way for future developments with similar functionalities for human patients.

To solve the above challenge, in this proposal, we proposed to build a flexible, wireless, battery-free, and wearable motion sensor patch incorporating accelerometers and gyroscopes to accurately measure animal locomotor activities. Additionally, we proposed to develop a Kalman filter based motion processing and machine learning algorithm that can automatically analyze the motion and activity data to generate a neurological severity score and evaluate the TBI rehabilitation process.

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PILOT RESEARCH GRANT RECIPIENT:

CBIR25PIL001
Meghan Davis Caulfield, Ph.D.
Seton Hall University
$75,130

Project Title: *Neurobehavioral correlates of traumatic brain injury in New Jersey college students*

This research project aims to investigate the behavioral, neural, and physiological impacts of brain injury in college students by measuring brain activity of the prefrontal cortex while participants complete a task of cognitive impulsivity and by assessing brain-stem mediated reflexes to identify novel neural and physiological biomarkers associated with brain injury history and severity in a high-risk population.

The prevalence of brain injury in young adults is a major public health issue, with far-reaching implications for individual health and societal resources. Young adults comprise the highest incidence of concussion of any age group. This high incidence is particularly concerning given that brain injury, even when classified as "mild" such as in a concussion, can have long-term consequences for cognitive and physiological processes. These consequences may include persistent difficulties with attention, memory, decision-making, and impulse control, potentially impacting academic performance, social relationships, and future career prospects. Despite the prevalence and potential severity of these injuries, there remains a critical need for more sensitive and accessible methods to detect, monitor, and treat brain injuries in this vulnerable population.

This study, which is a collaboration between scientists at Seton Hall University in South Orange, NJ and the US Department of Veterans Affairs in East Orange, NJ, looks at how brain injury impacts decision-making and brain activity in college-aged students at Seton Hall University. Specifically, we will assess how undergraduate students perform on a behavioral task that measures impulsivity and shortsightedness in decision-making.

Brain injury has been shown to alter decision-making behavior on a temporal discounting task that measures impulsivity and myopia for the future, and this alteration may persist years after the injury. Given that post-adolescents tend to perform more impulsively on temporal discounting tasks than older adults, we aim to determine whether brain injury exacerbates that behavior. Further, we will use measures of brain activity recorded via functional near infrared spectroscopy (fNIRS) to determine whether neural activity of the prefrontal cortex varies as a function of brain injury history and temporal discounting. By comparing behavior and brain activity of participants with and without a history of brain injury, we hope to identify key behavioral and neural patterns associated with concussion history and improve understanding of how concussion may alter decision-making in a high-risk population.

We will also further explore a novel non-invasive biomarker of brain injury by examining whether the acoustic startle response, a brainstem-mediated physiological response to a sudden loud noise, is related to behavioral and neural performance. An understanding of how brain

injury may impact physiological reactions can provide an objective measure of brain injury history and severity to complement self-reported histories provided by participants. This multifaceted approach combining behavioral tasks, neuroimaging, and physiological measures will offer a comprehensive understanding of how brain injury affects neural function and behavior in college-aged adults.

This research will address the unique vulnerability and characteristics of an age group that shoulders a high burden of brain injury incidence and hopefully offer crucial insights into the physiological and cognitive changes that occur following brain injury. Insights from our study can provide novel context into understanding and predicting behavioral changes after brain injury, may reveal novel non-invasive biomarkers of brain injury, and present new pathways for development of patient centered treatment approaches for a high-risk population.

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PILOT RESEARCH GRANT RECIPIENT:

CBIR25PIL006
Rajarshi Chattaraj, Ph.D.
New Jersey Institute of Technology
$180,000

Project Title: *Treatment of repetitive blast TBI with ultrasound-guided xenon and argon microbubbles*

The proposed work involves establishing a novel treatment platform of targeted therapeutic gas delivery to the brain for the treatment of traumatic brain injury caused by exposure to repetitive low-level blasts.

Traumatic Brain Injury (TBI) is a serious health problem, with mild injuries accounting for over 80% of reported cases. Of these, military and law enforcement personnel experience mild injury through low level blasts repeatedly as part of routine training and field use of heavy weaponry, repetitive blasts from breaching, and flash-bang stun grenades. Several government- and privately- investigated reports, including investigations by the New York Times, have found that such injuries can often lead to chronic conditions such as PTSD, depression, anxiety, and memory loss in veterans and current military personnel. These effects derive from degeneration at the brain cellular level following repeated injuries. In spite of extensive research in this field, treatments for brain injury are few and largely palliative. In the last few years, inhalation of therapeutic gases like xenon and argon have shown excellent promise in treating the mechanisms underlying the progression of injury in the brain. Importantly, both gases can freely diffuse through the blood brain barrier (BBB), overcoming a major hurdle for current TBI candidate drugs. However, inhalation is a non-targeted, systemic method of treatment, wherein the overwhelming majority of the administered gas goes to waste, increasing the probability of side effects, and making it, in the case of xenon, often prohibitively expensive. As a solution, we propose the utilization of microbubbles (MBs) to encapsulate gases in their core. As their name suggest, these are bubbles (gas core, protected by lipids, similar to ones found in our own cells) are micrometer-sized (less than a tenth of the width of human hair). These bubbles can be injected through a standard IV line and need hundreds of times less gas to treat the same magnitude of injury. Simple clinical ultrasound (found in all hospitals, and nowadays, connectable to phones and tables) can rupture bubbles and make the bubbles release gas locally near the brain instead of systemically throughout the body. We will test the extent of treatment by bubbles in mice by exposing them to rLLB using our in-house blast shock tube. We will assess the memory, motor functions, anxiety and depression levels of the animals, both in the acute and chronic stages, with and without treatment. We will then extract their brain tissue to look for molecular markers of injury progression using microscopy and flow cytometry. We will correlate the behavior and histological results to build a baseline which will help future research for examining and treating such injuries. Successful accomplishment of these aims will validate a novel local delivery agent (bubbles) with no adverse effects and BBB-permeabilizing ability (xenon and argon) for image-guided, controllable treatment of repetitive blast TBI, using a safe, non-invasive, commonly available, and relatively inexpensive technique (ultrasound).

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CBIR25FEL010
Vaidehi Apte
Rutgers, the State University
$168,000

Project Title: *Attenuating Mitochondrial Dysfunction to Restore Impaired Endothelial Barrier Integrity & Function*

We propose studies to attenuate mitochondrial dysfunction in injured endothelial barriers, modeling the endothelial component of the impaired blood brain barrier post-traumatic brain injury, to restore barrier integrity and cellular function, identifying a clinically translatable therapeutic target.

Traumatic brain injuries (TBIs) are common and strain healthcare systems. When patients experience a TBI, the blood-brain barrier, which protects the brain, becomes damaged. This allows harmful and inflammatory substances to enter the brain, which can lead to further brain damage and inflammation. One of the early problems after a TBI is mitochondrial dysfunction at the blood-brain barrier, which occurs within hours and plays an integral role in progressing the injury, highlighting mitochondrial dysfunction as a key target for treatment. The secondary effects of TBIs can lead to a range of symptoms, from headaches and blurry vision to more serious issues like cognitive and motor impairment. Current treatments focus on managing these symptoms and reducing brain inflammation with anti-inflammatory drugs. However, they cannot stop the early and ongoing entry of harmful molecules through the damaged blood-brain barrier, driving secondary TBI. Thus, early treatment that focuses on repairing the blood-brain barrier is essential. This study aims to investigate the therapeutic potential of attenuating mitochondrial dysfunction in in vitro endothelial barriers, the main component of the blood brain barrier, and in in vivo murine models of traumatic brain injury. Mitochondrial dysfunction can be attenuated via two approaches: mitochondria specific soluble drugs or mitochondrial transplantation, both of which have successfully recovered endothelial barrier injuries of the heart, lungs, and kidneys. Successful completion of these studies will provide evidence for a new therapeutic target, mitochondrial dysfunction, to restore the endothelial barrier in post-traumatic brain injury blood brain barrier breakdown. It will also evaluate the therapeutic potential of two mitochondria-specific approaches in in vitro and in vivo models of TBI.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CBIR25FEL014
Connor Dunn
The Trustees of Princeton University
$150,000

Project Title: *Understanding and preventing Toll-like receptor 9-induced dendritic loss in traumatic brain injury*

I aim to understand the mechanisms by which the cellular damage sensor TLR9 disrupts dendritic morphology, and to test TLR9-based approaches to ameliorate dendritic loss after traumatic brain injury.

Traumatic brain injury (TBI) is a major public health concern and poses a significant economic burden, but there are currently no effective treatment options. After the initial injury, there is a secondary, delayed phase of TBI in which additional injury occurs, offering a window for therapeutic intervention. Immune system activation is a hallmark of this secondary phase of TBI. In particular, after brain injury, molecular signals released by damaged cells activate the immunoreceptor Toll-like receptor 9 (TLR9). However, TLR9's effects on TBI progression and recovery remain unknown. We recently found that activation of TLR9 in healthy animals unexpectedly causes neurons to lose connections, and dampens their ability to communicate, resembling changes that occur after TBI. Our findings suggest that TLR9 could contribute to weakening and loss of brain circuitry during the second stage of TBI. The goal of this proposal is to learn more about how TLR9 activation impacts neurons and to determine if the negative effects of TLR9 can be prevented to protect neurons from secondary injury. To achieve those goals, we will identify the cell types that contain TLR9 in the healthy brain, and test if removing TLR9 from those cells can protect neuronal connections in a mouse model of TBI. We will also test if the resident immune cells of the brain, called microglia, drive TLR9's negative effects on neuronal connections, either by physically pruning neuronal connections or by releasing factors that cause neurons to retract. Together, these studies will provide insights into how TLR9 drives loss of brain circuits and could identify TLR9 inhibitors as a novel approach to protect neurons from secondary damage in the wake of TBI.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CBIR25FEL015
Eleni Papadopoulos
Rowan University
$168,000

Project Title: *The effects of chronic low dose methylphenidate on risk/reward decision making and expression of catecholamine transporters following repetitive mild traumatic brain injury.*

The goals of the project are to characterize the ability of a psychostimulant to mitigate repetitive mild TBI-induced executive dysfunction and determine how sex influences the interactions between repetitive mild TBI and treatment on behavior and pathology.

Head injury impairs complex decision-making processes mediated within the prefrontal cortex and often leads to increased risk-taking behaviors, such as gambling and substance use. Athletes and military personnel are highly susceptible to repetitive mild traumatic brain injuries (rmTBI), or concussions, leading to short- and longer-term cognitive deficits and poor quality of life. Imbalances of the catecholamine transmitters, dopamine and norepinephrine, have been theorized to underlie TBI-induced increases in risky decision making. Currently, there are no approved FDA treatments for post-concussion cognitive deficits that affect risk/reward decision making. The psychostimulant drug, methylphenidate (MPH), is effective at reducing risky behavior in patients with attention deficit hyperactivity disorder (ADHD) when administered at low doses. Because the cognitive deficits and transmitter imbalances associated with rmTBI and ADHD share similarities, we are interested in investigating if chronic low doses of MPH can alleviate rmTBI-induced increases in risky behavior and catecholamine imbalances. Using a preclinical animal model of rmTBI, our preliminary data suggest that low dose MPH mitigates rmTBI-induced increases in risky behavior and transmitter imbalance in female rats but potentiates these injury-induced outcomes in males. Therefore, the work conducted during this graduate fellowship will test the overarching hypothesis that chronic, low dose MPH will restore catecholamine regulation and ultimately resolve increased risky behavior induced by rmTBI. The results from this study will determine if chronic, low dose MPH improves or prevents further neurocognitive symptoms and biochemical changes induced by rmTBI and may reveal a potential future therapeutic strategy.

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