DIRECTORY OF GRANT AWARDS
2020 GRANT CYCLE

NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

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MARCH 2020

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 2020 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, 369 S. Warren 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.

2020 MEMBERSHIP INFORMATION

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NEW JERSEY COMMISSION ON BRAIN INJURY RESEARCH

GRANT AWARDS

INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR20IRG007
Peter Dowling, M.D.
Veterans Biomedical Research Institute
$540,000

Erythropoietin-Derived Therapy for a Mouse Model of Chronic Traumatic Encephalopathy

We will treat chronic traumatic encephalopathy in a mouse model with our potent candidate drug JM4 that modulates the immune system and reduces inflammation, as a step towards treatment in humans.

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease affecting individuals who have received repeated mild traumatic brain injury. The link between post-traumatic sequelae in professional football players and CTE is now well known. However, CTE may be caused by any repetitive head injuries within the general population of New Jersey. This includes injuries seen in youth-sports participants, victims of domestic violence or military service members. Symptoms may include depression, anxiety, aggression, and other behavioral problems, as well as memory loss and deficits in executive function. No treatment exists for this devastating disorder, and there is a critical need for continued investment in research aimed at developing breakthrough discoveries for the treatment of CTE.

We hypothesize that chronic neuroinflammation drives the development of CTE. We have developed a new drug (JM4) that has profound and long-term modulatory effects on the immune system and inflammation.

In this proposal, we will investigate the extent that JM4 reduces neurological deficits and abnormal inflammatory changes in the brain of a CTE mouse model. JM4 was recently approved by the FDA as an investigational new drug (IND) for the treatment of acute multiple sclerosis, if our experiments are successful then the findings are likely to move rapidly towards developing the first treatment for CTE in humans.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR20IRG020
Smita Thakker-Varia, Ph.D.
Rutgers University BHS
$540,000

Intranasal Administration of Therapeutic to Improve Outcomes in Mice with Specific Genetic Polymorphisms Following Repeated Mild Traumatic Brain Injury

Using a mouse model, we are studying how genetic variations in single nucleotide base pair of BDNF gene may affect recovery from TBI and if novel intranasal therapeutic strategies are beneficial.

Traumatic Brain Injury (TBI) often results in lifelong cognitive and motor disabilities. It is estimated that 15,000 TBIs occur in NJ alone. Currently, 175,000 NJ residents live with disability due to TBI. Clinicians have long noticed that certain patients recover better than others after TBI and determining what makes some patients more susceptible is critical. One way to better manage treatment of TBI would be to stratify patients into risk categories and even tailor treatments based on genetic makeup. One specific DNA single base pair variation that has been suggested to confer higher risk for poor recovery following TBI in preliminary clinical studies is brain-derived neurotrophic factor (BDNF). A specific base pair change in this gene results in the alteration in amino acid Val66Val to Val66Met. However, studies in humans have not resolved as to which BDNF variant is vulnerable, it is therefore important to use experimental mouse models to further explore this question.

Our study will investigate the effect of the Val66Met variation in genetically engineered mice on recovery following a repeated mild TBI, which mimics the pattern that is shown in human sports injuries. We will look at cellular and behavioral outcomes following the TBI in order to determine if the Val66Met genetic mice show worse recovery than the Val66Val variants. We will also examine biomarkers in serum and cerebrospinal fluid and use magnetic resonance imaging. The biomarkers we identify will allow physicians to monitor the injury and recovery process to improve diagnosis and decisions about return to regular activity. Finally, we will investigate the use of intranasal administration of compounds, which promotes the generation of a protective mechanism shown to be beneficial in seizures and strokes but has not been tested in repeated mild TBI. This study will explore how to best manage and treat at-risk patients to reduce the burden that NJ and its citizens currently suffer due to TBI.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR20IRG027
Joshua Sandry, Ph.D.
Montclair State University
$459,313

Cognitive and Neural Mediators of Working and Long-Term Memory Impairment in TBI

We apply updated models from cognitive neuroscience and cognitive psychology to clarify the relationship between the medial temporal lobe, working memory and long-term memory impairment in TBI.

Traumatic brain injury (TBI) can result in considerable difficulty learning and remembering new information and long-term memory impairment is one of the most common negative cognitive consequences of injury. Thus, there is a strong need to develop new clinical treatments to alleviate symptoms of impaired long-term memory. Unfortunately, effective treatments for memory problems are limited. This shortcoming may be partially a result of inadequate knowledge about the underlying cognitive and neural processes that contribute to memory loss following injury. It is crucial to clarify the dysfunctional neural and cognitive processes that underlie memory impairment in TBI to develop a strong foundation for treatment.

Recently we reported that inefficient processing in working memory may partially underlie acquisition deficits observed in TBI. This study builds on these findings and aims to translate updated methodological approaches and theoretical views from cognitive neuroscience and cognitive psychology to understand memory problems in TBI. The investigation uses magnetic resonance imaging and behavioral experimentation to (1) investigate the behavioral working memory - long-term memory relationship in TBI, and (2) identify how patterns of neural activation and neural connectivity during on-going working memory processing differs as a function of long-term memory. This investigation is a foundational first step in the development of innovative treatment strategies directed at process-specific remediation of the cognitive and neural mechanisms that underlie long-term memory impairment in TBI. This knowledge will potentially improve the quality of life for individuals suffering from TBI-related cognitive disability, both within and outside of New Jersey.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR20IRG003
Bonnie L. Firestein, Ph.D.
Rutgers University
$510,000

Cypin Activators as Treatments for Traumatic Brain Injury

We will optimize treatment with activators of the protein cypin to promote neurocognitive function after TBI.

Traumatic brain injury (TBI) is the leading cause of death in people under 45 years of age in the United States and continues to have an enormous impact on public health. Although some progress has been made in reducing the annual incidence of TBI, a majority of this progress is in brain injury prevention, and there remains a tremendous need to develop therapeutics for TBI to improve outcome and lower the morbidity associated with the disease. With previous funding, we identified two small molecule compounds that protect neurons from injury, promote nerve cell function, and protect learning and memory in animals with TBI.

In this proposal, we aim to optimize treatment with these two compounds for eventual development for use in humans. We will determine the optimal timing for administration and study how the drugs work to change specific compounds in the body. These studies will yield important results to inform strategies for improvement of outcomes after TBI.

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INDIVIDUAL RESEARCH GRANT RECIPIENT:

CBIR20IRG011
Madhuvika Murugan, Ph.D.
New Jersey Institute of Technology
$532,616

Targeting Adenosine Kinase for the Prevention of Post-Traumatic Epilepsy

We will investigate the mechanisms by which a metabolic enzyme initiates and regulates post-traumatic epilepsy and evaluate therapeutic strategies for epilepsy prevention after brain injury.

Epilepsy affects 60 million people worldwide and is a serious medical condition with limited success in treatment. It is estimated that one third of people with epilepsy do not respond to medication. Hence, there is an urgent need for the development of rationally designed treatment strategies that can prevent epilepsy altogether or at least suppress its progression. A significant proportion of epilepsies are acquired, implying it is caused by a precipitating injury, such as traumatic brain injury (TBI) and is often referred to as post-traumatic epilepsy. In all acquired forms of epilepsy, irrespective of the cause, a progressive increase in the expression of the adenosine-metabolizing enzyme adenosine kinase (ADK) has been noted. However, whether this enzyme plays a role in post-traumatic epilepsy remains unclear and is the basis for the current study.

In the proposed research, we will use a powerful combination of electrophysiology, novel transgenic tools, and pharmacological agents to identify the synaptic mechanisms through which ADK controls neuronal excitability. Moreover, findings of the proposed study will delineate the cell and isoform specific role of the ADK, thereby leading to the development first-in-kind therapeutic interventions for the prevention of post-traumatic epilepsy.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CBIR20PIL008
Miloni S. Dala
Rutgers University BHS
$100,500

Chronic Role of Myeloid Panx1 Channel's Activation in Traumatic Brain Injury

Investigating the role of myeloid panx1 channel's activation in long term after TBI.

Traumatic brain injury (TBI) has various neurobehavioral and neurological consequences such as seizures, neurodegenerative diseases, and psychiatric problems in chronic phase. This is a crucial problem because there are no promising treatments.

Our lab has been studying the role of pannexin-1 proteins in TBI because these proteins have been implicated to play a role in neuroinflammation through release of ATP leading to more tissue damage. Attenuation of the neuroinflammatory response after TBI might contribute to increase neuronal survival and improved behavioral outcomes. We will establish the specific role of myeloid pannexin-1 in chronic phases of TBI.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CBIR20FEL009
Srinivasa Gandu
Rutgers University
$100,500

The Role of the Ubiquitin-Proteasome System in Neuronal Recovery after TBI

This proposal will assess the role of the ubiquitin-proteasome system in neuronal recovery after traumatic brain injury (TBI).

Traumatic brain injury (TBI) can be caused by either direct impact or indirect acceleration-deceleration/blast injury to the head and leads to neuronal damage. Primary injury is mechanical, and secondary injury results from over-activation of receptors by excess glutamate that is released by damaged brain cells. TBI affects the interactions between neurons, and neuronal communication is crucial for neuronal survival. Accumulation of insults from primary injury over time can lead to neurodegeneration, affecting cognitive function, and repeated TBI is implicated in multiple neurodegenerative disorders, such as Parkinson's and Alzheimer's disease. After an injury, neurons need to maintain proper polarity and do so by degrading damaged proteins to counteract the stress caused by trauma.

In this proposal, we will assess the role of protein degradation systems in recovery after TBI and how they are regulated at different stages after the injury. The ubiquitin-proteasome system (UPS) is a major protein degradation pathway and plays a crucial role in maintaining cellular homeostasis and neuronal interactions. Our study will use both cellular and animal models of TBI to determine how the UPS is regulated at different phases after TBI and the effects on neuronal survival and functional recovery by manipulating the UPS with pharmacological tools. We will also study the effects of overexpression of one key regulator of this pathway, cytosolic PSD-95 interactor (cypin), shown to have a neuroprotective function after a TBI. Our study will aid us in identifying potential therapeutic targets in both the early, or mechanical, and late, or chemical, stages of TBI.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CBIR20FEL007
Jamie Zhan
Princeton University
$100,500

The Role of Immune Proteins on Synapse Loss after Traumatic Brain Injury

We are investigating how immune proteins contribute to synapse loss after traumatic brain injury, with the ultimate goal of developing treatments that prevent neuronal connections from being damaged.

About 2.9 million people in the United States suffered from a traumatic brain injury (TBI) in 2014 alone, and about 5.3 million US residents currently live with a TBI-related disability. Despite the significant economic and human costs of TBI, there are currently no approved treatments. Traumatic brain injury causes loss of neuronal connections, called synapses, in the hippocampus, a part of the brain that is responsible for many kinds of learning and memory. While many therapies in development focus on stimulating growth of new synapses, an alternative approach is to prevent synapses from being lost after TBI.

We propose to investigate an unexpected mechanism that might contribute to synapse loss after TBI: upregulation of specific immune proteins, members of the major histocompatibility complex class I (MHCI). MHCI is a central component of the immune response, and MHCI levels increase after injury, enhancing protection from infection. However, we and others have found that these same MHCI proteins play completely different roles in the nervous system, where they help eliminate excess synapses during development. However, when MHCI levels rise beyond normal levels—as they do during aging—essential synapses can be eliminated, impairing brain function. Our preliminary data suggest that MHCI levels rise in the brain after TBI. Therefore, our specific hypothesis is that TBI causes MHCI levels to rise, which in turn triggers synapse loss. We will directly test this hypothesis by "knocking out" MHCI genetically, and then assessing if this protects the animals against synapse loss after TBI. We will also attempt to block synapse loss in normal, non-mutant mice using a small peptide that can cross cell membranes and may block the non-immune functions of MHCI in the brain.

These studies, if successful, will clarify the role of immune proteins in synapse loss after TBI, and will provide valuable information about the mechanisms by which synapse number is regulated, information that is crucial to developing new TBI treatments. These studies will also provide the first tests of a novel peptide reagent that has the potential to reduce or even prevent synapse loss after TBI and improve clinical outcomes in patients.

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FELLOWSHIP RESEARCH GRANT RECIPIENT:

CBIR20FEL019
Erika J. Davidoff
Rutgers University
$100,500

Self-Healing Electrode Coatings for Improving Treatment of TBI Secondary Injury

We hope to improve treatment of chronic TBI-induced conditions by making the devices used to treat those conditions more biocompatible, using two types of specialized gel coatings.

Severe TBI is associated with several long-term chronic conditions. For example, post-traumatic epilepsy (PTE) often arises after a serious TBI. People with PTE suffer seizures due to neuron signaling abnormalities caused by TBI-induced brain damage. PTE can be chronically treated via the implantation of electrodes into the brain that deliver electric current to counteract these abnormalities. However, friction between the stiff metal implant and surrounding brain tissue triggers a foreign body response (FBR), causing inflammation, which can lead to further tissue damage, and gliosis, the formation of scar tissue around the electrode. Many researchers have suggested using soft coatings made of hydrogels—water-rich networks of chain-like polymer molecules—to lessen the FBR. Existing coatings, however, are made from gels held together by covalent bonds, which irreversibly break under high strain.

We are working with self-healing non-covalently linked gels, which use other types of molecular interactions to form and can regenerate after high stresses. One of the gels is made of a system of molecules that link together like Velcro based on interactions between a "host" part of one molecule and a "guest" part of the other. The second gel is made from a customized sequence of peptides, the building blocks of proteins, that naturally assembles into an accordion-like layered structure which makes up the gel. Coatings made of these gels are more effective and more durable. We are also developing a custom bioreactor to test the effectiveness of these coatings in cultured cells, reducing the number of expensive and lengthy animal studies needed to evaluate different coatings. We aim to develop coatings that more effectively protect brain tissue from the negative effects of the implant, enabling the implant to work longer and more efficiently.

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PILOT RESEARCH GRANT RECIPIENT:

CBIR20PIL021
Jean Lengenfelder, Ph.D.
Kessler Foundation
$168,001

The Application and Modification of an Emotional Processing Intervention in Pediatric TBI

The current proposal will modify an existing treatment for emotional processing deficits for children and then apply the treatment in pediatric TBI.

Following a Traumatic Brain Injury (TBI), children often experience a number of symptoms which are both physical and cognitive. Children with TBI often have difficulty with social interaction and relationships even years after their injury. Difficulty in emotional processing may contribute to such social problems. Specifically, some individuals with TBI have difficulty correctly identifying emotions from facial expressions. Deficits in emotional processing can have a significantly negative impact on social interactions, mood, and quality of life. While there has been much research on emotional processing problems in adults with TBI there has been much less research examining emotional processing deficits in children with TBI. Developing and applying treatments to improve emotional processing in critical to improve these functions in children with TBI.

The current study will examine an emotional processing treatment in children with TBI. A 12-session treatment that teach children how to correctly recognize emotions of faces. First, the existing treatment, which is used in adults, will be changed so that it is suitable for children. Next, the treatment will be examined in children with TBI so test whether it is effective in improving emotional processing problems.

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PILOT RESEARCH GRANT RECIPIENT:

CBIR20PIL017
Joshua Berlin, Ph.D.
Rutgers University
$172,400

Development of a Novel Mouse TBI Model for Real Time Imaging of Neuronal Activity in the visual Cortex

We propose to develop a unique TBI model that permits real-time in vivo imaging of neuronal activity in the visual cortex of mice subjected to fluid percussion injury.

Traumatic brain injuries (TBI) can result in a variety of acute visual problems that are particularly problematic because they interfere with ability to perform daily living and work activities, therefore degrading quality of life. Adolescents patients with concussion seem particularly prone to suffering vision problems. Visual disturbances after TBI can be triggered at any level of the visual system from the eye to the occipital lobe of the brain. Even so, a common finding is that visual problems after TBI are associated with the lesion in the occipital lobe, where the visual cortex is located. These clinical findings point to the visual cortex as a possible site of injury in a significant population of patients following TBI. Given the frequency of acute vision problems after TBI attributable to lesions in the occipital lobe, even after mild TBIs such as concussion, it is then surprising that no experimental models focus on the visual cortex in TBI.

Thus, this pilot grant application seeks to remedy that gap in investigation by developing a novel TBI model that will allow real-time imaging of neuronal function in the visual cortex of mice during TBI. To achieve this goal, a team of investigators propose to combine their expertise in TBI models, in vivo measurements of neuronal function in the visual cortex and analysis neuronal network function to design, build and test the proposed TBI model. Once this model is operational, the investigators will be in a unique position to study the evolution of acute TBI-induced pathophysiological changes in neuronal function in real time, whether in the visual cortex or in other cortical regions. As a result, they can advance their on-going research projects aimed at defining mechanisms underlying the acute injury process and possible therapeutic interventions to reduce or abolish acute TBI effects.

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PILOT RESEARCH GRANT RECIPIENT:

CBIR20PIL004
Rachel Navarra, Ph.D.
Rowan University
$180,000

Negative Impact of Mild Traumatic Brain Injuries on Risk-Based Decision Making and Potential Therapeutic Strategies

The proposed project will describe the effects of multiple mild traumatic brain injuries, often referred to as concussions, on risky behavior in male and female subjects and suggest atomoxetine, an ADHD drug, as a treatment option.

Mild TBIs occur commonly and cause both acute and chronic neurological impairments that affect daily behavioral functions. Many individuals, particularly young adult athletes, experience multiple mild TBIs in the form of sports-related concussions. Higher order executive functions, including complex decision making under conditions of uncertainty, are particularly susceptible to injury-induced disruption following head trauma. Executive functions are governed within the prefrontal cortex (PFC), but regulated by neuromodulatory systems, such as the locus coeruleus (LC)-norepinephrine (NE) system. Decision making and cost/benefit choice behaviors that involve risk and reward seeking are often negatively impacted following mild TBIs.

Risky decision-making following head trauma is a major public health concern as it is a self-defeating characteristic associated with addiction, psychopathological behavior, and compulsive gambling. After experiencing a single concussion individuals are more vulnerable to future head injury and may likely experience more severe and/or more prolonged symptoms following repeated head trauma. Although many studies have focused on the consequences of single, moderate to severe brain injuries, fewer investigations have examined outcomes following repeated instances of mild TBI. In addition, the impact of single versus repeated concussions on females is often neglected despite reports that females suffer worse outcomes for longer periods of time following head injury.

The results of these studies will advance our understanding of the effects of repetitive head injury on a specific dimension of cognitive function, link these effects to a CNS transmitter network that is very likely to be vulnerable to repetitive mild TBI, and establish a platform for evaluating the efficacy of potential drug therapies for TBI. The proposed project represents a new direction for the Navarra laboratory but a significant opportunity to partner with established senior investigators in the fields of TBI research, noradrenergic system biology, and executive functions as a means of developing and testing targeted drug treatments for mild head injury.

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