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About the Office of Higher Education

The Minnesota Office of Higher Education is a cabinet-level state agency providing students with financial aid programs and information to help them gain access to postsecondary education. The agency also serves as the state's clearinghouse for data, research and analysis on postsecondary enrollment, financial aid, finance and trends.

The Minnesota State Grant Program is the largest financial aid program administered by the Office of Higher Education, awarding up to $224 million in need-based grants to Minnesota residents attending eligible colleges, universities and career schools in Minnesota. The agency oversees other state scholarship programs, tuition reciprocity programs, a student loan program, Minnesota's 529 College Savings Plan, licensing and early college awareness programs for youth.

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Introduction

The State of Minnesota established the Spinal Cord Injury and Traumatic Brain Injury (SCI-TBI) Research Grant Program on July 1, 2015, in accordance with Minnesota 2015 Session Law, Chapter 69. This statute directed the Minnesota Office of Higher Education (OHE) Commissioner to establish a grant program for institutions in Minnesota to conduct research that would lead to new and innovative treatments and rehabilitative efforts for the functional improvement of people with spinal cord injuries and traumatic brain injuries. Research areas include, but are not limited to, pharmaceutical, medical devices, brain stimulus, and rehabilitative approaches and techniques. Appendix A provides a copy of the grant program's founding statute.

In July 2018, the Spinal Cord Injury and Traumatic Brain Injury Grant Program was given a Special Revenue Account by Minnesota Management and Budget in order to extend project periods from one to two years to a two to five year timeline. Beginning in FY 2020, new grantees are given two to five years to complete their research projects, with a possibility for an extension based on their progress and the complexity of the research. The timeline extension is crucial for the completion of projects based on the lengthy institutional review board (IRB) review processes. It also accounts for any unexpected challenges that occur naturally with complex research and experimentation. The Special Revenue Account continues to support the program and its grant recipients, as these projects have proven to take several years to complete.

For the 2021-2022 biennium, $3,000,000 was made available for each year from the 2021 Omnibus Higher Education Bill (Minnesota 2019 Session Law, Chapter 69) to support the SCI-TBI Grant Program, with a three percent administrative fee. As directed by the program's statute, the Commissioner of the Office of Higher Education, in consultation with the program's Spinal Cord Injury and Traumatic Brain Injury Advisory Council (Advisory Council), allocated 50 percent of the grant funds to research involving spinal cord injuries and 50 percent to research involving traumatic brain injuries throughout the biennium.

Spinal Cord Injury and Traumatic Brain Injury Advisory Council

The 2015 statute language establishing the grant program also required creation of the Spinal Cord and Traumatic Brain Injury Advisory Council. The Commissioner, in consultation with the Advisory Council, has the responsibility of awarding the SCI-TBI grants and developing the program. In 2015, an initial 12-member Advisory Council was set up using the Open Appointments process of the Minnesota Secretary of State's office. In 2017, the statute language was updated to include two new seats: 1) Veteran with a Traumatic Brain Injury, and 2) Physician Specializing in the Treatment of Spinal Cord Injury. Both seats were filled in 2018, although the Veteran with a Traumatic Brain Injury representative resigned at the end of 2018 due to personal reasons.

Veteran representation is a persistent challenge for maintaining continuity within the Advisory Council. Since the resignation our veteran representative in 2018, this seat has remained open despite many attempts to recruit eligible community members. Many veterans who have joined the council do not persist through their first year for personal reasons, mainly related to their health and wellness. A future consideration is to reconfigure those

FY 2022 Annual Research Grant Timeline

In FY22, $3 million was available to award to research projects through the SCI-TBI Annual Research Grant. The timeline for the annual research grant opportunity was as follows:

February 8, 2022	Request for Proposals available to applicants
March 4, 2022	Deadline for receipt of intent to submit forms
4:30 p.m., April 15, 2022	Deadline for receipt of proposals
May 11, 2022	Proposal Review Meeting/Project Presentations
June 1, 2022	Notification of recommendation for grant award
July 1, 2022	Project funding begins with grant contract encumbrance

On April 15, 2022 OHE received a total of 27 proposals (14 TBI and 13 SCI) totaling nearly $7 million in requests. Despite uncertainties and delays due to the continued COVID-19 pandemic, the volume of requests submitted by applicants indicates high levels of interest in ongoing collaboration and innovation in SCI and TBI research. All proposals included protocols for navigating a post-COVID-19 world in which temporary closures, outbreaks, and increased safety measures are commonplace and expected.

Of the $3,013,426 in total requests for TBI research, the Advisory Council selected eleven projects to receive awards, totaling $1,427,438. The total request for SCI research was $4,420,590. The Advisory Council selected seven projects totaling $1,720,000. The extra funds allocated for Spinal Cord Injury projects was from leftover funds in the Special Revenue Account. Summaries of funded projects can be found below:

Spinal Cord Injury Research Grants

Regulatory Pathway to Approve Spinal Cord Injury Stimulation for Chronic Spinal Cord Injury, University of Minnesota, receives $500,000

The specific goals of this research project is to identify the fastest way to achieve FDA approval and to design a clinical study that demonstrates broad efficacy to facilitate insurance approval with the ultimate goal to make this Spinal Cord Stimulation (SCS) available to the SCI community. The researchers' approach is to identify the minimum study necessary to achieve FDA approval for SCS implantation for SCI, which they hypothesize is a major limitation to accessing the therapy. Once implanted, patients can undergo rehabilitation and optimization to maximize the benefit of the therapy. The research team has identified two possible approaches for achieving regulatory approval, and their first aim is to determine, through pre-submissions with the FDA, which is most feasible. Their second aim will be to collect and refine data collection to design a responder based efficacy trial, which may be necessary for FDA approval and will be essential for insurance approval. The final aim will be to further develop remote programming, to lower the barrier of optimization post-implant. The aims of this project not only address treatment for SCI, but also explore ways to make the treatment more accessible to the SCI community.

Principal Investigator: Dr. Theoden Netoff, 612-625-3616, tnetoff@umn.edu

CE-STAND: Cervical Epidural Stimulation after Neurologic Damage, University of Minnesota, receives $400,000

While motor paralysis is the most obvious SCI effect, autonomic dysfunction including cardiovascular, respiratory, urinary, and gastrointestinal complications, are equally disruptive. The accompanied blood pressure imbalance leads to decreased cognition in this population. It affects their quality of life, morbidity, and mortality. Epidural spinal cord stimulation has been more widely tested for thoracic SCI patients with volitional and autonomic dysfunction. These results were independently reported across at least three sites including a group at the University of Minnesota (UMN) in the E-STAND trial. Though autonomic dysfunction is more common in those with higher injuries, research in patients with chronic cervical injuries is under-represented and must be addressed to identify novel, feasible treatment options for this population. Our primary hypothesis is that eSCS will provide the same autonomic benefits in a cervical injury population as the thoracic injury population in the E-STAND trial. The secondary outcomes will include hand function (i.e.,grasping function); and the ratio of hand/leg function); truncal stability; and questionnaire-based information such as bowel and bladder function; spasticity; and quality of life measurements. The investigator will also investigate stimulator settings to identify common patterns related to improved function.

Principal Investigator: Dr. Ann Parr, 612-812-6365, amparr@umn.edu

Safety and Feasibility of Early Epidural Spinal Cord Stimulation with Spinal Cord Injury, Minneapolis VA Healthcare System, receives $300,000

This pilot study investigates the extent of improvement that earlier epidural spinal cord stimulation offers in comparison to later stimulation, particularly with regards to restoring volitional movement, and preventing muscle atrophy and loss of bone density after spinal cord injury. The project's central hypothesis is that early stimulator intervention, starting within 6 weeks of injury, will result in improvements in retaining muscle mass and bone density after acquiring a motor-complete spinal cord injury. T prheimary objective is to determine the safety and feasibility of early epidural spinal cord stimulation. Secondary outcomes will assess 1) the ability of early epidural spinal cord stimulation in conjunction with standard of care rehabilitation to enable better restoration of volitional movement and 2) the extent that early epidural spinal cord stimulation prevents muscle atrophy and bone density loss after spinal cord injury. This initial pilot study will recruit 12 new patients and provide continued therapy for up to six patients, who previously received epidural stimulation therapy from the group. The overall goal of this study is to explore the safety and feasibility of early epidural stimulation intervention by recruiting six patients within six weeks of acquiring a motor-complete or near-complete SCI as compared to those who receive their device after six weeks of acquiring a motor-complete or near-complete SCI.

Principal Investigator: Dr. Uzma Samadani, 917-388-5740, uzma.samadani@va.gov

Using focused ultrasound to enhance the delivery of intravenous umbilical cord derived MSCs in chronic spinal cord injured rats, Mayo Clinic, receives $100,000

Many different cell-based therapies have been investigated for spinal cord injuries. Umbilical cord mesenchymal stem cells (UCMSCs) have gained the interest of researchers as they have demonstrated the ability to exert a

neuro-regenerative effect. Despite its potential, there has been minimal success of this treatment in the chronic phase of spinal cord injury. This may be due to the blood-spinal cord barrier, which acts as a physical barrier to reduce drug delivery to the injury site. Focused ultrasound (FUS) represents a non-invasive technique that can open the blood-spinal cord barrier, thus allowing for enhanced drug delivery. This study will be a pilot evaluation of FUS on an animal model of chronic spinal cord injury to assess increased uptake of treatment therapies. UCMSCs will be obtained from consenting humans at Mayo Clinic and injected to rat models six weeks post-injury. Functional outcomes will be measured through BBB scoring and rotarod testing. Histopathological outcomes will also be assessed. This study will lay the groundwork for future clinical evaluations of FUS in human subjects with chronic spinal cord injury. Positive results indicate localized drug administration, which could increase its effects. Such therapies have the potential to improve motor function in patients with chronic spinal cord injury.

Principal Investigator(s): Dr. Mohamad Bydon, 507-284-4477, bydon.mohamad@mayo.edu

Evaluating performance of an individualized computational model for real-time visualization of spinal stimulation electrical fields and downstream functional output, Mayo Clinic, receives $200,000

Current clinical treatment options for spinal cord injury (SCI) mostly focus on strengthening and maintaining intact functions above the injury site rather than recovering functions impaired by SCI. To this end, several clinical trials of spinal electrical stimulation have generated promising results, including recovery of volitional control over standing and stepping activities, in humans diagnosed with permanent, complete loss of function below the level of SCI. Across previous studies, electrical stimulation has been delivered to the spinal cord using either transcutaneous electrical spinal stimulation (TESS) or epidural electrical stimulation (EES). However, the mechanisms and neural structures that underlie stimulation-enabled functions remain unknown. To address this gap in knowledge of the underlying mechanisms that drive stimulation-enabled functions, the researcher is conducting a clinical trial of EES in 32 participants with varying severities of SCI, which is supported by a 5-year research grant (R01NS115877) from the National Institute of Neurological Disorders and Stroke. Unfortunately, state-of-the-art techniques to identify stimulation parameters that lead to functional gains is challenging due to the time-consuming process of manual adjustment of stimulation parameters, such as electrode location and configuration, pulse frequency and pulse amplitude. To address this challenge, last year the research team submitted a proposal that was awarded partial funding to build a computational model of the electrical fields generated by spinal stimulation. In the time that has passed since receiving the partial award, they have made significant progress toward establishing a computation model of spinal cord stimulation. Therefore, this project allows the researcher to finish their original aims by fully funding the model development.

Principal Investigator: Dr. Peter Grahn, 507-316-5556, grahn.peter@mayo.edu

Remotely delivered Cognitive Multisensory Rehabilitation for Sensory and Motor Recovery after Spinal Cord Injury, University of Minnesota, receives $160,000

About 296,000 Americans have a spinal cord injury (SCI). Most of them have long-term reduced or complete loss of sensation and movement, and loss of awareness of where their limbs are in space. This body awareness deficit compromises movements and daily life function. This research team recently conducted a clinical trial, applying a physical therapy approach termed “Cognitive Multisensory Rehabilitation” (CMR) to improve body

awareness. CMR was originally developed as a therapy for adults with stroke, resulting in significant improvement in body awareness, sensation, and movement. Thus, they tested whether CMR could benefit adults with chronic SCI with similar results: 26 adults, 1-56 years post-SCI, with paralyzed limbs and trunk, received 18 CMR sessions. After CMR, 12 out of 20 adults could stand up for the first time; 17 out of 18 adults with balance problems while sitting could lean forward and sideways confidently and perform transfers better because they now felt their legs and the contact of the soles of the feet with the floor. They observed brain function improvement along with functional recovery. The results persisted at the 6 week follow-up. There were no improvements in the observation period before they started CMR. In sum, adults with chronic SCI had functional improvements, attributed to recovery of sensation and movement after CMR. The results of this research study indicate the efficacy of CMR for restoring function in adults with chronic SCI (manuscript in preparation). Yet, during the study, the investigator encountered an important problem: a fair number of adults were unable to access in-person rehabilitation because of transportation issues and/or living in a rural area. This problem has prompted us to consider the idea of delivering CMR "remotely". If patients can access CMR at home, it will expand their ability to offer the treatment to more people. Thus, the researcher will investigate the effect of remotely delivered CMR vs remotely delivered exercises (used in rehabilitation centers in the Twin Cities), for improved function due to improved sensation and movement. The reason for remote delivery is to make therapies accessible to adults with SCI who do not have access to transportation or who live rurally.

Principal Investigator: Dr. Ann Van De Winckel, 612-625-1191, avandewi@umn.edu

Gene Therapy for Treating Acute Spinal Cord Injury, University of Minnesota, receives $160,000

A major goal for spinal cord injury research is the regeneration of the spinal cord for complete repair after chronic injury. To address this issue the researcher is conducting studies using gene therapy for cell reprogramming to convert astrocytes into neurons following spinal cord injury by the viral delivery of NeuroD1, a key protein for neuronal development. In these studies they observed not only the conversion of astrocytes to neurons, but also the survival of endogenous neurons that express reporter proteins associated with the expression of NeuroD1. This observation raises the important question as to whether the forced activation of NeuroD1 by damaged neurons soon after injury may protect them from injury-induced cell death. Confirmation of this concept would provide an approach to minimize damage to the spinal cord after injury and preserve motor and sensory functions. The central hypothesis of this research is that gene therapy for NeuroD1 expression in neurons of the spinal cord can prevent their loss and maintain the function of the motor and sensory systems. Traumatic injury to the spinal cord causes the death of neuronal cells that, in turn, affect the ability to move and detect somatic sensations such as pressure and pain. During the development of the nervous system, NeuroD1 gene expression is critical for the differentiation of neuronal cells. Activation of the NeuroD1 gene after injury to nerve cells may engage gene networks that lead to the survival of damaged neuronal cells. Survival of these neuronal cells, in turn, maintain neural circuits that are responsible for critical motor and sensory functions.

Principal Investigator: Dr. Walter Low, 612-626-9203, lowwalt@umn.edu

Traumatic Brain Injury Research Grants

Impact of Traumatic Brain Injury on Opiate Addiction, University of Minnesota, receives $125,000

Based on the research team's finding that persistent activated macrophages are associated with decreased thresholds for drug preference and increased consumption of drug in animals suffering from a mild TBI, they propose that the proinflammatory macrophage response to mTBI accelerates remodeling of neuronal synapses in the mesolimbic pathway leading to increased sensitivity and consumption of opiates. To test this hypothesis they will (1) characterize the structural and inflammatory changes to the NAc and VTA consequent to mild TBI and (2) to determine if altering the macrophage activation profile reverts the addiction behavior in the rodent model. The researcher will use a well-established controlled cortical impact (CCI) mouse model of mTBI. Addiction behavior will be assessed by (1) conditioned place preference assay to measure sensitivity to drug and (2) a short access self-administration protocol to measure drug consumption. Damage to neural circuitry and inflammation will be assessed by a immunohistochemistry evaluation. A clarity technique, called the PEGASOS, will be used for direct visualization of NAc/VTA neuronal tracts in 3-dimension. Inflammation in the brain will also be assessed by measuring cytokine responses and immune cell phenotypes using PCR based transcriptomic and flow cytometry analysis respectively.

Principal Investigator: Dr. Maxim Cheeran, 612-626-9930, cheeran@umn.edu

Chronic Neuroinflammation associated with repetitive TBI in a rodent model, University of Minnesota, receives $177,000

Mild traumatic brain injury (TBI) is the most common type of TBI and most patients recover without significant CNS pathology. But these patients are susceptible to development of neurodegenerative and neuropsychiatric complications after repetitive TBI, which is common among soldiers and athletes. The cumulative effect of repetitive TBI can result in chronic neurological damage. Persistent inflammation in the brain is the dominant secondary injury mechanism associated with development of neurodegenerative disorders. Despite extensive efforts to develop neuroprotective therapies, there are currently no therapeutic options for the treatment of TBI to restore neurologic functions lost from injury. Novel approaches are needed to provide relief from the long-term complications of TBI. Cellular therapy is a potential strategy to repair and regenerate injured brain. The researchers propose to use two well-established mouse models of TBI, controlled cortical impact (CCI) model and closed head injury (CHI) model induced by weight-drop device. Neuroinflammation after repetitive TBI will be assessed by three different approaches- (i) flow cytometry to assess changes in immune cell phenotypes, (ii) immunohistochemistry to determine the extent of neuronal damage and localization of infiltrated cells, and (iii) RT-PCR to determine altered gene expression levels of inflammatory cytokine in brain. In addition, behavioral tests to evaluate both sensory motor and cognitive function will be performed. Use of UCBSC for the treatment after first injury in our repetitive injury model, if successful, may shorten the safe interval between concussions and subsequent return to work.

Principal Investigator(s): Dr. Venkatramana Krishna; Dr. Maxim Cheeran, 612-625-7755, vdivanak@umn.edu

Circuit-based neuromodulation to improve mental fatigue after Traumatic Brain Injury, University of Minnesota, receives $83,333.33

Mental fatigue develops in up to 70% of persons with traumatic brain injury (TBI), is often long-lasting, and leads to significant disability. Despite its importance, treatment options available for mental fatigue remain limited. One reason for these past failings is that mental fatigue has been difficult to quantify; another is that available interventions do not target the brain circuits disrupted after TBI. Understanding how to improve mental fatigue during the recovery period after TBI remains a major gap in the field. The impaired mental effort and increased mental fatigue after TBI is linked to the dysfunction of brain network oscillations. Transcranial alternating current stimulation is a form of non-invasive neuromodulation that targets brain network oscillations that offers promise for improving mental effort and fatigue after TBI. In this project, the researchers will: 1) leverage advances in neuroeconomics to make quantitative measurements of mental fatigue and effort and cognitive impairment after mild to moderate traumatic brain stimulation, 2) be the first to apply beta-frequency transcranial alternating current stimulation for cognitive rehabilitation after traumatic brain injury, 3) develop a novel, cost-effective, and widely accessible platform which is computationally informed, neuroplasticity-based, and non-invasive for treating mental fatigue after TBI.

Principal Investigator(s): Dr. Alexander B. Herman, 612-625-1194, herma686@umn.edu

Feasibility of a purpose in life renewal intervention for adults with post-concussion syndrome, Allina Health, receives $41,664.33

While most people fully recover from a mild traumatic brain injury in a matter of weeks, a significant minority continue to have physical, cognitive, and emotional problems for months to years. This condition is called post-concussion syndrome (PCS). People with PCS experience decreased functioning and quality of life. Because of this, many people with PCS experience a shaken sense of who they are and a disrupted sense of purpose in their lives. Purpose in life is defined as a central aim that frames a person's goals, daily decisions, identity and provides a sense of meaning in life. Having a sense of purpose in life is important to general health and well-being as well as functioning and quality of life. However, challenges related to purpose in life disruption typically go unaddressed in routine rehabilitative care. So far, the benefits of purpose in life renewal been not been studied on people with PCS.

In response to this gap, this research team developed an 8-session group, purpose renewal intervention called the Compass Course (CC). Over the course of 12 weeks, participants rediscover their "inner compass", which is composed of their current strengths, values, sources of personal meaning. Using this information, they develop and implement plans so their everyday choices more closely align with their "inner compass." In doing so, they experience a greater sense of life purpose. The researchers have tested the CC on women who have breast cancer and found that (1) participants liked it (as evidenced in high levels of attendance and comments on surveys); (2) we could deliver the CC as planned; and (3) participants made significant before and after improvements in purpose in life that were maintained 2 months later. Now, they propose to leverage their expertise in brain injury rehabilitation and purpose in life research to evaluate the extent to which the CC is also acceptable and beneficial for people with PCS.

Principal Investigator(s): Dr. Mary Radomski, 651-402-5457, mary.radomski@allina.com

Therapeutic effects of non-hematopoietic umbilical cord blood stem cells in the treatment of traumatic brain injury in mice, University of Minnesota, receives $250,000

Traumatic brain injury (TBI) is a devastating neurological condition that has proven difficult to treat. Primary injury to the head can initiate a cascade of cell signaling events leading to the death of brain tissue and long-term physical and mental disability. A key component of this cell signaling cascade is the involvement of infiltrating immune cells following injury. Using funds from a previously awarded Minnesota SCI/TBI grant mechanism, the research team identified a stem cell-based therapy that can reduce inflammation at an early time point following TBI. They have also developed and characterized a mouse model of TBI with a well-defined neuroinflammatory and behavioral profile that can provide a baseline for investigating the therapeutic effects of umbilical cord blood stem cells (UCBSCs). The goal of the current research proposal is to build upon this SCI/TBI funded work in mitigating neuroinflammation following TBI using UCBSCs. To address the central questions of this research, the researcher is proposing a series of experiments using a mouse model of TBI where we intravenously infuse UCBSCs 24 hours after injury. Using immunohistochemical and behavioral assays, they will investigate the therapeutic benefits of UCBSC administration. State of the art spatial transcriptomic tools will identify the signaling occurring between UCBSCs and host tissue. Using transgenic mice, the researcher will identify how monocytes are recruited into the brain following injury, and if UCBSC therapy changes recruitment and/or inflammatory phenotype.

Principal Investigator: Dr. Andrew W. Grande, 612-624-6666, grande@umn.edu

Towards Personalized Cognitive Rehabilitation: Validating a Brief Clinical Assessment of Multiple Memory Systems, University of Minnesota, receives $124,715

Each person who has sustained a traumatic brain injury (TBI) is unique. We know from previous research that even when two people look like they have had similar brain injuries, they can recover in very different ways. The goal of rehabilitation after brain injury is to help people reach the best recovery possible. To do this, therapists involved in rehabilitation do their best to *personalize* treatment after brain injury for each person that they work with. But right now, we don't have enough research evidence to personalize rehabilitation very well. Most of our research findings take a "one-size-fits-all" approach. Even though therapists know that every person is different, they don't have the research they need to make decisions about which treatments will work best for a particular person. The goal of this project is to give therapists the information they need to personalize treatment for brain injury, so that people getting treatment for TBI can get the most out of their rehabilitation. The researcher will test whether a set of memory tests can help us to predict what kind of treatment works best for individual people with TBI. The participants in the study will first take a set of short memory tests. These memory tests are comprehensive: they will test multiple types of memory that are important for daily life. We think that how a person performs on these memory tests will tell us something about how well they will respond to certain types of rehabilitation treatments. The researcher will use statistics to see if people's performance on these memory tests *predicts* how much benefit they get from different treatment approaches. The ultimate goal of this project is to understand how people recovering from TBI will respond to personalized treatments.

Principal Investigator: Dr. Natalie V. Covington, 402-321-6679, nvcoving@umn.eu

Combined Effects of TBI and Covid19 on Developing Alzheimer's Disease, University of Minnesota, receives $83,333.33

Covid19 has become a pandemic infecting nearly 80 million people in the U.S. Many of these individuals suffered mild to moderate neurological symptoms, while others are completely asymptomatic. Recent studies demonstrate that individuals with the APOE4 genotype are the most susceptible to infection by SARS-CoV2. Moreover, the APOE4 genotype is also a risk factor for developing Alzheimer's disease (AD), and for increased neurological severity following traumatic brain injury (TBI). Together these observations raise the alarming possibility that individuals with the APOE4 genotype who were infected by the SARS-CoV2 virus and subsequently experience TBI may be at high risk for developing AD. Consequently, this may exacerbate the number of AD cases in future years. To determine if this may be the case the researcher proposes to study TBI following Covid19 to determine if this can lead to an early onset of AD symptoms. Importantly, they will study the molecular pathways that bind TBI, Covid19, and AD to reveal targets for potential therapeutic development in future studies that may blunt the consequences of TBI and Covid19 that may lead to AD. The overarching hypothesis of this research is that TBI can impact subjects previously infected by the SARS- CoV2 virus to increase their risk for AD.

Principal Investigator(s): Dr. Walter Low, 612-626-9203, lowwalt@umn.edu

A Randomized Controlled Trial of Accelerated Theta Burst Stimulation for Headaches after Traumatic Brain Injury, University of Minnesota, receives $83,333.33

Chronic headache is the most debilitating clinical symptom in individuals who have suffered a mild traumatic brain injury (mTBI). Unfortunately, the debilitation caused by headaches is often accompanied by dysfunction in mood, attention, and memory which results in a profound negative impact on these individuals' quality of life. Conventional pharmacological treatments have been shown to be ineffective in alleviating headaches in the posttraumatic injury population. This is reflected by the fact that there are no FDA-approved treatments for posttraumatic headache. Thus, there is an urgent need to develop noninvasive interventions. In this project, the researcher proposes an innovative, non-invasive intervention to treat posttraumatic headaches and alleviate the suffering associated with this clinical syndrome. This study will be a randomized controlled trial. 42 participants will be enrolled in the study. Participants will complete 2 weeks of pre-intervention assessment via Ecological Momentary Assessment (EMA). The EMA is a small application that participants will download on their personal phones that will assess their behaviors and headache symptoms in real-time. Participants will be required to complete 70% or more of the EMA questions prior to initiation of the TBS intervention. They will then receive either TBS or sham once a week for four weeks. TBS will be administered in 4 minute sessions, 6 times per day with 20 minutes between intervention sessions. After TBS/sham intervention, participants will complete an additional 4 weeks of EMA and return for a 1-month follow-up assessment.

Principal Investigator(s): Dr. C. Sophia Albott, 651-787-5146, albot002@umn.edu

Maladaptive avoidance and associated circuitry disruption following repetitive mild TBIU, University of Minnesota, receives $62,462.50

Traumatic brain injury (TBI) is a significant public health problem, with an estimated 5.3 million TBI survivors coping with one or more long-term neurobehavioral disabilities. A mild traumatic brain injury (mTBI), also known as a concussion, accounts for up to 90% of all TBIs. A single mTBI can result in a range of neurological impairments that usually resolve quickly. On the other hand, repeated mTBIs (rmTBI), which are common in contact sports athletes (including American football, boxing, ice hockey, mixed martial arts, and soccer) and military personnel can leave the patient at a high risk for developing progressive neurological dysfunction many years after the injury. Multiple mTBIs make a person more vulnerable to new injuries and their effects become cumulative, increasing the risk of long-term disability. Up to 20% of people who suffer a rmTBI develop psychiatric disorders such as anxiety disorder, major depressive disorder (MDD), and post-traumatic stress disorder (PTSD). These disorders are associated with increased avoidance, such as excessive fears that they are unable to control, and this can negatively impact the quality of life. There are currently no effective therapeutic interventions for this problem mainly due to a lack of understanding of the changes in the brain that occur following mTBI. Therefore, it is important to understand the underlying mechanisms to develop an effective treatment strategy. Previous studies suggest that an increase in avoidance is typically accompanied by an alteration in the neuronal communication between critical brain regions such as the medial prefrontal cortex (mPFC), the basolateral amygdala (BLA), and the hippocampus (HPC). This communication happens via low frequency (Theta band 4-8 Hz) rhythmic neuronal oscillations and changes in these rhythmic oscillations in the mPFC, BLA, and HPC are associated with psychiatric disorders. Therefore, this project's central hypothesis is that rmTBI induced avoidance is associated with alteration in neuronal communications between brain regions in the mPFC- BLA-HPC circuitry.

Principal Investigator(s): Dr. David Joseph Titus, 608-770-2646, adaik023@umn.edu

Targeting Trem2 on Monocytes to Regulate Neuroinflammation following Traumatic Brain Injury, University of Minnesota, receives $125,000

Traumatic brain injury (TBI) is a severe and debilitating disease that is driven, in part, by a dysregulated immune response. Specifically immune cells of the myeloid lineage play a key role in the acute and chronic phases of disease that result in either appropriate inflammation resolution or pathogenic remodeling that leads to non-resolving inflammation and increased disease burden. Microglia are the primary tissue resident myeloid cell in the brain and monocytes are an inflammatory subset of blood immune cell that infiltrates into the brain following TBI. This researcher developed unique mouse models to address the differential contributions of these important cell types to TBI inflammation. We will use our new approach to target a known neuroinflammatory regulator, TREM2, in microglia and monocytes to advance knowledge that may be translatable for future clinical trials. Now, they will test the hypothesis that Trem2 is a key immunomodulatory receptor utilized by newly recruited inflammatory monocytes following TBI injury, which can be therapeutically targeted to attenuate neuroinflammation and promote wound healing.

Principal Investigator(s): Dr. Jesse W. Williams, 612-625-3109, jww@umn.edu

Is cerebrospinal fluid diversion underutilized after traumatic brain injury?, Center for Veterans Research and Education, receives $248,130

Hydrocephalus, or excessive accumulation of fluid within the brain, is associated with head injury, headaches and cognitive decline in both veteran and civilian populations both acutely and chronically. It is treated by cerebrospinal fluid (CSF) diversion, most commonly with a shunt, or catheter that enables fluid to exit the brain and be absorbed elsewhere. Approximately 20% of veterans with shunted hydrocephalus report having had at least one head injury in the past (McKee and Robinson 2014). It is unknown what percentage of people who have had prior brain injury develop hydrocephalus in either its clinically recognized form or a subclinical form that impacts function but is not ultimately treated. Some of these people may ultimately be diagnosed with so-called idiopathic normal pressure hydrocephalus (iNPH), which is considered to be the most treatable form of dementia. iNPH mimics some of the chronic effects of neurotrauma such as cognitive difficulties and memory loss. The exact cause of iNPH has yet to be elucidated but it is known that brain injury may potentially play a role in both overproduction and under absorption of cerebrospinal fluid (CSF). In addition, the atrophy associated with brain injury may cause cortical loss which results in the appearance of ventriculomegaly and expansion of extraventricular CSF spaces. The purpose of this project is to understand whether shunting of people with large or misshapen ventricles, or in people with prominent extraventricular CSF spaces after brain injury will result in improved survival or lessen disability relative to those with similar cortical morphology who were not shunted. The researcher hypothesizes shunting will improve survival with a decreased risk of disability for veterans of similar age, gender and cortical morphology.

Principal Investigator(s): Dr. Uzma Samadani, 917-388-5740, uzma.samadani@va.gov

Updates from the Field

Updated progress and/or outcomes of the projects listed in this report are typically disseminated to the public during the Minnesota Spinal Cord Injury and Traumatic Brain Injury Research Symposium. The date of the event was scheduled for February 2021; however, it was postponed due to COVID-19 disruptions. Once rescheduled, an invitation will be extended to legislators so that the stories and experiences of patients can be heard. Discoveries and innovations will also be shared with the scientific community through national presentations, journal articles and publications, and future collaborations. For a list of preliminary accomplishments from completed projects, see **Appendix B.**

The Spinal Cord Injury and Traumatic Brain Injury Advisory Council anticipates that through the innovations cited in the recommended research projects, and collaboration with other nationally-renowned researchers, the novel outcomes from the funded projects should lead to advances in the fields of spinal cord injury and traumatic brain injury.

Patient Testimonies

> *"I am writing you this email in support of research funding and would like my story to be included in the Minnesota SCI-TBI Legislative Report.*
>
> *My name is Geoff Jessup. On June 22, 2014, I suffered a spinal cord injury while out recreationally riding off road dirt bikes with my 2 younger sons. At the time I didn't believe I was participating in any sort of high risk activities but in a blink of an eye I laid on the ground without the ability to move my legs. My official injury status is a T4 complete spinal cord injury. To describe what the feeling of not being able to move my lower body to people who take it for granted is very difficult as I could imagine someone doing the same to me before I was injured and not even remotely understanding what they were describing. The uncontrollable muscle spasms, the neuropathic pain, the bladder/bowel issues to name only a few were things that would never cross my mind if and when I saw someone in a wheelchair or were told they had a spinal cord injury.*
>
> *I was asked what being included in to the Estand study meant to me once. I think the first time asked my eyes welled up as I recall hearing I was accepted the very first time. Beyond some ability to move my legs for the first time in 4 years, almost completely eliminate my muscle spasms and give me some better control over my bladder and bowel issues It also gave me hope. Hope that there were still opportunities to improve my quality of life and also hope for the many young guys that I had met in my original rehabilitation after surgery. You see I was 54 at time of injury and even though I was very active playing all types of sports that I very much miss I had 30 years on some of the young guys that I met in rehab and could only imagine that they had no idea of what great things in life they were going to miss because of their injury.*
>
> *Alaina If you thought it was beneficial I would be more elaborate with some details and I could forward a short video of my leg movement after 4 years of not being able to.*
>
> *Really in the end those of us with a spinal cord injury just want to feel that our numbers and not too small that they don't deserve the funding to work towards a cure."*

Geoff Jessup

> *"I am a quadriplegic on a ventilator for 13 plus years now. I am messaging to say Thanks for keeping the funding for spinal cord research! I know it is expensive but the impact of a successful treatment will result in more than anything can pay for many individuals!"*

Nick Doriott

"I'd like to thank you for your support in continuing funding for spinal cord injury and traumatic brain injury cure research! I'm personally affected by this because when I was barely 13 in 1994 I was crossing the street on my bike, I had the right-of-way, when a negligent driver who wasn't watching the road, his turn signal, or the upcoming next turn that corresponded with his turn signal, (where I was crossing from), drove his El Camino into me doing over 55 mph.

Among the MANY other physical injuries & trauma I sustained from that, (shattered femur & shin, head trauma which nearly knocked my eye out of my skull & the doctors had to push it back in, brain swelling, hematomas, & countless surgeries to save my life, going into my head several times, needing a shunt put in my brain to drain fluid to my stomach for life, hardware put in my entire left leg, exploratory surgery to check for internal bleeding, having piece of my skull removed to accommodate my brain swelling and having it put back in weeks later, having a rib removed and relocated into my neck with hardware to fuse it, a tracheostomy, a feeding tube in my stomach that was later able to be removed, needing a pacemaker put in because I was literally dying/my heart stopping/the crash cart called in to my ICU room every 5 minutes for several weeks, having the pacemaker removed later on, & countless other surgeries after all of that but because of it), my neck was broken at the 2 highest levels possible, C1 & C 2, (same levels that Christopher Reeve was), leaving me quadriplegic & 100% ventilator dependent 24/7. Since then I've undergone more physical & emotional trauma than most people would have in 10 lifetimes. I'm literally on life support 24/7 & completely dependent on others for all of my needs from below my jaw down. I have been this way for 26+ years.

Spinal cord injuries can happen to anyone at any time. It doesn't matter how old or young you are, (there was another kid at Gillette Children's hospital for his physical rehab at the same time I was, same level of injury as me, & he was only 7), it doesn't matter what your race is, it doesn't matter what your gender is, it doesn't matter what your beliefs are, it doesn't matter how it happens. 10,000 Americans alone, (& probably more by now, I got this statistic years ago when writing a letter similar to this, I'm a very big advocate about SCI cure research & funding for it), suffer a spinal cord injury every year leaving them paralyzed to some degree, including the highest degree that I am. Continued funding for researching SCI & TBI is INCREDIBLY IMPORTANT & could even lead to finding cures for other nervous system or neurological injuries or ailments. Medical science is mysterious that way, just look at penicillin. Who would've thought mold would be the cure for so many things that used to kill people all the time.

I, my family, everyone who has suffered a SCI & has been living with the aftermath for years-decades, & peoples who are going to suffer a SCI leaving them paralyzed to any degree, (could be someone you know, could be someone you love, could be you), needs this funding& thanks you for supporting it!!! TBI research funding that is included with this is important as well. Head injuries can happen at any time to anyone & can severely mess the person up. I've seen the aftermath of head injuries personally."

Angelique Novak

"I have been a quadriplegic for over 33 years and have been a cure advocate since day one. Since 1987, everything has changed, cars, houses, landscapes, even your breakfast cereal, not paralysis. With the help of the Research Grant Program, this is no longer true. The State of MN is now partnering with and helping drive some of the most innovative science toward a common goal to eradicate this most ugly human affliction known to man. Additionally, because the State is paying for the cares for these people, ANY improvements in bodily function will most certainly pay off huge dividends in reducing cares costs and not to mention, what a health IMPROVEMENT would do to someone's life and mental well-being…put a price on that!"

Jeffrey Toby

"To Whom it may Concern:

In October of 2006, I suffered a T8, ASIA A spinal cord injury from a fall during sleepwalking. At the 2016 W2W (Working 2 Walk) Symposium Minneapolis, I listened to a presentation about an epidural stimulation clinical trial starting soon at HCMC (Hennepin County Medical Center) called ESTAND (Epidural Stimulation After Neurologic Damage). I met with Dr. David Darrow to discuss what the trial would entail and about the surgery itself.

After looking through my medical records and discussing with the clinical trial team, Dr. Darrow told me that they were not sure this would work for me, given the severity of my injury, the length of time that had passed since my injury and my age-52 at the time of surgery. I went into this clinical trial with no preconceived notions of success. If it didn't work, then we knew what the limitations were.

On September 27, 2017, I had the epidural stimulator implanted! 2 weeks later, on the 11th anniversary of my spinal cord injury, we turned the stimulator on. It worked! There was quite a bit of excitement in that room and yes, I did shed a few tears of joy!

As the trial progressed, I noticed that my shoulders didn't hurt anymore. My left shoulder was so painful before the trial. I was worried that I may need surgery. I am able to sit up straighter in my wheelchair and that has allowed me to push more efficiently. My gray area of nerve sensitivity has disappeared and the pins and needles nerve pain has gotten much better! My legs don't bounce around anymore. I can ride in a car without becoming stiffer than a board and being thrown back in my chair. I can maintain a more even body temperature. It is nice not to take 2 hours to warm up. My bowel program is shorter. My bladder is still a work in progress. I didn't expect all of these changes. In the past few years, our community has made it clear that while walking again would be great, it is all of the other stuff the affects our quality of life.

Without the Minnesota Spinal Cord Injury/Traumatic Brain Injury Research Grant program, the ESTAND clinical trial would not have happened. Why deny people a good quality of life after injury? Let's prevent shoulder injuries due to overuse, drug use for spasms, nerve pain, bladder

> *leakage, long bowel programs, poor temperature control. The list is long. Please continue to fully fund the MN SCI/TBI Research Grant Program! Thank you for reading about my experience!"*

Kathy Allen, SCI survivor, Crosslake, MN

Appendix A: Copy of Statute

Laws of Minnesota 2021

136A.901 SPINAL CORD INJURY AND TRAUMATIC BRAIN INJURY RESEARCH GRANT PROGRAM.

Subd 1. Grant program

The commissioner shall establish a grant program to award grants to institutions in Minnesota for research into spinal cord injuries and traumatic brain injuries. Grants shall be awarded to conduct research into new and innovative treatments and rehabilitative efforts for the functional improvement of people with spinal cord and traumatic brain injuries. Research topics may include, but are not limited to, pharmaceutical, medical device, brain stimulus, and rehabilitative approaches and techniques. The commissioner, in consultation with the advisory council established under section 136A.902[1], shall award 50 percent of the grant funds for research involving spinal cord injuries and 50 percent to research involving traumatic brain injuries. In addition to the amounts appropriated by law, the commissioner may accept additional funds from private and public sources. Amounts received from these sources are appropriated to the commissioner for the purposes of issuing grants under this section.

Subd. 2. Report

By January 15, 2016, and each January 15 thereafter, the commissioner shall submit a report to the chairs and ranking minority members of the senate and house of representatives' committees having jurisdiction over the Office of Higher Education, specifying the institutions receiving grants under this section and the purposes for which the grant funds were used.

136A.902 SPINAL CORD AND TRAUMATIC BRAIN INJURY ADVISORY COUNCIL.

Subd 1. Membership

The commissioner shall appoint a 14-member advisory council consisting of:

1) one member representing the University of Minnesota Medical School;
2) one member representing the Mayo Medical School;
3) one member representing the Courage Kenny Rehabilitation Center;
4) one member representing Hennepin County Medical Center;
5) one member who is a neurosurgeon;
6) one member who has a spinal cord injury;
7) one member who is a family member of a person with a spinal cord injury;
8) one member who has a traumatic brain injury;

[1] https://www.revisor.mn.gov/statutes/cite/136A.902

9) one member who is a veteran who has a spinal cord injury;
10) one member who is a veteran who has a traumatic brain injury;
11) one member who is a family member of a person with a traumatic brain injury;
12) one member who is a physician specializing in the treatment of spinal cord injury;
13) one member who is a physician specializing in the treatment of traumatic brain injury; and
14) one member representing Gillette Children's Specialty Healthcare.

Subd. 2. Organization

The advisory council shall be organized and administered under section 15.059[2], except that subdivision 2 shall not apply. Except as provided in subdivision 4, the commissioner shall appoint council members to two-year terms and appoint one member as chair. The advisory council does not expire.

Subd. 3. First appointments and first meeting

The commissioner shall appoint the first members of the council by September 1, 2015. The chair shall convene the first meeting by November 1, 2015.

Subd. 4. Terms of initial council members

The commissioner shall designate six of the initial council members to serve one-year terms and six to serve two-year terms.

Subd. 5. Conflict of interest

Council members must disclose in a written statement any financial interest in any organization that the council recommends to receive a grant. The written statement must accompany the grant recommendations and must explain the nature of the conflict. The council is not subject to policies developed by the commissioner of administration under section 16B.98[3].

Subd. 6. Duties.

The advisory council shall:

(1) develop criteria for evaluating and awarding the research grants under section 136A.901[4];
(2) review research proposals and make recommendations by January 15 of each year to the commissioner for purposes of awarding grants under section 136A.901[5]; and
(3) perform other duties as authorized by the commissioner.

[2] https://www.revisor.mn.gov/statutes/cite/15.059

[3] https://www.revisor.mn.gov/statutes/cite/16B.98

[4] https://www.revisor.mn.gov/statutes/cite/136A.901

[5] https://www.revisor.mn.gov/statutes/cite/136A.901

Appendix B: Status/Accomplishments of Funded Projects and the Dissemination of New Knowledge

Project Title: Switching off the Thrombin Receptor to Enhance Recovery after Traumatic Brain Injury
Institution: Mayo Clinic
Principal Investigator: Dr. Isobel Scarisbrick
Grant Cycle: FY2020

Accomplishments

We have established a reproducible mild repetitive TBI model (r-mTBI). We are preparing a manuscript to detail the procedure involved in this unique and clinically relevant model as well as the neurobehavioral and histopathological outcomes that are relevant. An Abstract has been submitted for presentation at the 2022 Society for Neuroscience Meeting. The r-mTBI is "mild" and meant to replicate multiple concussive injuries rather that severe neurotrauma. As a result, we have rigorously tested a number of behavioral measures and have identified anxiety in the open field test and social interaction as highly sensitive. These tests were able to clearly differentiate not only Sham and TBI mice, but also differences based on treatment. As this model is clinically relevant, this information will be highly valuable to the TBI research and clinical fields.

In the first phase of these studies, we demonstrated that increases in anxiety in the open field test and reductions in social interaction in mice with r-mTBI are highly sensitive measures of neurobehavioral decline. We documented that mice with genetic blockade of the thrombin receptor across all cell types show significant improvements in social interaction relative to genotype controls at the 4-week post-injury time point. To date, histopathological outcomes demonstrate that reduced gliosis may underpin these neurobehavioral improvements, however repeating the experiments will be necessary to increase subject number for statistical rigor. We are preparing a new grant application to extend these studies.

Given the significant ability of constitutive knockout of the thrombin receptor to promote improvements in social interaction and to minimize gliosis in the mild repetitive TBI model, we made additional genetic crosses between a new conditional ready PARI mouse with a mouse containing a microglial specific Cre- driver. The results of these studies demonstrate for the first time that microglial PARI is a key driver of behavioral declines in social interaction and increases in anxiety and astrogliosis we observed after r-mTBI. We documented that switching off the function of PAR I in microglia in adult mice resulted in significant improvements in social interaction relative to genotype controls 2-week after r-mTBI. Switching off PARI selectively in microglia also reduced anxiety levels at 2-week post r-mTBI. The histopathological analyses of brain tissue from these mice are underway. These studies are important because they begin to pinpoint the mechanism that PAR I drives neural injury in the context of mild repetitive TBI. The data from these mechanistic studies will permit us to apply for NIH funding that will be needed to move the results of these studies closer to clinical translation. We are working to finalize the results of these studies for publication. We are also completing all analyses phases of studies to demonstrate the neurobehavioral impact of pharmacological inhibition of PARI initiated after r-mTBI.

Dissemination

We will use the findings generated from this grant to garner new NIH funding to take the important next steps in this novel line of clinically relevant research. This funding will be used to pursue PAR1 as a target for neuroprotection and regenerative repair after TBI.

Project Title: Multilineage 3-dimensional brain organoids to model intracranial pressure linked to chronic traumatic encephalopathy
Institution: University of Minnesota
Principal Investigator: Dr. Andrew T. Crane
Grant Cycle: FY2020

Accomplishments

The overarching goal of the current proposal was to establish an *in vitro* model of chronic traumatic encephalopathy (CTE) using human brain organoids exposed to repeated stress via an increase in pressure. To generate the brain organoids, first human induced pluripotent stem cells were transfected with a lentivirus forcing expression of green fluorescent protein linked tau. These stem cells were then used to form 3-dimensional brain organoids as well as microglia-like cells that could then be seeded in the organoid and then transferred to a pressure chamber and stressed through repeated transient increases in pressure. High-throughput fluorescent imaging of individual organoids will be used to identify conditions that lead to CTE-like accumulation of pTau, as indicated by an increase in organoid fluorescence relative to non-stressed organoids.

When the *in vitro* model of CTE was established, commercially available FDA drug-screen libraries would then be used in a high-throughput setting to identify drugs that ameliorate accumulation of pTau, as indicated by a decrease in organoid fluorescence, relative to untreated, stressed organoids. We have established a line of human induced pluripotent stem cells (iPSCs) that have been transduced with a lentivirus expressing Tau linked to GFP. Individual colonies of transduced iPSCs were expanded and genotyped using primers targeting the GFP gene. Clones with high amplification of GFP (iPSCTau-GFP) relative to the housekeeping gene actin were selected for downstream growth into organoids. Phenotyping of iPSCTau-GFP demonstrated that iPSCs were capable of expansion and maintained expression of pluripotency genes POU5F1, SOX2, and NANOG as determined by immunofluorescence (data not shown). Organoids were then generated from iPSCTau-GFP using three methods: brain organoids (bOrg), neural spheroids (NS), and cerebral organoids (CO).

Dissemination

Given the negative results of the research and major unanswered questions regarding the platform technology, no plans for dissemination have been made.

Project Title: Therapeutic targeting of cellular senescence to promote repair of the chronically injured spinal cord
Institution: Mayo Clinic
Principal Investigator: Dr. Isobel Scarisbrick
Grant Cycle: FY2020

Accomplishments

Aim 1: To determine if pharmacologic clearance of senescent cells at chronic stages after spinal cord injury improves neural repair alone or in combination with treadmill training.

We have completed two independent experiments to determine if administering senolytic agents (Dasatinib (5 mg/kg)+ Quercetin (50 mg/kg) to animals with chronic spinal cord injury improves neurobehavioral outcomes. Drug was delivered weekly by oral gavage starting at 14 days after compression spinal cord injury in adult (12 week old) female mice with all outcomes compared to delivery of vehicle alone. All mice received D+Q or vehicle at 14, 21 and 28 days post injury and mice were harvested at a 35 day end point. Quantification of neurobehavioral outcomes in the Basso Mouse Scale open field test and in the incline plane test has been completed. In the first pilot set of experiments, we validated that no deleterious effects of treatment dose or timing were noted, indicating safety of this approach even in the context of spinal cord injury. In the first cohort of mice, while there was a strong trend for the subjects treated with the senolytic cocktail to show improved sensorimotor recovery compared to vehicle alone, a Power Analysis suggested that increased animal numbers were needed. We therefore established a second full experiment, leveraging experience from the first. In the second experiment, D+Q was delivered starting at 14d after SCI to 7 female mice and an additional 7 mice received parallel administration of vehicle alone weekly until the 35 day endpoint. D+Q treated mice showed improvements in motor coordination and stepping in the BMS score and subscore at day 28 and 35 after SCI ($P<0.05$, Two Way Repeated Measures ANOVA). In addition, D+Q mice showed improvements in strength in the Incline plane test ($P<0.01$, Two Way Repeated Measures ANOVA). These results are exciting since they indicate that a cocktail of senolytic agents delivered at a chronic time point after experimental SCI improves sensorimotor outcomes. All spinal cord tissues have been prepared for histological analyses to document the associated cellular and molecular mechanisms that may be driving the improvements in function.

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sensorimotor outcomes. All spinal cord tissues have been prepared for histological analyses to document the associated cellular and molecular mechanisms that may be driving the improvements in function.

Dissemination

Presentation of this work at a National meeting through Abstracts and publication of an associated manuscript in in preparation. We have used preliminary data generated under the grant to apply to other agencies for additional funding to continue this important line of research.

Project Title: A Multi-Dose Safety and Feasibility Study of Autologous Culture Expanded Adipose Derived Mesenchymal Stem Cells (AD-MSC) in the treatment of Traumatic Spinal Cord Injury
Institution: Mayo Clinic
Principal Investigator: Dr. Mohamad Bydon
Grant Cycle: FY2020

Accomplishments

Activities: The major activities that were accomplished was the enrollment of 39 participants in the ongoing phase II trial (31 fully enrolled, 5 screen fails and 2 consent denials screened), as well as 10 patients completing the phase I trial. 39 patients between two trial phases (10/10 phase I, 29/31 phase II) have completed/received stem cell administration. 16 patients between both phases (10/10 phase I, 6/39 in phase II) have completed the trial in its entirety. The routine evaluation assessment of adverse events, biomarkers, and functional/sensory assessments in all patients.

Objectives: The primary objective achieved was a safety-profile for AdMSCs in patients with traumatic SCI.

The secondary objective achieved was preliminary results regarding functional and sensory improvement based on the collection of neurological examinations, biomarkers from CSF and blood, and somatosensory evoked potential results.

Key Outcomes: 1) AdMSCs are a safe biologic drug in patients with traumatic SCI. 2) AdMSCs can provide functional and sensory improvement in patients with traumatic SCI. 3)Results of functional and sensory improvement fall on a spectrum between no-improvement to super-responders. 4)From our phase I preliminary data, 8/10 patients showed some sort of improvement, with two patients showing no improvement in terms of neurological status

Other Achievements: From our phase I study: (Data collected from PROMIS scores) i. 7/10 patients stated improvement in carrying out everyday activities

Dissemination

The results of our phase I trial are currently in the process to be published, where the results can be accessed by readers from the scientific/medical community, prospective patients, and the general public. We have finalized the manuscript and will be submitting it for peer-review.

Project Title: Non-Invasive Transcutaneous Spinal Cord Stimulation for Recovery of Hand Function after Spinal Cord Injury
Institution: University of Minnesota
Principal Investigator: Dr. David Darrow
G**rant Cycle:** FY2020

Accomplishments

We hired our study therapist in January 2021. Our site was approved on March 9th, 2021. The first participant was enrolled on April 8th, 2021. We completed our site data collection on March 31st, 2022 with 4 participants completing the study. During the study, over 200 hours of functional task practice were completed by study staff. Our site was also a top contributor to the larger multi-site project. At this time, the multi-site project has screened 99 people, 65 have been enrolled, and 4 have withdrawn. The multi-site trial was estimated to be completed in May 2022. All specific objectives and aims were completed. All participants reported beneficial changes in hand function (aim 1) and functional abilities (aim 2). We are unable to formally report outcomes or any data at this time due to an embargo from the industry-sponsor as they prepare for their FDA submission.

Study completed for FDA approval.

Dissemination

The results of this work are under embargo by the industry sponsor. Results will be published and disseminated in partnership with the industry partner, ONWARD Medical.

Project Title: Training Transplanted Spinal Neural Progenitor Cells (sNPCs) to Function after Chronic Spinal Cord Injury
Institution: University of Minnesota
Principal Investigator: Dr. Ann Parr
Grant Cycle: FY2019

Accomplishments

Chronic spinal cord injury (SCI) is a devastating condition that has no available treatments. We plan to utilize with cell transplantation and to provide a more permissive environment for cell integration and function. This therapy included transplantation of spinal Neural Progenitor Cells (sNPCs). These are the cells that we have developed in our laboratory, and are a type of stem cell that develop into spinal neurons after transplantation. These cells are human, and are generated from induced Pluripotent Stem Cells (iPSCs). We hypothesize that maximal benefit will also require “learning” by the new neurons. In human brain and spinal cord development, there are many unnecessary connections formed between neurons, and it is only by the process of reinforcing the useful ones, and “pruning” the useless ones that we function efficiently. Therefore, we suggest that reinforcing the useful connections will optimize function of the transplanted neurons, also referred to as activity-dependent plasticity. Plasticity is the ability of neurons to rearrange their anatomical and functional connectivity in response to environmental input, thereby achieving new or modified outputs. Neuromodulation via spinal cord stimulation (SCS) is one neuroengineering approach for facilitating neuroplasticity [1-3] We

propose to use TANES in order to optimize function and “teach” the new neurons. Epidural stimulation in humans has recently been shown to be beneficial in both motor and autonomic recovery of function [4]. this project we combined sNPCs transplantation with TANES. A total of 30 nude rats were used for this long-term (functional) study. All rats received a moderate contusive thoracic injury (Ultimate Horizons Impactor), and treatment was deferred for 56 days to receive the treatment/s. Adult female rats were randomly assigned to one of the three groups (10 rats per group). Group 1 received culture medium only (Control); Group 2 received injections of sNPCs (sNPCs only); Group 3 received injections of sNPCs followed with TANES (sNPCs+TANES) treatment. Rats were sacrificed at 16 weeks post transplantation and tissue was processed and analyzed utilizing standard histological, IHC and tissue clearing techniques. Functional testing was performed. Outliers will be removed from the study. Outliers are defined as being outside of two BBB scores of the average BBB score. We found that human iPSC derived sNPCs were multipotent and retained the ability to differentiate into mainly neuron or oligodendrocytes when transplanted into the chronically injured spinal cords of rats. Sixteen weeks after cell transplantation we observed that more of the transplanted cells differentiated into neurons and oligodendrocytes however, rats that were electrically stimulated with TANES showed significantly higher percentage of cells expressed oligodendrocytes and synaptophysin when compared with no TANES cells only group. We observed functional improvement when rats were treated with sNPCs and electrical stimulation with TANES. Therefore, we observed TANES promoted human iPSC derived sNPCs to advance functional recovery in chronically injured rats. Though there is no significant difference between any of the treatment groups, improvement in BBB scores to consistence coordination stepping in sNPC+TANES group is a remarkable recovery of locomotor function with sNPC transplantation and TANES combinatorial treatment [6].

Dissemination

TBD.

Project Title: Optimizing Epidural Spinal Cord Stimulation to Restore Cardiovascular Function after Spinal Cord Injury
Institution: Hennepin Healthcare Research Institute
Principal Investigator: Dr. David Darrow
Grant Cycle: FY2018

Accomplishments

Using established methodologies in combination with our optimization algorithm, we have been able to determine SCS parameters that restore cardiovascular function in those with autonomic dysreflexia. Our tablet application has allowed us to collect data on autonomic parameters, remotely, through questionnaires. In addition, using the tilt-table, we are able to collect autonomic data, with and without stimulation, to assess changes in cardiovascular function. Through this, we are able to determine parameters that aid in restoring cardiovascular function. This finding has shown to improve cognitive function and increase energy levels.

Moreover, the development and implementation of our application has allowed us to collect data remotely through the home-exercise in conjunction with accelerometers and questionnaires. Such data allows us to assess the efficacy of each setting with regards to improvements in volitional movement, autonomic function, and bowel/bladder control while the participant is in the comfort of their own home. Through this, we are able

to continuously refine setting parameters based on participant preference. In addition, this home-exercise also serves as a form of therapy that can either enhance the participants' current regimen or provide a form of activity for those that do not participate in rehabilitation programs for various reasons.

Dissemination

The media has been our primary vehicle for disseminating our results to communities of interest. We have used our updated website to create blog posts that include links to our publication, news articles and presentations given by our investigators. Through Dr. Darrow's social media, study updates and information have been provided as well. Moreover, patient progress videos have been posted on social media accounts, such as YouTube, where they have been shared by others in the community. Additionally, a study guide was also created for our participants which entails information on our study and links to our publications and news articles. We also send monthly updates to each subject via email, which includes current findings, presentations, and articles.

Project Title: Therapeutic Application for Non-hematopoietic Umbilical Cord Blood Stem Cells (nh-UCBSCs) in Traumatic Brain Injury: Immune Modulation with Acute and Long Term Benefits
Institution: University of Minnesota
Principal Investigator: Dr. Andrew Grande
Grant Cycle: FY2018

Accomplishments

Major Goal #1:

- Activities included creating a controlled cortical impact in rats and treating injured rats with nh-UCBSCs at 48 hours post-injury. Animals were tested using a battery of behavioral tasks quantifying lateral asymmetry in injured animals. Live animals were also imaged using Ferumoxytol enhanced MRI, in an effort to identify macrophage activity in the brain of injured animals. At the conclusion of the study, animals were euthanized and brains isolated for flow-cytometric analysis of immune cells within the brain.
- Specific objectives of this study were to reduce neuroinflammation associated with TBI through intravenous infusions of nh-UCBSCs, as measured by MRI and flow cytometry. Reductions in neuroinflammation would be correlated with reductions in behavior deficits.
- Results from this study are variable and inconclusive. The behavioral data indicate the presence of lateral asymmetry in injured animals, with a preference towards using the forepaw of the uninjured hemisphere, although treatment with nh-UCBSCs did not ameliorate this deficit (Figure 1A). Live imaging through MRI proved highly variable and no conclusions could be made. Inflammation measured through flow cytometry noted a trend towards reduction in the number of neutrophils present in the injured (ipsi) hemisphere of treated rats, relative to injured rats injected with vehicle (Figure 1B). No other alterations in immune cells were observed in injured animals. The results from this study led us to re-examine the premise on which this study was designed. Our initial assumptions were that the neuroinflammation following TBI should be similar to stroke, on which we have well established data indicating a robust immune response at 9 days post-stroke. Given a minor difference was observed in

the diversity and number of immune cells present in the brain post-TBI we decided to establish a timeline of neuroinflammation in a mouse model (Major Goal #2).

Major Goal #2:

- Activities include developing a unilateral controlled cortical impact model in mice with time and injury severity as variables. A mild-injury was developed with the goal to create minimal gross pathology to the brain. A moderate-injury was developed with the goal to create a cavitation in the brain. Animals were tested using a battery of behavioral tasks quantifying lateral asymmetry and memory deficits. Animals were euthanized at 6-hours, 24-hours, 3-days, 7-days, 14-days, and 28-days post-injury and brains isolated for flow-cytometric analysis of immune cells within the brain.
- Specific objectives were to quantify the diversity and total numbers of a wide-range of immune cells within the brain and whether these changes can be correlated with behavioral deficits.
- Results from this study confirms our hypothesis following analysis of the results from Major Goal #1. The infiltration of immune cells within the brain following injury is very dynamic, particularly in the total number of macrophages and the unique macrophage phenotypes (Figure 2A-D). We were also able to identify behavioral deficits associated with the mild- and moderate-TBI mouse (Figure 2E-F).

Major Goal #3:

- Objective: To determine the source and impact of migrating brain macrophages induced in response to TBI.
- Activities:
    - Evaluation of BM Chimeras and Macrophage depletion. Two experiments were performed to standardize the BM transplant and macrophage depletion characteristics. Blood was collected from animals at 4 weeks post transplantation and chimerism was assessed using the congenic markers on myeloid cells (CD45.1-recepient and CD45.2-donor).
    - Evaluation of macrophage migration into the brain (from the periphery) post TBI. Bone marrow chimeras were used to determine the number of cells that migrated from the bone marrow through peripheral circulation (compared to a resident tissue origin).
- Results: In the first experiment standardizing the transplant procedure, we lost 60% of our transplant recipient animal and less than 25% of animals had >80% blood chimerism with donor leukocytes ($CD45.2^{+}$). After changing the irradiation protocol for myeloablation and transplant bone marrow cell preparation, we achieved 75% survival with >80% donor chimerism observed in 2/3 of the animals and > 50% chimerism in all transplanted animals. Three months after transplantation, 8 chimeric animals with 80 to 90% leukocyte chimerism were selected and treated with diphtheria toxin (DT, 100 ng/mouse) to deplete DTR tagged donor cells in the chimera. At 24 h after DT treatment, bone marrow, brain, blood, spleen, cervical lymph node, inguinal lymph node, and peritoneal cavity cells were analyzed for macrophages and lymphocytes. No depletion of macrophages was observed in DT-treated mice. Escalating DT dose was titrated in F1-DTR-mCherry transgenic mice to determine the threshold for DT effect by analyzing brain, blood, bone marrow, spleen and CLN at 24 h. There was reduction in number of Ly6C(hi) macrophages in the blood at 100 and 200 ng doses, but these doses did not affect total macrophages in all tissues analyzed, including the brain. This result indicates that the macrophage depletion with this system was effective only for certain subpopulations of macrophages and did not

impact the tissue compartment. We hypothesized that poor drug penetration into tissues, rapid repopulation of depleted populations or insufficient expression of DTR in certain populations of macrophages (i.e. tissue macrophages). We tested mCherry expression in tissue macrophages as a surrogate for DTR expression and found low expression levels in tissue macrophages, suggesting a low DTR expression in these cells. mCherry was detected predominantly in the ly6C population in blood. Other methods for macrophage depletion are being explored.

- We then used chimeric mice with congenic markers (CD45.1/CD45.2) to ask if peripheral (bone marrow derived) macrophages migrated into the brain post TBI. At 7 d post TBI, chimeric mice (>50% donor cells in blood, bone marrow, and CLN) were assessed for donor and recipient contribution to the neuroinflammatory response to TBI. As expected, all the microglial cells in the brain were of host (recipient) origin, i.e. not repopulated from the BM. Since these experiments were done >20 weeks post-transplant we also confirm that replacement of microglia from peripheral sources is a slow process, if at all. This finding also alludes to a brain source for replenishment of these resident brain macrophages. Post TBI, CD45(hi) total infiltrating macrophages numbers were high (as previously shown) and were of both recipient and donor origin. However, CD45(hi) Ly6C(hi) inflammatory macrophages were mostly (>75%) derived from recipient, even in animals with 80% donor derived cells in the blood. This finding suggests either (1) there is a local tissue source for macrophages or (2) there is selective recruitment of host derived cells into sites of inflammation (even when blood chimerism is as high as >80%). This also means that our therapeutic modulation of macrophage responses in the brain would need to be directed to a tissue source (than circulating cells), giving more credence to the hypothesis that umbilical cord blood stem cells use a distal tissue directed mechanism to modulate brain inflammation.

Dissemination

Results from these studies have been presented at the 2019 Minnesota Neurosurgery Society Annual Meeting as an oral presentation, the 2019 NexGen Stem Cell Conference as an oral presentation, 2019 National Neurotrauma Society Annual Symposium, and the Society for Neuroscience conference 2019.

Two manuscripts describing the kinetics of neuroinflammation in (1) mild- and (2) moderate-injured mice are currently being written with the intent to submit before the end of 2020.

Project Title: Epidural Stimulation for Spinal Cord Injury
Institution: Hennepin Healthcare Research Institute
Principal Investigator: Dr. David Darrow
Grant Cycle: FY2018

Accomplishments

The development and implementation of our application has allowed us to collect data remotely through the home-exercise in conjunction with accelerometers and questionnaires. Such data allows us to assess the efficacy of each setting with regards to improvements in volitional movement, autonomic function, and bowel/bladder control while the participant is in the comfort of their own home. Through this, we are able to continuously refine setting parameters based on participant preference. In addition, this home-exercise also serves as a form

of therapy that can either enhance the participants' current regimen or provide a form of activity for those that do not participate in rehabilitation programs for various reasons.

Using the MOTOmed bike, a motorized therapy device, we now have the capability of capturing various elements of interest regarding volitional movement. Specifically, we are able to collect data related to the duration of active pedaling, power generated, spasticity, muscle tone, and sidedness among others. This data is collected with and without stimulation to assess the aforementioned variables. Such data allows us to assess changes, either improvements or declines, in subjects' volitional movement throughout the duration of the study. In addition, it has provided the ability to reinforce the relationship between our developed tablet application and optimized setting parameters. Current analysis is preliminary but holds promise.

Dissemination

The media has been our primary vehicle for disseminating our results to communities of interest. We have used our updated website to create blog posts that include links to our publication, news articles and presentations given by our investigators. Through Dr. Darrow's social media, study updates and information have been provided as well. Moreover, patient progress videos have been posted on social media accounts, such as YouTube, where they have been shared by others in the community. Additionally, a study guide was also created for our participants which entails information on our study and a link to our publication. We also send monthly updates to each subject via email, which includes current findings, presentations and articles.

Project Title: Combined tDCS and Cognitive Training to Reduce Impulsivity in Patients with Traumatic Brain Injury
Institution: Center for Veterans Research and Education
Principal Investigator: Dr. Casey S. Gilmore
Grant Cycle: FY2019

Accomplishments

All necessary study approvals, including IRB approvals from both the VA and the University of Minnesota (UMN), and the subcontract with UMN to allow us to collect MRIs at the Center for Magnetic Resonance Research there, have been obtained. We have enrolled the first subject in the study. Through coordination with the Rehabilitation and the Addiction Recovery Services care teams at the VA, we have a list of potential participants whom we have begun to contact.

Dissemination

None.

Project Title: Head-Mounted Display Virtual Reality in the Treatment of Upper Extremity Function in Acute TBI Rehabilitation: A Comparison Study to Conventional OT Treatment Alone
Institution: Center for Veterans Research and Education
Principal Investigator: Dr. Gary Goldish
Grant Cycle: FY2019

Accomplishments

We have worked on optimizing the flow of our study. We have developed a standardized study definition of a 'repetition'. A rep is defined as a volitional movement of the more-affected UE that describes any of the following:

UE leaves a starting point and returns to a resting position (Score as 1 rep given the return to rest is a more passive, non-purposeful movement)

UE leaves a starting point and has a purposeful, active, controlled return (Score as 2 reps given the purposeful, active return movement)

UE starts and has a clear stop before changing directions (Score as 1 rep)

If simultaneous movement is occurring at multiple joints, the joint most distal is counted. Based on this definition, two research staff were trained on how to count reps. Counters independently counted reps during 17 instances of VR and table top activities. Our biostatistician (Amy Gravely) computed intra-rater reliability (ICC > .9). Due to the high ICC we feel confident using one counter going forward.

All study personnel were trained on how to implement the VR intervention, how to conduct the assessments used in study, and best practices when conducting research. Our clinician collaborators continue to be excited about the potential use of VR in the clinic for rehabilitation.

The study has been actively recruiting subjects since October 2019. The study team meets weekly to discuss recruitment and problem solve barriers to participation. We have screened 14 potential subjects and enrolled none (see consort below). The primary reasons for excluding subjects have been no UE impairments, other medical conditions that prevent participation (e.g., wearing a c-collar on the neck), and dual TBI/stroke diagnoses. We had originally excluded cases of dual TBI/stroke diagnoses due to the differences in recovery trajectories, but after discussion with the study team have decided to include these subjects in the future as clinicians state that dual diagnoses can be common in the Veteran population served at the Minneapolis VA. Therefore, to have a representative sample, we will include Veterans with dual TBI/stroke diagnoses moving forward.

In December, 2019 we met with Jack Avery, the Minneapolis VA's CARF Administrator, to get insight into the Polytrauma census over time. In our meeting we discovered that there has recently been a lower number of TBI admits than is typical in prior years.

We have submitted an amendment to include active duty service members along with Veterans in this study. The Minneapolis VA polytrauma center has a partnership with the Department of Defense (DoD) in which the polytrauma program serves active duty military members in addition to Veterans. The DoD and VA have a strong commitment to the identification and patient-centered treatment of active duty service members and Veterans who are in recovery from a TBI. Including active duty service members in this study helps underline this commitment and may aid in recruitment.

Dissemination

None.

Project Title: Intranasal Insulin to Improve Recovery following Cervical Spinal Cord Injury
Institution: HealthPartners Institute
Principal Investigator: Dr. Leah R. Hanson
Grant Cycle: FY2019

Accomplishments

The start-up activities of this project continue to take longer than anticipated including delivery of tools/devices and successful implementation of the model in the lab. We anticipate that we will need the one year cost extension. We continue to meet bi-monthly with the research team.

We have the necessary equipment and training to conduct the behavioral testing and the biochemical analysis. While we received the FEJOTA clip last summer, it did not work properly and we needed to return it for modification and re-calibration. Customs also delayed that process. Upon its return, we still were not able to successful cause a reliable cord injury. So, we have amended our IACUC application to include an alternate model of inducing injury with the impactor. The amendment was approved. The machine was ordered, but some of its parts are currently on back order from China. We are hopeful that we will receive the impactor before March, 2020.

Dissemination

None.

Project Title: Spinal Cord Tissue Regeneration through Schwann Cell Seeded Hydrogel Scaffolds with Spatial-Selective Electrical Stimulation
Institution: Mayo Clinic
Principal Investigator: Dr. Igor Lavrov
Grant Cycle: FY2019

Accomplishments

For the purpose of the project we further developed a comprehensive combinatorial approach that combined an hydrogel (OPF+) scaffold that contained drug eluting microspheres and loaded with genetically modified Schwann cells with electrical stimulation and motor training in spinal cord injured rats. Immediately following transection, a scaffold embedded with glial-cell derived neurotrophic factor (GDNF) expressing SCs and drug-eluting microspheres will be combined with EES for neuromodulation of spinal cord circuitry with locomotor training.

The treatment tested in this study is a combination of many individual therapies investigated by our group in the past. We combined genetically modified cells, with small molecules, scaffolds, electrical stimulation, and motor

training on a treadmill in a rat model of spinal cord injury. Electrodes were placed in the muscles as well as above and below SCI. The spinal cord was transected at T9 and the GDNF/SC-RAPA-OPF+ was implanted.

Adult, female Sprague Dawley rats were trained to step on a treadmill system for one week after which they were implanted with an epidural stimulation electrode (L2) and intramuscular EMG electrodes into the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. Following one week after the first surgery, a complete spinal cord transection will be performed at the T9 thoracic level followed by implantation of a GDNF/SC-RAPA-OPF+. Custom-built electrode for EES was implanted on top of the scaffold covering the segments T8-T10. Following implantation and recovery, EES with locomotor training will be performed for 8 weeks. Implanted rats were followed for 7 weeks following thoracic spinal cord transection. We analyzed gait recovery using open field testing, kinematics, and electromyography from the hind-limbs. At week 6, a group of rats were re-transected through the scaffold to determine the extent of recovery.

The functional effect of this treatment was determined by treadmill assisted kinematic analysis, electrophysiological assessment, and open field testing. Rats implanted with scaffolds recovered better EES-enabled stepping than rats with no scaffold (Figure 2). Specific improvements in gait parameters such as step height, step length, toe fluctuation, and drag phase were demonstrated. In addition, there were significant improvements in the knee, ankle, and MTP angle displacements.

As early as 2 week following SCI we found some improvement in stepping in animals that were implanted with the scaffolds compared to no scaffolds when they were electrically stimulated (40 Hz, 1-2.5V) below injury.

Rats that received our combinatorial therapy (scaffold group) had better stepping on the treadmill when induced by epidural electrical stimulation than those that did not get the regenerative therapy (no scaffold group). (A) Representative stick diagrams of the gait from kinematic analysis. Although there was a trending difference in (B) BBB motor scores without EES assistance, there were significant improvements in (C) step height, (D) step length, (E) toe fluctuation, (F) drag phase, (G) hip angle displacement, (H) Knee angle displacement, (I) Ankle angle displacement, and (J) MTP angle displacement. No-Scaffold EES VS Scaffold EES*, Scaffold No-EES VS Scaffold EES#, No-Scaffold EES VS Scaffold No-EES$.

In particular we saw improvements in angular displacement of the knee, ankle, and MTP as well as step length, step height, toe fluctuation, and drag phase (Figure 2 and 3). There were no significant differences in stepping when there was no electrical stimulation. After re-transection of the scaffold we found some reduction in motor function, still, the motor performance was better compare to rats with no scaffold that could indicate on the influence of regenerated fibers on sub-lesional network spasticity.

Average (8 responses) spinal cord motor evoked potential (SCMEP) for rats with scaffolds and EES assisted motor training 1 week, 6 weeks, and post re-transection. Two representative rats that were treated with scaffolds and EES are shown (A and B). Red dotted lines indicate time of EES pulse and the middle response (MR and later response (LR) are indicated in the blue box. (C) The peak to peak amplitude of the middle response is shown for rats 6 weeks after injury and following retransection with stimulation at S1.

Overall, our results indicate that there is sub-functional reconnection through the scaffold and that this connection influences organization of spinal circuitry and stepping induced by EES.

We were also recording the BBB open field test with and without electrical stimulation. Kinematic analysis is very sensitive in picking up changes in gait and we wanted to see if any gait benefits of EES could be observed in open field testing. Novel modifications were made to our behavioral testing for this study by record the BBB locomotor open field test with and without ongoing electrical stimulation (Figure 5). Hind-limb BBB motor scores improved in rats with scaffolds and EES during stimulation at 6 weeks when compared to those without scaffolds (Figure 5B). Rats with scaffolds and EES before re-transection (Figure 5C) demonstrated no differences on BBB motor scale with stimulation on or off. After re-transection (Figure 5D) the rats with scaffolds declined in motor function when the EES was off. With EES on, their function was similar to before the re-transection. These findings support the hypothesis that the sublesional circuitry is augmented through stimulation and regeneration of axons prior to retransection. After re-transection of the regenerated fibers, EES assisted gait functions measures through BBB scoring and kinematics persisted (Figure 5). Combinatorial treatment may therefore aid functional recovery though the influence of regenerated connections on reorganization of the sub-lesional circuitry.

Basso, Beattie, and Bresnahan (BBB) motor scores for rats implanted with scaffolds or only transected. (A) BBB score was record by 3 observers when then EES was off. Rats with scaffolds that received EES (blue) or no EES (green) trended to do better than the rats with no scaffold (red). (B) When the BBB scores were recorded with subthreshold EES on, the rats with scaffolds did significantly better than the rats without scaffolds 6 weeks post injury. (C) Rats with scaffolds and EES had similar BBB scores with EES on or off before the rats were retransected. (D) After retransection, there was an expected drop in BBB score when the EES was off, however, the BBB score was better with EES on, similar to before retransection.

The rats that were regularly stimulated during motor training and kinematics were compared to the rats that did not receive any stimulation. These rats were implanted with scaffolds loaded with GDNF Schwann cells and Rapamycin microspheres. We demonstrated that stimulated rats have better angular displacement of their hip, knee, ankle, and MTP.

Angular displacements of joints in rats implanted with scaffolds that received EES during motor training and testing compared to those that did not. Stimulated rats had greater hip, knee, ankle, and MTP angle compared to non-stimulated rats. After re-transection (week 7, past red dotted lines), stimulated rats had similar angle displacement to non-stimulated rats without re-transection.

The stimulated rats also had greater stride length, step height, toe fluctuation, stance phase, and swing phase duration with reduced drag phase compared to non-stimulated rats (Figure 7). Improvements in step height, stance phase, and drag phase persisted in re-transected stimulated rats compared to unstimulated rats with no second injury. This re-emphasizes our thought that there may be changes facilitated at the circuitry below injury that is strengthened with our regenerative therapy and repeated stimulation.

Improvements in motor function on treadmill testing. Stimulated rats had greater stride length, step height, toe fluctuation, stance phase and swing phase duration. Drag phase decreased in stimulated rats. The stimulated rats that were re-transected had improvements persist over the unstimulated rats that did not receive a re-transection (week 7, past red dotted lines).

Immunohistochemical analysis was performed to determine the number of axons passing the lesion site through the scaffold, as well as characterize the synaptic connections in the lumbar spinal cord segment. Staining with neurofilament showed evidence of axons traversing through the scaffold (Figure 8). Staining on scaffold sections, along with myelin basic protein, helped to identify the number of myelinated and unmyelinated axons are passing through the length of the scaffold. Axons were observed to regenerate across the scaffold length. At the same time, there was no differences in axon numbers between rats with scaffolds regardless of EES.

Scaffold implanted at thoracic level 9 after spinal cord transection can be seen containing axons (white) 7 weeks after injury. In rats implanted with scaffolds there was no difference in the amount of axons through the scaffold in those that received EES or those that did not. Therefore, our scaffold supports axon regeneration which is not affected by EES in the lumbroscaral cord.

As there was an improvement in gait in rats with scaffolds during treadmill walking with the assistance of EES, we investigated synapse formation within the sublesional circuitry at the level of the lumbar cord, corresponding to the anatomic location of the central pattern generators Immunostaining co-localized synaptophysin, a marker of synaptic vesicles, with either choline acetyltransferase for motor neurons and calbindin for interneuron populations (Figure 9A-D). The number of synaptic vesicles was measured by QuPath image analysis software and was normalized to the cell area for each of the neuronal subtypes (Figure 9E-F). The median number of synaptophysin on ChAT and calbindin positive neurons was greater in rats that had scaffold implantation and stimulation than in rats with scaffolds alone (no EES) or those injured with stimulation (no scaffold control). The distribution was intermediate for rats with scaffolds but without EES stimulation This result parallels the observed in motor recovery seen in the kinematics analysis where the recovery of rats with scaffolds was intermediate to those with no scaffold and to those with scaffold with stimulation. Regenerating fibers through the scaffolds influenced the reorganization of the sublesional circuitry at the motor and interneuron synaptic level. The combination of epidural electrical stimulation of the sublesional circuitry with regenerating fibers through the scaffold further enhanced synaptic modification, which may correspond to improved kinematic, electrophysiologic and BBB functional improvements.

Behavioral data showed that rats with scaffolds even after re-transection performed better than rats with no scaffolds. ChAT (cyan; B) labelled the motor neuron populations, calbindin (green; C) labelled a subpopulation of interneurons, synpatophysin (red; C) was used to label synaptic vesicles. This data demonstrates that rats with scaffolds and retransection had greater synpatophysin on ChAT (E) and Calbindin (F) labelled neurons. The number of synaptophysin points on neurons from rats with scaffold without EES was intermediate to that of no scaffold and scaffold with EES. Therefore, there were greater synaptic connections in the lumbroscaral spinal cord of scaffold rats after retransection than rats with no scaffolds. Median +/- 95% confidence interval. Kruskal-Wallis test with Dunn's multiple comparisons. * compared to no scaffold; # compared to scaffold with no EES.

Dissemination

The results of this study were presented at several international and local meetings and were disseminated to communities of interest.

Project Title: Direct Comparison of Transcutaneous and Epidural Spinal Stimulation to Enable Motor Function in Humans with Motor Complete Paraplegia

Institution: Mayo Clinic
Principal Investigator: Dr. Kristin Zhao
Grant Cycle: FY2019

Accomplishments

Upon receiving approval of our IDE protocol from the FDA, as well as protocol approval from Mayo Clinic's IRB, we conducted a preliminary screening of a list of potential study participants that were eligible based on the inclusion and exclusion criteria of this clinical trial. We identified the first potential participant and, after obtaining informed consent, performed screening tests. During the screening phase, a baseline MRI identified a possible unhealed fracture in the medial femoral condyle of the right leg. The subject passed all other screening criteria; however, the presence of a possible unhealed fracture resulted in screen failure. This potential participant expressed interest in repeating the screening once adequate time had passed to allow the fracture to heal, and therefore, re-screening was conducted at a later date. Imaging showed that the fracture lines had resolved, however, the subject then exhibited bilateral gastrocnemius tendon tears, and thus failed screening again.

We identified and obtained informed consent to screen a second potential participant. This candidate passed the screening phase and was enrolled in September 2019 to participate in 6 months of TESS, followed by one month of rest and another 6 months of TESS. To date, this participant has completed 46 sessions of TESS with rehabilitation and has achieved bouts, each lasting approximately one minute, of TESS-enabled independent standing.

A third participant recently consented to the study, passed screening, and was enrolled in January, 2020 to participate in 6 months of TESS, followed by implantation of an EES system, one month of rest, and then 6 months of EES. To date, this participant has completed 5 sessions of TESS with rehabilitation. To date, no serious adverse events have occurred.

The first two clinical trials participants are currently completing the initial TESS phase of this study. We have observed positive outcomes for both subjects during TESS, such as improvements in standing and seated posture. To date, we have not reached the study phase of EES system implantation. Therefore, we are unable to compare TESS-enabled outcomes to EES-enabled outcomes at this time.

Dissemination

None.

Project Title: New Combinatorial Strategies for Regenerative Repair of the Injured Spinal Cord
Institution: Mayo Clinic
Principal Investigator: Dr. Isobel Scarisbrick
Grant Cycle: FY2019

Accomplishments

Specific Aim 1: To determine if genetic inhibition of PAR1 function initiated at an acute time point after SCI improves axon regeneration and recovery of function and any additive effects of BDNF gene therapy. These studies are in progress. We have demonstrated successful expression of recombinant BDNF in the spinal cord of adult mice following microinjection of AAV-BDNFGFP.

Specific Aim 2: To determine if pharmacologic inhibition of PAR1 initiated at an acute time point after SCI improves axon regeneration and recovery of function and additive effects of BDNF gene therapy. We have completed animal studies delivery a PAR1 small molecule inhibitor daily, 5d per week for 60d alone or in combination with AAV-mediated delivery of the powerful growth factor BDNF. The final analyses of behavioral outcomes and histopathological assessment of changes in the spinal cord, including signs of neural repair are currently underway.

We are excited to report that early outcomes assessments point to improvements in function in mice treated with a PAR1 inhibitor. Histological analyses and quantification of changes in axons and synapses are currently underway.

Specific Aim 3: To identify small molecule inhibitors of PAR1 with potent pro-regenerative effects toward human neurons and synergistic effects in combination with recombinant BDNF.

We have established the growth conditions, staining and quantitative PCR protocols for the human iPSC derived ventral spinal cord neurons in our laboratory at the Mayo Clinic. We have also implemented a robotic screening approach to monitor changes in neurite outgrowth with PAR1 inhibition in a high throughput manner in conjunction with Dr. Dutton's laboratory at the University of Minnesota. Results to date suggest that inhibiting PAR1 improves neurite growth in human neurons as our parallel studies suggest occurs in murine model systems.

Early results suggest that administration of a PAR1 small molecule inhibitor improves clinical and histopathological outcomes in a murine compression model of traumatic spinal cord injury, as was suggested by our preliminary studies at the time of grant submission. We are currently determining if combining this approach with delivery of recombinant BDNF further enhances the regenerative potential of the injured spinal cord. Early results from cell culture studies support the hypothesis that blocking PAR1 will improve neuron survival and neurite outgrowth in response to growth factor therapy.

Dr. Scarisbrick along with the Co-I Dr. Dutton have submitted several grant applications using new preliminary data generated as a result of this project. This includes an NIH R01 grant application and a Minnesota Partnership Grant application. While these new applications were not funded, they form the basis for additional future studies.

Dissemination

None.

Project Title: iRehab: Discovering Outpatient Rehabilitative Measures for Epidural Stimulation Assisted Movement
Institution: Hennepin Healthcare Research Institute
Principal Investigator: Dr. David Darrow
Grant Cycle: FY2019

Accomplishments

Hennepin Site: Thus far, 1,012 people with spinal cord injury have completed our prescreening survey and 30 of these people have completed in-person formal screening. Of these potential participants, 13 subjects have been enrolled. These participants have successfully undergone stimulation implantation surgery. Five participants have completed the study, while the other participants are undergoing the study protocol.

Currently, seven subjects are participating in at home therapy exercises, which are tracked through an app made for the study. Additionally, these patients are undergoing bicycle therapy with and without spinal cord stimulation, during their routine follow ups.

Minneapolis VA Site: Of the 1,014 people screened, 65 indicated that they were veterans. Veterans were also contacted through information obtained from the Minneapolis VA and referred by Minneapolis VA physicians. Of these candidates, 4 have been screened in person and 1 subject was enrolled and has successfully undergone stimulation implantation surgery. This subject has completed the study as of July 2019.

To date, six subjects have demonstrated ability to bike with the stimulator on. One of our subjects is enrolled in the ABLE program through Courage Kenny while participating in our study. She has seen major improvements in strength with and without the stimulator on documented in the rehab notes. Her experience will be useful in developing a rehab plan that can be used by cSCI patients using eSCS.

Dissemination

None.

Project Title: iOptimize: Optimization of Epidural Stimulation for Spinal Cord Injury
Institution: Hennepin Healthcare Research Institute
Principal Investigator: Dr. David Darrow
Grant Cycle: FY2019

Accomplishments

Hennepin Site: Thus far, 1,014 people with spinal cord injury have completed our prescreening survey and 30 of these people have completed in-person formal screening. Of these potential participants, 14 subjects have been enrolled. These participants have successfully undergone stimulation implantation surgery. Five participants implanted had 13 follow-up visits and completed the study. Additionally, the most recent participants (thirteen and fourteen) have had their one month follow-up visit. Each of the fourteen subjects has undergone spatial mapping (specific aim 1) for volitional movement. This data has been processed by our UMN engineering team to help determine patient specific spatial settings to pair with the temporal optimization protocol, which was

previously developed in our study. This multifaceted approach has improved our rate of setting optimization and will be used to guide our intensive spatial setting testing at the UMN when that portion of the study begins later this year.

Ten of our patients were found to have cardiovascular dysfunction with enrollment in the autonomic arm. Autonomic subjects are also given a set of device parameters for autonomic dysreflexia and are optimized using application guided survey responses about effectiveness. In-person testing with the Finapres has been used to guide determination of what autonomic settings are strongest. Our Canadian collaborators have come to HCMC for autonomic testing with these individuals per the protocol. We have successfully purchased the finapres MIDI as outlined in the grant budget.

University of Minnesota Site: A postdoctoral student was hired as described in the grant proposal and has been instrumental in temporal and spatial setting optimization. She works with subject survey and accelerometer data from the subjects' home training from the study created tablet application. Her work is guided by Dr. Netoff and his lab is instrumental in guiding setting optimization.

Aim 2 and 3 of the grant application laid out a plan for 2 subjects to undergo intensive in patient testing after implantation with a boston scientific epidural stimulator. The devices have been donated and the site IRB is being pursued to begin the enrollment and surgeries. The process of procuring IRB approval has been slower than anticipated in the grant timeline. This will likely drive back our anticipated timeline for the surgeries and follow ups. However, progress is being made in the meantime. A protocol and consent have been developed, training on study assessments have been administered, and other collaborators have been added to the study. Additionally, we've been working closely with Boston Scientific to get the documents necessary to prepare and FDA submission, so the study may be started at the University of Minnesota. We anticipate that the study will start very soon and have organized all aspects in order to be as prepared as possible.

The spatial mapping protocol implemented as part of this grant (Aim 1) has been incredibly successful. A majority of device programming before protocol implementation relied on temporal setting optimization (stimulation frequency and pulse width). Now that setting optimization has been expanded to consider the thousands of spatial settings, we have found that spatial settings may be very pivotal for ensuring control of both lower extremities independently and for recruiting new sets of muscles previously not innervated by the stimulation. These spatial setting findings can help create a map of each subject's spinal cord to ensure that stimulation is directed to the correct nerve roots and muscles to allow for controlled volitional movement in more muscles.

Dissemination

None.

Project Title: Cortical Spreading Depolarization after Severe Traumatic Brain Injury
Institution: Hennepin Healthcare Research Institute
Principal Investigator: Dr. Samuel Cramer
Grant Cycle: FY2019

Accomplishments

We have enrolled a single subject in the study. We are actively developing the analytic tools to stream line analysis of the ECoG recordings we have obtained from the single subject. We are actively recruiting subjects. We have also submitted a manuscript describing the study protocol which is currently under review.

We are happy to have finally enrolled a subject after failing to enroll several subjects during the screening phase.

Dissemination

None.

Project Title: Targeting Estrogen Receptors to Restore Spinal Plasticity in Acute Spinal Cord Injury
Institution: University of Minnesota
Principal Investigator: Dr. Brendan J. Dougherty
Grant Cycle: FY2019

Accomplishments

Overall, funding from this Tier 1 Pilot Project has been efficiently utilized to advance the overall research goals of our laboratory, address initial goals of our proposed research Aims, and establish baseline preliminary data critical for future funding. Specific to the Aims of our initially SCI/TBI proposal, we have made progress towards both proposed Aims. Graduate student Rebecca (Feczer) Barok is independently completing all SCI surgeries and post-operative care. Findings include preliminary evidence supporting our Aim 1 hypothesis that activation of spinal, membrane associated estrogen receptors using E2-BSA is sufficient to restore plasticity of respiratory motor output. In addition, we completed trials of immunohistochemistry for the three known estrogen receptors in the cervical spinal cord as proposed for Aim 2 in support of on-going studies.

These preliminary data have been used as the basis for multiple additional grant submissions including an NIH R01, A Craig H. Neilsen Foundation Pilot SCI study and multiple internal UMN Research proposals. Critiques from those submissions have significantly shaped the emphasis of our research in year 2 of this SCI/TBI funding period to include more supportive evidence of the role of estrogen in respiratory neuroplasticity. We are currently collecting data for a study exploring whether one-week of hormone supplementation (estrogen or DHT, a testosterone derivative) will improve respiratory function and the expression of plasticity in rats with sub-acute SCI (2-wks post injury). This study is planned for completion prior to the conclusion of our funding and will be submitted for publication by the end of the year. Additionally, we have completed preliminary neurophysiological studies identifying estrogen receptor beta as the critical receptor permitting plasticity in female rats, while both estrogen receptor beta and estrogen receptor alpha are needed to permit plasticity in males. Further, it appears that estrogen may act as a critical homeostatic regulator of spinal cord microglia, and that reductions in estrogen availability in both females and males, as seen following SCI, may alter microglial phenotype and impair the ability to express spinal neuroplasticity. This is a research direction that we are actively pursuing.

Dissemination

None.

Project Title: Training Transplanted Spinal Neuronal Progenitor Cells (sNPCs) to Function after Spinal Cord Injury
Institution: University of Minnesota
Principal Investigator: Dr. Ann M. Parr
Grant Cycle: FY2019

Accomplishments

The project has two Specific Aims:

- To determine whether the application of rose Bengal phototoxic glial scar ablation will improve the survival, differentiation, and integration of sNPCs in the chronically injured rat spinal cord; and,
- To determine whether the transplantation of sNPCs (the addition of glial scar ablation will be determined by Specific Aim 1) can produce functional synapses and locomotor recovery in our rat model of chronic moderate contusion SCI and whether the addition of TANES would enhance this recovery.

Progress so far:

- Chronically contused injured rats were either glial scar ablated or not ablated and injected with human iPSC derived sNPCs.
- Rats were sacrificed 4 weeks, 8 weeks and 16 weeks and spinal cords were harvested.
- The harvested cords were cryosectioned.
- The cords are currently being processed for histological and immunohistochemical assay.

Dissemination

None.

Project Title: Optogenetics for Corticospinal Tract Stimulation in Combination with Transplanted Spinal Neuronal Progenitor Cells after Spinal Cord Injury
Institution: University of Minnesota
Principal Investigator: Dr. Ann M. Parr
Grant Cycle: FY2019

Accomplishments

We are currently testing optimal hindlimb stimulation strategies. We have optimized transduction of virus in our human spinal neuronal progenitor cells, in lumbar segments of the spinal cord and in the cortex. Currently, we have developed robust protocols for transducing cells in motor cortex from hindlimb motor pools within the spinal cord. We have also developed a technique to map viral transduction within the entire brain and spinal cord by tissue clearing the brain and spinal cord and measuring the normalized fluorescent intensity within the brain, then registering the fluorescent intensity to an atlas. Finally, we have optimized coordinates for

stimulation of hindlimb motor-evoked potentials but we are still in the process of optimizing stimulation parameters.

Dissemination

None.

Project Title: Evolution of Acute and Chronic Effects on Neuronal Activity and Morphology following Mild Cerebral Cortical Traumatic Brain Injury using Multi-Scale Optical Imaging in Behaving Mice
I**nstitution:** University of Minnesota
Principal Investigator: Dr. Timothy J. Ebner
Grant Cycle: FY2019

Accomplishments

In the first 18 months of funding, we have: 1) developed a modified See-Shell (fenestrated See-Shell) to allow single or multiple controlled cortical impact as a mTBI model; 2) developed and implemented sophisticated analyses including novel ways to dissect out temporal-spatial patterns of activity, functional network connectivity and automated single cell identification; 3) assembled a team of investigators and identified additional recourses for the project; 4) studied two cohorts of mice (impact and sham) with a single controlled cortical impact; and 5) studied two cohorts of mice (impact and sham) with repeated controlled cortical impacts. The two cohorts of mice were studied with wide field and two-photon (2P) Ca2+ imaging, behavioral assays (rotarod and open field), and immunohistochemistry.

We reported results from the single mTBI group in the 12 month report. The Ca^{2+} imaging data suggested modest decreases in cortical functional connectivity following mTBI. Given the clinical observation that multiple mild TBIs are more likely to result in long-term deficits, we decided to study multiple cortical impacts. Therefore, in this report we focus on the experimental results in which the controlled cortical impact was repeated 3 times. Using the fenestrated See-Shells that allow opening of the window and access to the cortical surface, a single cortical impact of 1 mm depth at 0.4 m/sec was delivered over 3 days in GCaMP6f or wild type C57Bl/6 mice. The later were used for histological and/or behavioral assessments and the former for wide field and 2P Ca^{2+} imaging. Importantly, the fenestrated See-Shell allows for excellent optical access with repeated impacts, and therefore, we can perform imaging of neuronal activity before and following mTBI.

In a subgroup of animals, immunostaining for inflammatory markers was performed at 24, 48, and 72 hours. These included GFAP as a marker for gliosis and Iba-1 for microglia activation. Repetitive mTBI results in a transient elevation of GFAP and Iba-1 at 24 hrs which does not persist at 48 or 72 hrs (a total of 20 mTBI and sham animals have been evaluated across time points). The transient increase in inflammatory markers is consistent with other models of mTBI and confirm that our model does not generate major structural damage in the cerebral cortex.

We have performed open field (data not yet fully analyzed) and rotarod testing. The rotarod data shows no difference between the sham and impact groups. Therefore, the multi-impact mTBI model does not appear to

impart a significant motor deficit. This observation is consistent with clinical findings that focal motor behavior remains intact following mTBI.

Data suggests that repetitive mTBI has effects on the functional organization of the cerebral cortex for up to 4 weeks.

Although the changes did not result in focal motor behavior impairment, our hypothesis is that disruptions of cortical organization may effect more cognitive and executive functions, as observed in humans after mTBI.

Dissemination

None.

Project Title: The Roles of Tau in Chronic Traumatic Encephalopathy
Institution: University of Minnesota
Principal Investigator: Dr. Dezhi Liao
Grant Cycle: FY2019

Accomplishments

- At this very moment, we are focusing on experiments to test whether tau is required for mechanical injury-induced tau mislocalization. We have recently submitted our experimental results to Proceedings of National Academy of Science. The reviewers require that we perform our TBI experiments in cultures that had been made from tau knock-out mice. Accordingly, we have ordered tau knock-out mice from Jackson Lab and are collecting data for the revision of our article. We believe that it is of critical importance to publish our results in this prestigious journal.
- The in vivo TBI device has been built and we are performing surgeries to test the device.
- We are refining our hypothetical signaling framework that is responsible for neural deficits caused by tau phosphorylation, which is the key mediator for CTE:
  When we proposed the initial hypothesis, the specific residues in tau that are responsible for neural deficits associated with CTE were not known at that time. We have now narrowed down two distinct domains that are responsible for the pathways: the C sites of Ser396 and SerS404 as well as the B sites of Ser202, Thr205, Thr212, Thr217, and Thr23. The results have now been published in the Journal of Physiology.
- We have now synthesized a novel tau peptide that may potentially be used to treat CTE. The University of Minnesota has filed a patent for the usage of this peptide.

Submitted Manuscript: Nicholas J. Braun, Patrick W. Alford, and Dezhi Liao (2019). Mechanical injuries of neurons induce tau mislocalization to dendritic spines and tau dependent synaptic dysfunction (requesting revision in PNAS)

Status: We have submitted our manuscript to Proc Natl Acad Sci U S A. It has passed the initial screening of editorial board. We will receive very positive feedbacks from the journal. However, *the reviewers request that we perform experiments in tau knock-out mice.* We are currently doing the experiment now.

Significance: Athletes and soldiers exposed to repeated traumatic brain injuries have increased risk of developing chronic traumatic encephalopathy (CTE), which is a neurodegenerative disease characterized by tangled deposits of the protein tau in the brain and loss of cognitive function. This study provides the first experimental evidence showing that mechanical stretching of neurons induces tau to be mislocalized to dendritic spines where it causes synaptic dysfunction. This cross-disciplinary study utilizes computational modeling, imaging, and electrophysiology to unravel a new cellular framework for how tau phosphorylation mediates trauma-induced synaptic dysfunction, highlighting the essential role of tau in functional deficits caused by traumatic brain injury.

Publication: Teravskis PJ, Oxnard BR, Miller EC, Kemper L, Ashe KH, Liao D. Phosphorylation in two discrete tau domains regulates a stepwise process leading to postsynaptic dysfunction[6]. J Physiol. 2019 Jun 13. doi: 10.1113/JP277459.

Significance: The published experimental results have refined our initial hypothesis in this proposal because of the in-depth characterization of tau phosphorylation sites.

Publication: Teravskis PJ, Covelo A, Miller EC, Singh B, Martell-Martínez HA, Benneyworth MA, Gallardo C, Oxnard BR, Araque A, Lee MK, Liao D. A53T Mutant Alpha-Synuclein Induces Tau-Dependent Postsynaptic Impairment Independently of Neurodegenerative Changes[7]. J Neurosci. 2018 Nov 7;38(45):9754-9767. doi: 10.1523/JNEUROSCI.0344-18.2018.

Significance: Some CTE patients also suffer from motor deficits. The results reported in this manuscript will provide new insights on the neurobiological mechanism underlying these deficits.

Patent:
Institution: The University of Minnesota
Title: TAU PEPTIDES, METHODS OF MAKING, AND METHODS OF USING
OTC #: 20170226
Date: February 29, 2019
Docket No.: 0110.000572US01
Previous Provisional Patent Number: 62/636,523 (filed on February 28, 2018)
Inventor: Dezhi Liao
Unit: Department of Neuroscience
Objective: Using tau peptides to treat neurodegenerative diseases (AD, FTD, PD and CTE) by blocking tau mislocalization to dendritic spines.
Funded federal grants:
Application ID: 1 R61 NS115089-01 [Ebner-PI, Liao-PI, Koob-PI (CONTACT)]
Title: Full human gene-replacement mouse models of ADRDs
Source of Support: NIH

[6] https://pubmed.ncbi.nlm.nih.gov/31194886/

[7] https://pubmed.ncbi.nlm.nih.gov/30249789/

Award Period Covered: 09/01/2019 – 08/31/2024
Months/year: 1.8 calendar
Annual Direct Cost: $492,669
Total Cost: $3,824,524

“Targeting tau phosphorylation and missorting to treat Alzheimer’s Disease”

Major Goals: To the present, most animal models were made by random insertion of cDNA. In the proposed project, we will replace the whole mouse tau gene with human tau genes with mutations linked to tauopathy.
Role: multiple PI
Application ID: BMMB 1935834 (Alford-PI, Liao-co-PI)
Title: Mechanics of trauma-induced tauopathy
Source of Support: NSF
Award Period Covered: 09/01/2019-08/31/2021
Total direct cost: $400,000
Major Goals: To test how mechanical parameters affect tau mislicalization and associated synaptic deficits in chronic traumatic encephalopathy models.

Dissemination

None.

Project Title: Harnessing Exosomes as a Biomarker and Therapeutic Approach to Traumatic Brain Injury
Institution: University of Minnesota
Principal Investigator: Dr. Andrew W. Grande
Grant Cycle: FY2019

Accomplishments

The effort of the past year was to focus on validation of the rat model of TBI in our lab. We needed to purchase a new impactor device in order to improve standardization of injuries across animals and have been able to observe significant deficits associated with the injury and replicable lesion volumes.

We are also optimizing protocols to isolate exosomes from minute quantities of blood from rats as this is necessary for long-term tracking of biomarkers from individual animals.

Finally, we have successfully isolated exosomes from our non-hematopoietic umbilical cord blood stem cell line, which will be used to treat rats with TBI.

We have established a collaboration with a bio-tech company which will isolate exosomes from our non-hematopoietic umbilical cord blood stem cell line using their isolation platform and will provide exosomes from this line for therapeutic applications in TBI to be tested alongside exosomes isolated at the University of Minnesota.

Dissemination

None.

Project Title: Reprogramming Astrocytes into Neurons to Provide Therapeutic Benefit in TBI
Institution: University of Minnesota
Principal Investigator: Dr. Andrew W. Grande
Grant Cycle: FY2019

Accomplishments

To identify all cells infected with the adeno-associated virus (AAV), we developed a strategy using an AAV expressing Cre on a GFAP promotor with the Ai9 transgenic mouse following TBI. Ai9 mice have a Lox-Stop-Lox tdTomato insert on the Rosa26 locus. In this approach, all infected cells will expressed Cre, excising the stop sequence, permanently expressing tdTom, regardless of reprogramming status. Intracranial injection of AAV6 resulted in few tdTom+ cells, while many astrocytes and neurons were tdTom+ following AAV9 injection. AAVrh10 injection into the injured brain resulted in many tdTom+ cells, more of which appeared to have an astrocyte morphology.

Given many $tdTom^{+}$ cells had a neuronal morphology at 7-DPI, we wanted to interrogate the phenotype of the cell soon after AAV administration. To test this, Ai9 mice were injected with AAVrh10 one week after TBI and euthanized 1-DPI for immunohistochemistry. Intracranial injection of AAVrh10-hGfABC1D::hASCL1:Cre resulted in tdTom+/Cre+ neurons. tdTom+ fiber tracts are also observed in the striosomes of the striatum. This suggests that in our system the hGfABC1AD promoter is not tightly regulated and results in leaky expression, or that GFAP is expressed in neurons not detectable through immunohistochemistry.

While many cells can be initially infected with the AAV construct, the number of astrocytes exiting the cell cycle during reprogramming is likely limited. We therefore were interested in the effects of AAV infection on the whole population of astrocytes. Immunohistochemistry of tdTom+ cells at three time points following intracranial injection of AAVs demonstrates an increase in the number of tdTom+ cells, particularly along the corpus callosum of the ipsilateral hemisphere. This suggests that a population of infected cells carrying the excised stop sequence have proliferated throughout the brain.

These data have been presented as a poster at the International Society for Stem Cell Research as well as the Society for Neuroscience annual conferences. The topic of astrocyte reprogramming following cerebral injury has led to a platform session at the American Society for Neural Therapy and Repair annual conference, building strong collaborations with faculty from multiple universities.

Dissemination

None.

Project Title: Enhancing Rehabilitation with Neuromodulation for Veterans with Spinal Cord Injury
Institution: Center for Veterans Research and Education

Principal Investigator: Dr. Uzma Samadani
Grant Cycle: FY2019

Accomplishments

Only one subject has been recruited thus far in the study. The VA has many restrictions on how veterans will be recruited and finding candidates that fit the eligibility requirements has proved challenging. Six devices have been donated from Abbott Labs, so five devices remain for implantation. The team is currently primarily focused on obtaining additional recruits and developing outreach strategies that may increase our chances of recruitment. Over 50 veterans have reached out on our website, but have been excluded for various reasons. A total of 4 in person screenings have been completed. Unfortunately, the most recently screened participant did not progress to enrollment. We are currently looking for other outreach opportunities.
The first subject at the VA has completed the study, and we are currently working on finding other veterans to screen. Through a combined effort through HCMC and the VA, we have been able to implant a total of 14 subjects and have seen incredible results with regards to partial restoration of volitional movement and autonomic function. Our hope is to find additional veterans who fit the criteria for the study.
Dissemination: None.

Project Title: ESTAND 2.0 – Bridge to Clinical Approval of eSCS for SCI
Institution: Hennepin Healthcare Research Institute
Principal Investigators: Dr. David Darrow, Dr. Ann Parr and Dr. Thomas Bergman
Grant Cycle: FY2020

Accomplishments

Since the grant has been awarded, the E-STAND study has made enormous strides towards accomplishing the aims of the grant. Thus far, 1,014 people with spinal cord injury have completed our prescreening survey and 30 of these individuals have completed in-person formal screening. Of these potential participants, 14 subjects have been enrolled (5 of which since this grant has been awarded).

These participants have successfully undergone stimulation implantation surgery and have marked benefits from the stimulator. Five participants have completed 13 follow-up visits and finished the study. Additionally, the most recent participants (thirteen and fourteen) have completed their one month follow-up visit. Each of the fourteen subjects has undergone spatial mapping for volitional movement and submit daily surveys that help access the functionality of each setting, with regards to their volitional and autonomic function. This data is processed by our UMN engineering team to help further optimize and categorize each patient's settings. This has been particularly effective when looking at specific functionalities, such as core-balance, transferring, digestion, etc. This multifaceted approach has improved our rate of setting optimization.

Additionally, ten of our study participants have been found to have autonomic dysreflexia and were enrolled in the autonomic part of the study. Currently, they are undergoing tilt-table testing to gain more insight on the effects of eSCS and blood pressure regulation, as well as cognition. Moreover, we have been able to implement

EEG during these assessments to further categorize the type of dysfunction these individuals are experiencing, and how eSCS helps improve these conditions.

Lastly, a long-term protocol and consent have been developed. We are hoping to move forward and submit this study to the FDA/IRB soon.

Equipment/Grant Purchases: All EEG headcaps and accessory equipment has been purchased.

An additional headbox for our Neuralynx machine has been obtained, which allows us to conduct EMG and EEG simultaneously on SCI patients.

Since the grant has been awarded we have successfully enrolled and implanted 5 additional study participants, which has brought us closer to our goal of studying eSCS in a more diverse and generalizable population. We anticipate to enroll several more subjects this spring. Additionally, we've been able to implement EEG and preliminary results suggest that eSCS helps cognitive function in AIS A/B paraplegia patients with cardiovascular dysautonmia.

Dissemination

None.

Project Title: Non-invasive Transcutaneous Spinal Cord Stimulation for Recovery of Hand Function After Spinal Cord Injury
Institution: Hennepin Healthcare Research Institute
Principal Investigator: Dr. David Darrow and Dr. Thomas Bergman
Grant Cycle: FY2020

Accomplishments

The protocol and consent form have been written to assess the outcomes of transcutaneous stimulation on hand and arm function in individuals with chronic cervical injuries. Once we have IRB approval for the study, Neurorecovery Technologies, a subsidiary of GTX medical, will provide us with the devices to be used for the study. We will also begin the hiring process for an occupational therapist, who will be responsible for providing each subject with a tailored hand/arm exercise program and for administering the stimulation therapy. The components of each exercise program will include warm-up and cool down periods, active and assisted range of motion exercise, strength training, re-education of motor skills through task specific progressive functional training for performing ADL (pinching, grasping, reaching, pulling). The study will be published on clinicaltrials.gov and we will begin screening interested individuals. Currently, we have identified 221 individuals that may fit the screening criteria for the study.

A study protocol detailing the methodology for this clinical trial has been written and we are currently seeking approval from the IRB for the study.

Dissemination

None.

Project Title: Spinal Cord Regeneration by Cell Reprogramming in Chronic Spinal Cord Injury
Institution: University of Minnesota
Principal Investigator: Dr. Walter Low
Grant Cycle: FY2020

Accomplishments

Following the award of the above referenced project on cell reprogramming we performed the time lapse imaging in vitro, to better understand the temporal kinetics of when the reprogramming begins to occur. This is important to better elucidate the cellular mechanisms of reprogramming. Through these experiments, we have determined the following.

Transduction was a rapid process, as we saw a fluorescent signal (indicating that mRuby was transduced and expressed in cells) after only a few hours.

After ~2.5 to three days, we found that the astrocytes began to undergo morphological rearrangements, suggesting that they were in the reprogramming process. This is something that we saw with several biological replicates in two separate experiments. To note the timeframe we determined in these reprogramming experiments aligns with the timeframe in which Gong Chen has reported differential changes in transcripts in qPCR experiments.

We compared the efficiency of reprogramming in mouse astrocytes and humans. Interestingly the human astrocytes showed a different behavior and appeared less responsive to the reprogramming, which is something that we will be following up with.

We also verified in vitro and in vivo that NeuroD1 was ectopically expressed in cells that express the reporter. In both applications, we saw the faithful expression of NeuroD1 expressed in transduced cells, which indicates the functionality of our system.

We have also performed experiments where we administered the reprogramming constructs to astrocytes 3 days prior to transplantation into the mouse nervous system. We have done this in both uninjured and noninjured mouse nervous system. Once we know the result of these experiments it may suggest the possibility of using the transplantation of reprogrammed astrocytes into spinal cord-injured mice, which may be helpful for severe injuries that have a large cavitation and cell loss.

We also designed and ordered additional reprogramming constructs using the human GFAP Cre in order to compare the efficiency of reprogramming. While the plasmid arrived, we are waiting for the gene engineering core facility to clone the hGFAP promotor into our Cre constructs. Based on conversations with investigators at the Society for Neuroscience annual meeting, we believe that this promotor will be more efficient. Once we receive the construct, it will be tested in vitro and in vivo in the spinal cord to optimize the titer and determine the efficiency.

Dissemination

None.

Project Title: 3D Bioprinted spinal Neural Progenitor Cell (sNPC) Scaffolds Accelerate Functional Neuronal Network Formation both In Vitro and In Vivo after Spinal Cord Injury
Institution: University of Minnesota
Principal Investigator: Dr. Ann M. Parr
Grant Cycle: FY2020

Accomplishments

We have discovered that our bioprinted spinal organoids are able to survive *in vitro* for at least six months and maintain a neural identity throughout that time. We have also validated the orthotopic layering of cell types within our spinal organoids through next generation sequencing techniques such as RNA-sequencing. We have found that our organoids are capable of producing all six layers within the ventral spinal cord and that they maintain a spinal cord positional identity 21 days post-printing. Further, we have optimized tissue clearing techniques with our organoids that allow us to visualize the organoids in their entirety and map their projections. Finally, we have been able to optogenetically stimulate neurons within the organoids even after six months post-printing. We are now preparing to transplant our spinal organoids into a rat spinal cord injury model.

Dissemination

None.

Project Title: Optimization of iPSC-Derived Oligodendrocyte Progenitor Cell (OPC) Manufacture – A Key Step Toward Patient Treatment
Institution: University of Minnesota
Principal Investigator: Dr. James Dutton
Grant Cycle: FY2020

Accomplishments

Since the receipt of the funding we have started to implement the research plan as set out in the proposal and laboratory experiments are ongoing. For Aim 1 we have initiated the cell aggregate experiments, introducing our accelerated hiPSC-derived ventral spinal neural progenitor cells in undirected aggregate differentiation protocols and are currently assessing the timing of phenotype transitions and comparing the results with the protracted “industry standard” protocols. For the work of Aim2 we are continuing to optimize the directed differentiation protocol and have made an interesting and potentially significant discovery regarding the differentiation signaling required in our approach to maintain the desired pre-oligodendrocyte progenitor cell phenotype. We are now examining this finding in greater detail. We have also started the 3D hydrogel co-culture experiments designed to provide an in vitro model to demonstrate myelination by oligodendrocytes generated from iPSC-derived OPCs. Our initial testing of the proposed method indicated no practical issues with incorporating iPSC derived cells in the hydrogel and initiating the prolonged culture periods and we are now testing methods for analyzing cell phenotypes and function. We are excited by the potential of this approach and will have more to report in the future.

Dissemination

None.

Project Title: Improving Communication About Sexual Health for Persons Undergoing Acute Inpatient Rehabilitation for Traumatic Brain Injury (TBI)
Institution: Center for Veterans Research and Education
Principal Investigator: Dr. Melanie Blahnik
Grant Cycle: FY2020

Accomplishments

The TBI research grant activities to date have been centered around the start up of the project. An application for the study was submitted for review by the Minneapolis VA Health Care System's (MVARCS) Institutional Review Board (IRB) and Research and Development Committee (RDC), from whom we have received approval to commence the study. A research assistant was hired and trained to support the research project, as well as the MVARCS Neurorehabilitation (TBI) Sexual Health and Intimacy Work Group that is involved in developing components of the research project focused around the clinical teams, such as the Sexual Health TBI Inpatient Rehab Template for use in the computerized patient record system and the development of the staff training curriculum.

The Sexual Health TBI Inpatient Rehab Template was developed and trialed and is now fully implemented into the computerized patient record system (CPRS) at the MVARCS. The principal investigator and research assistant for the project have completed in person trainings on use of the clinical template with Inpatient Neurorehabilitation (TBI) Team members by rehabilitation discipline. A manual with photos of the template and corresponding instructions also was created for staff as a reference. This template also serves as a research data collection method. Patient measures also were finalized and participant files were assembled for the team psychologists who are administering the measures as an additional date collection method.

A staff survey was developed and trialed for use with REDCap, a digital survey tool, which also will serve as research data collection and will be administered to staff serving as participants in the research in the next couple of weeks.

The research assistant has compiled four study protocol binders. The binder has a step-by-step guide for the research project, copies of the patient measures, scoring information for the patient measures, and clinical templates. The research assistant developed scoring and clinical documentation templates to assist the team psychologists with streamlining the process of entering clinical information obtained from the patient measures into CPRS at the MVAHCS.

The research assistant has compiled over 115 articles pertaining to the project in a spreadsheet as a resource for the Work Group. This spreadsheet has acted as an annotated digital library allowing members of the Work Group to quickly access the information they are looking for. This spreadsheet also contains links for accessing the actual articles. Databases for both patient and staff data have been setup. The codebook to help identify variables has also been written to accompany the databases.

Our Work Group has maintained biweekly meetings to address challenges and questions as they come up. Within these biweekly meetings we are continuing to plan for the upcoming interdisciplinary staff training. The Work Group has developed training materials, including 20 written case studies to provide examples and guidance for putting the training into place. We are now transitioning to the "pre-staff training" data collection phase of our project.

Dissemination

None.

Project Title: Theta Burst Stimulation for Headaches after Traumatic Brain Injury
Institution: Center for Veterans Research and Education
Principal Investigator: Dr. C. Sophia Albott
Grant Cycle: FY2020

Accomplishments

TBD.

Dissemination

None.

Project Title: Acupuncture Treatment for Chronic Post-Traumatic Headache in Individuals with Mild Traumatic Brain Injury
Institution: HealthPartners Institute
Principal Investigator: Dr. Amanda A. Herrmann
Grant Cycle: FY2020

Accomplishments

We received Institutional Review Board approval for this study on January 10th, 2020. We plan to begin volunteer acupuncture training sessions at the beginning of February and recruitment and enrollment of participants by the end of February/early March.

Dissemination

None.

Project Title: Identification of Brainwide Network Activity Changes in Post-Traumatic Epilepsy to Optimize the Therapeutic Effect of Vagus Nerve Stimulation on Post-Traumatic Epilepsy
Institution: Mayo Clinic
Principal Investigator: Dr. Su-Youne Chang and Dr. Azra Alizad
Grant Cycle: FY2020

Accomplishments

To reach our goal, we proposed two aims. In Aim 1, we plan to optimize fUSimaging protocol for in vivo behaving rats (Aim 1-1) and will detennine changes in brain-wide network activities associated with PTE development and seizure on-set area in the brain (Aim 1-2). In Aim 2, we will perfonn VNS and validate therapeutic effects of VNS on PTE rats. Since the grant started in July 2019, we fully optimized the surgical procedures for fUSimaging and TBI as well as fUSimaging protocol in anesthetized rats. We also designed, fabricated, and evaluated the cuff-style stimulation electrode for the VNS. Furthermore, we recently got the approval for the IACUC protocol for the chronic fUSimaging and completed chronic surgeries onto two rats for fUSimaging. After the surgery, the rats were survived longer than 1 month and there was little sign of inflammation and infection in the surgery animals. The rats were euthanized after 1 month of the surgery. We are currently trying to determine the brain areas which are activated by the VNS in normal anesthetized rats and completed the first batch of PTE model surgery. We will soon start video-EEG to identify PTE animals and then will perform fUSimaging on to the PTE rats. Since there were some staffing changes, we plan to increase Dr. Su-youne Chang's effort and she will perform animal surgery and electrophysiology recording to successfully complete the project within the timeline. Since we optimized fUSimagin g protocol for anesthetized rats, we plan to submit a poster abstract to the 8th Annual Minnesota Neurotnodulation Symposium, which will be held in April 19-20, 2020.

Dissemination

None.

Project Title: Characterizing the Neuroinflammation Associated with Sequential TBI in a Rodent Model
Institution: University of Minnesota
Principal Investigator: Dr. Maxim C. Cheeran
Grant Cycle: FY2020

Accomplishments

The central hypothesis of this present study is that a second injury after a mild traumatic brain injury (TBI) will result in an enhanced neuroinflammatory response that persist longer and leads to behavioral deficits in the affected animal. To study inflammatory response in the brain consequent to TBI, we characterized immune cell phenotypes that infiltrate the brain in 9-week-old C57BL/6 mice after single moderate TBI.

Moderate TBI was achieved by delivering an impact over the dura mater with velocity of 6m/s, a dwell time of 100ms reaching a cortical impact depth of 1 mm using an impactor device mounted on a stereotactic frame. Control animals for this experiment received a sham injury, where animals received anesthesia and a craniotomy, but did not receive an impact injury. Immune cell phenotypes in the brain and cervical lymph node were characterized by flow cytometry at various times starting at 6 h to 30 d following injury.

The results showed that migration of neutrophils and macrophages into ipsilateral hemisphere of the brain, occur early after injury with peak neutrophil infiltration at 24 h post injury (dpi), and macrophages at 3 dpi. The CD45(hi) macrophages in the brain showed a higher expression of proinflammatory activation markers like

CD86, Ly6c, and MHCII. Notably, a temporally biphasic macrophage activation profile was observed in the brain, where proinflammatory CD86(+) macrophage numbers increased at 3 dpi then reduced to control levels by 7dpi and increased again at 30 dpi.

In addition, we observed significant increase in CD4(+) T lymphocytes at 14 dpi and increased microglial activation with higher MHCII expression at 30 dpi. These results suggest that inflammation persists in the brain after a moderate TBI, even up to 30 dpi. This increase in CD86(+) macrophages at 30 dpi was also observed in a mild TBI model (impact velocity of 4m/s) long after the minor motor deficits were resolved (7 dpi). Apart from transient increase in neutrophils at 24 hpi, there was no significant change in immune cell numbers on contralateral hemispheres. To characterize inflammation in the brain after repetitive TBI (double hit), first mild injury (impact velocity of 4m/s) was delivered on the right hemisphere and the animal was allowed to recover for 7 days. At 7 days after the initial injury, a moderate second injury was delivered on the left (opposite) hemisphere. Immune cell phenotypes were characterized at 7 d after second injury on both hemispheres of the brain by flow cytometry. Although immune cell infiltration and activated phenotype of immune cells were observed predominantly in the left (ipsilateral) hemisphere after moderate injury, an increase in infiltrating macrophages and MHC II(+) activated microglia was seen in both hemispheres 7 d after second injury.

This data suggests an exaggerated inflammatory response in the brain after second injury on the contralateral (right) brain hemisphere that received a mild injury 7 d prior. We are currently repeating this experiment to increase the numbers for analysis and plan to perform gene expression analysis to evaluate inflammatory cytokine genes by RT-PCR in addition to characterizing immune cell phenotypes. Additionally, behavioral analysis to assess the impact of the “second hit” on sensory motor function will be evaluated. In the next funding year, experiments are planned to study the impact of altering the macrophage activation profile with nhUCBSC treatment on the neuroinflammatory response to second TBI. The observation of an exaggerated inflammation on the previously affected side of the brain after a second trauma given 7 days after the first hit supports our initial hypothesis. We are working on assessing the impact of nHUCBSC treatment on this phenomenon.

Dissemination

None.

Project Title: Validation of Cardiovascular Exercise Tests for Individuals with Traumatic Brain Injury
Institution: ExercisAbilities
Principal Investigator: Melanie Brennan
Grant Cycle: FY2020

Accomplishments

To date, ExercisAbilities has acquired the Madonna ICARE and the SciFit arm crank ergometer, which has enabled the researchers to recruit participants and begin the intake process. IRB approval was finalized in November of 2019. At this time four participants have been recruited to begin the study. In January of 2020 we started our first participant. We have the next 3 scheduled to begin incrementally every 4 weeks through March. Recruitment for the remainder of participants is ongoing.

We are thrilled to be in initial stages of participant recruitment and data collection and have many interested participants that we are working to enroll currently.

Dissemination

None.

Project Title: Effectiveness of a Neck-Strengthening Program for the Prevention or Mitigation of Sports Concussion Injuries in Student Athletes
Institution: CentraCare Health – St. Cloud Hospital
Principal Investigator: Dr. Uzma Samadani
Grant Cycle: FY2019

Accomplishments

513 subjects were enrolled in this study between 8/2017 - 4/2018. Enrollment has now ceased. Data analysis and manuscript writing has now commenced.

- https://pubmed.ncbi.nlm.nih.gov/29998204/
- https://pubmed.ncbi.nlm.nih.gov/31637268/

Dissemination

None.

Project Title: Improving Functional Outcomes Through Optimization of Surgical Subdural Hematoma Evacuation Technique
Institution: CentraCare Health – St. Cloud Hospital
Principal Investigator: Dr. Uzma Samadani
Grant Cycle: FY2019

Accomplishments

We have formed an official collaboration with Dr. Yuk Sham from the Computer Sciences department at the University, who will be overseeing and mentoring Atishya Ghosh who is a PhD student. She will be focusing her PhD on this specific problem. Data acquisition has begun.

Dissemination

None.

Project Title: Traumatic Brain Injury Classification and Outcome Assessment
Institution: CentraCare Health – St. Cloud Hospital
Principal Investigator: Dr. Uzma Samadani
Grant Cycle: FY2019

Accomplishments

Over 700 subjects have been enrolled in the study and enrollment has now concluded. One manuscript detailing the predictive power of certain biomarkers to predict positive head CT's has been published in the journal – World Neurosurgery, and multiple others are in the process of being finalized, which can be accessed here: https://pubmed.ncbi.nlm.nih.gov/31051301/

Dissemination

None.

Project Title: Vagus Nerve Stimulation to Augment Recovery from Traumatic Brain Injury: Evaluation of Patients with Moderate Injury
Institution: CentraCare Health – St. Cloud Hospital
Principal Investigator: Dr. Uzma Samadani
Grant Cycle: FY2019

Accomplishments

Fourteen subjects were enrolled in this study and enrollment has now concluded. Data analysis and manuscript writing has commenced.

A medical textbook chapter using the pilot data from this study has been submitted for review. Additionally, the data was presented at the International Brain Injury Alliance meeting in Toronto.

Dissemination

None.

Project Title: Acute Biomarkers for Traumatic Brain Injury Classification Across the Severity Scale
Institution: CentraCare Health – St. Cloud Hospital
Principal Investigator: Dr. Uzma Samadani
Grant Cycle: FY2020

Accomplishments

Over 700 subjects were enrolled in the previous study. With Dr. Uzma Samadani transferring hospitals, the amount of data already collected, and the advanced statistical and machine learning required to continue analysis – this grant funding has been reallocated to analyzing and publishing the data from the pilot study.

Dissemination

None.

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