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Donor Progress Report for the Darrell K Royal Research Fund for Alzheimer's Disease of the Dallas Foundation

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Neurovascular Decoupling and Memory Impairment after Traumatic Brain Injury

Traumatic brain injury (TBI) is a heterogeneous condition that results in both focal and diffuse neuronal injury. Each year in the United States, at least 1.7 million people suffer a TBI. This condition is a contributing factor in a third of all injury-related deaths that occur in the U.S. An estimated 3.2 to 5.3 million people live with the long-term physical, cognitive, and psychological health disabilities of TBI. Annual direct and indirect costs are estimated to be more than $60 billion.

Cognitive impairment—including learning, memory, and executive dysfunction—is common in TBI survivors. In fact, multiple studies have shown that TBI is an important risk factor for dementia, especially in TBI survivors who live with a chronic deficit. However, there is very little research that addresses the pathophysiology of TBI-related dementia or that could help identify early and pre-clinical biomarkers and be used to develop effective therapies to improve brain health and prevent post-traumatic dementia.

Conversely, a growing body of evidence indicates that neurons, glia, and cerebral endothelial cells are closely related developmentally, structurally, and functionally to constitute a neurovascular unit to maintain normal brain function. Alterations in neurovascular coupling contribute to declines in cognitive function. As such, we hypothesize that impaired cerebral autoregulation and neurovascular decoupling persist in chronic TBI contributes to neurocognitive impairment in TBI survivors.

The purpose of this pilot study is to assess neurovascular coupling status in TBI survivors who have chronic neurocognitive deficit. In the attached report, we document progress in our second year of the study, showing that our project is currently on schedule to complete our primary aims during the grant period.

Cognitive impairment including learning, memory, and executive dysfunction, is common in TBI survivors. In fact, multiple study cohorts have shown that TBI is an important risk factor for dementia, especially in the TBI survivors with chronic deficit. However, very little research to address the pathophysiology of TBI-related dementia and the identification of early and pre-clinical biomarkers that can be used to develop effective therapies has been completed. A better understanding of the biological underpinnings of TBI-related dementia could help us improve brain health and prevent post-traumatic dementia in TBI patients.

A growing body of evidence indicates that neurons, glia, and cerebral endothelial cells are closely related, and that they developmentally, structurally, and functionally constitute a neurovascular unit that helps maintain normal brain function. Alterations in neurovascular coupling contribute to declines in cognitive function. As such, we hypothesize that impaired cerebral autoregulation and neurovascular decoupling persist in chronic TBI contributes to neurocognitive impairment in TBI survivors. This proposal is an add-on study to the National Institutes of Neurological Disorders and Stroke (NINDS)-funded, multicenter study titled Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI). TRACK-TBI is a large, high quality data registry that integrates clinical, imaging, proteomic, genomic, and outcome biomarkers to develop precise methods for TBI diagnosis and prognosis, refine outcome assessment, and compare effectiveness and cost of TBI care.

During our present study, we propose to enroll patients from TRACK-TBI to 1) investigate cerebral autoregulation (CA) function and brain perfusion in TBI survivors with chronic neurocognitive impairment; and 2) examine the association of CA and cerebral perfusion with neuroplasticity and core outcome measured by NIH TBI common data element (TBI-CDE).

In the second year of the study, TRACK-TBI study changed the protocol to limit enrollment only to patients with severe traumatic brain injury. In order to meet our enrollment goal and have reasonable sample size to address our scientific question, we expanded our study to include the subjects who are enrolled in the TBI Model System (TBIMS) funded by the National Institute on Disability, Independent Living, and Rehabilitation Research and the TBI exercise intervention study funded by the Texas Institute of Brain Injury and Recovery (TIBIR).

With the modified protocol, we received consent from a total of 34 patients and 26 of them completed the study. We utilized a transcranial Doppler exam to evaluate cerebral blood flow. Our team assessed central hemodynamics using applanation tonometry and ultrasonography of the carotid artery. Carotid-femoral pulse wave velocity and carotid stiffness parameters, including compliance, distensiblity, β-stiffness, and young's modulus, were then calculated. We presented the preliminary data at the National Neurotrauma Society Annual Symposium in July 2017.

We found that TBI patients have augmented blood pressure variability during sit-stand maneuvers with altered dynamic cerebral autoregulation gains when compared with age/sex-matched healthy subjects. Our preliminary results suggest that TBI patients have a diminished capacity to adjust to hemodynamic variability during postural changes, which may explain their residual neurological symptoms. During the third year, we will focus on data analysis and publications. In summary, our project is currently on schedule and we expect to complete our primary aim during the grant period.