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DEPARTMENT OF ANESTHESIOLOGY

August 15, 2017

The Darrell K Royal Research Fund for Alzheimer's Disease
P.O. Box 5839
Austin, Texas 78763

Dear Mrs. Edith Royal and The Board of Directors of the DKR Fund,

It is with pleasure that I write the annual report for the period of 2016-2017 for the project titled "Using a Novel Tau Monoclonal Antibody Immunotherapy to Prevent Dementia After TBI".

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality, accounting for approximately 2.5 million annual Emergency Department visits, hospitalizations, and deaths in the United States. TBI affects millions of American civilians and military service personnel worldwide and a single severe or multiple mild TBIs during a person's lifetime may increase the likelihood of developing dementia or neurodegenerative disorders later in life. Although many people live with the memory loss, inability to focus, headaches, pain, sleep disruption, mood changes, etc. that may occur following a TBI, currently no effective therapies exist, although physicians often treat symptoms.

A novel antibody that binds to a toxic protein (tau) implicated in Alzheimer's disease has been created at the University of Texas Medical Branch. This tau antibody was effective in restoring learning and memory deficits in a mouse model of Alzheimer's disease. Since TBI may also increase tau proteins in the brain, we tested the novel antibody in a rodent model of TBI and found it to be effective at decreasing the number of brain cells that died following injury. We are in the process of testing this same novel antibody to see if the rodents experience fewer learning and memory deficits after their brain injury than those treated with a control. These proposed studies, which will test the efficacy of this novel antibody, will provide valuable and currently unavailable preclinical information that may lead to a novel therapeutic approach which is ideally suitable (small, lightweight and noninvasive) for application in combat situations or on a football field.

Thank you again for the great honor of receiving this award,

Bridget E. Hawkins, PhD, MBA
Assistant Professor and Director of the Administration and Data Science Core
The Moody Project for Translational Traumatic Brain Injury Research

The goal of our project is to test the novel tau antibody in our preclinical (rodent) model of traumatic brain injury (TBI). Our project is on track to complete the aims outlined in the proposal.

Gene Expression Studies:

Traumatic Brain Injury (TBI) is considered an event that can lead to the development of chronic disease pathology and is thought to induce a predisposition towards dementia. Evidence suggests that formation of soluble tau oligomers may be an early event responsible for the spread of pathology. We designed this study to look at the molecular connections between TBI and Alzheimer's Disease (AD) by using a real-time PCR array following an brain injection treatment with an immunotherapy (the novel tau antibody) designed to reduce the soluble tau oligomers that occur after TBI. Fifteen days later, brain regions (cortex near the injury site, hippocampus and thalamus) were dissected and homogenized separately. AD pathway-focused PCR arrays, containing 84 genes implicated in AD development, were performed. Normalized gene expression was analyzed by ANOVA for each gene, and differences among treatment groups were assessed by Tukey adjusted contrasts, followed by Benjamini-Hochberg control of false discovery rate. Results suggest that down-regulation of neurodegenerative genes in the novel tau antoibody treated animals was brain region specific, indicating different processes might be occurring and additional time points should be studied.

Histology & Behavior Studies:

Evidence suggests that formation of soluble tau oligomers may contribute to the early spread of pathology following traumatic brain injury (TBI). We hypothesized that if an immunotherapy targeted at removal of tau oligomers were given an hour post TBI, it would result in decreased tau oligomers and increased brain tissue sparing, thus improving behavior. Animals underwent learning and memory testing. We stained their brains for myelin (Weill) and inflammation markers (Iba-1 and CD-68). Ventricle volumes and cortical thicknesses were assessed using ImageJ, and volumes ipsilateral and contralateral to the lesion were compared. Preliminary evaluation of the novel tau antibody treated TBI animals show cortical thinning, ventricle enlargement, and decreased white matter volume on the injured side, while the control treated animals showed smaller histological changes. Preliminary comparisons suggest that the animals with more severe brain pathology also show learning and memory impairment. Sham animals did not show this pattern of brain pathology and behavioral deficits.

Presentations and Published Abstracts (specifically related to this project):

1. S Yamamoto, IJ Bolding, DR Boone, CR Andersen, DS Prough, DS DeWitt and **BE Hawkins**. Brain region specific changes in gene expression after fluid percussion injury and tau oligomer targeted immunotherapy in rats. National Neurotrauma Society Symposium, Snowbird, UT, July 2017.
2. J Wolf, IJ Bolding, KM Johnson, MA Parsley, CR Andersen, DS Prough, DS DeWitt and **BE Hawkins**. Brain histopathology and behavior changes after fluid

percussion injury of tau oligomer targeted immunotherapy treated rats**.** National Neurotrauma Society Symposium, Snowbird, UT, July 2017.

3. IJ Bolding, KM Johnson, MA Parsley, DR Boone, CR Andersen, HL Hellmich, DS Prough, DS DeWitt and **BE Hawkins.** Effects of fluid percussion traumatic brain injury and targeted immunotherapy on gene expression using custom PCR array. National Neurotrauma Society Symposium, Snowbird, UT, July 2017.
4. J Wolf, IJ Bolding, K Johnson, Y Zeng, R Kayed, DS Prough, DS DeWitt and **BE Hawkins**. Tau Oligomer Monoclonal Antibody Treatment of Fluid Percussion Injury in Rats: Behavioral Effects. Mission Connect Symposium, Houston, TX, December 2016.
5. IJ Bolding, K Johnson, Y Zeng, DR Boone, U Sengupta, R Kayed, DS Prough, DS DeWitt and **BE Hawkins**. Tau oligomer specific antibody and fluid percussion traumatic brain injury: vascular responses and brain region dependent changes in gene expression. Mission Connect Symposium, Houston, TX, December 2016.
6. **BE Hawkins**. Nose to Brain: Intranasal Drug Delivery for Treatment of Traumatic Brain Injury. Invited lecture and panelist in Traumatic Brain Injury Panel (chaired by Pramod Dash, PhD) at UT System/TX FreshAIR Neuroscience Conference, Austin, TX, October 6-7, 2016.
7. IJ Bolding, K Johnson, Y Zeng, MA Parsley, U Sengupta, R Kayed, DS Prough, DS DeWitt and **BE Hawkins**. Tau oligomer specific monoclonal antibody and fluid percussion traumatic brain injury: vascular, learning and memory outcomes. Moody Project TBI Symposium, Galveston, TX, September 23, 2016.
8. **BE Hawkins**. TOMA Therapeutics for Traumatic Brain Injury. UTMB Health Innovations Event (DemoDay), Galveston, TX, July 12, 2016.
9. JM Martinez, Y Zeng, IJ Bolding, DR Boone, R Kayed, DS DeWitt and **BE Hawkins**. Gene expression changes in the hippocampus of traumatic brain injured rats: TOMA therapy effects. MSSRP poster session, Galveston, TX, June 22, 2016.
10. I Bolding, K Johnson, Y Zeng, MA Parsley, Sengupta U, Kayed R, Prough DS, DeWitt DS and **BE Hawkins.** Tau oligomer specific antibody and fluid percussion traumatic brain injury: vascular responses, neuronal injury and learning and memory tests. National Neurotrauma Society Symposium, Lexington, KY, June 2016. Published in *J. Neurotrauma* 33 (13): PSB-346.
11. S Yamamoto, IJ Bolding, DR Boone, DS Prough, DS DeWitt and **BE Hawkins**. Vascular effects and brain specific changes in gene expression after fluid percussion and tau oligomer targeted passive immunotherapy in rats. International Anesthesia Research Society Annual Meeting, Washington, D.C., May 2017.