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TITLE: Development of in vivo Biomarkers for Progressive Tau Pathology after Traumatic Brain Injury

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14. ABSTRACT

- To assess extracts from the brains of human tau transgenic mice subjected to experimental traumatic brain injury for tau aggregating activity in a cell-based assay.
- To determine whether mouse blood and cerebrospinal fluid tau aggregating activity quantitatively predicts brain tau pathology and neurodegeneration in mouse models of chronic traumatic encephalopathy.
- To test whether antibodies that block tau aggregating activity and propagation of aggregates in cultured cell-based assays also block tau pathology and neurodegeneration in mouse models of chronic traumatic encephalopathy. This could lead to future therapeutic targets.
- To develop an antibody-based assay for tau aggregating activity to complement the cell-based assay.

15. SUBJECT TERMS

None provided

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Development of *in vivo* Biomarkers for Progressive Tau Pathology after Traumatic Brain Injury

Final Progress Report
June 7, 2019
Marc Diamond, M.D.
University of Texas Southwestern Medical Center

TASK 1: To assess extracts from the brains of tau transgenic mice subjected to experimental traumatic brain injury for tau aggregating activity using a cultured-cell based assay.

We developed strong assays to detect pathological tau seeding based on cellular biosensors. These proved capable of detecting pathological tau in animal models at very early time points, e.g. 4 weeks of age in the PS19 mouse, which expresses a human disease-associated variant (P301S) (1,2). This assay also detects incipient tau pathology in Alzheimer's patients prior to the occurrence of neurofibrillary pathology(3). In mouse models of traumatic brain injury, however, we could not find evidence of trauma-induced tau pathology. We evaluated multiple mouse models, including PS19, hTau, 5xFAD, and wild-type mice. We studied mice acutely (within hours and days) and weeks after trauma, and after repetitive trauma. While in some cases tau seeding activity was present at the time of trauma, in no case did seeding activity increase following trauma. In parallel (in a study separately funded) we observed tau seeding activity in human cases of chronic traumatic encephalopathy. Thus we are very confident that we have tools sufficient to detect tau seeding activity in brain tissues from mice or humans. In the absence of detectable trauma-induced seeding in the mouse models, we conclude that in our laboratories and given our methods of inducing trauma that it is not possible to induce the type of tau pathology in mice that is observed in humans after traumatic brain injury.

In future work, to develop an accurate mouse model, it will be necessary for investigators to determine the right combination of mouse model and brain injury paradigm to create tau pathology that results in seed-forming species that mimic those found in human tauopathies.

TASK 2: To determine whether mouse blood and cerebrospinal fluid tau aggregating activity quantitatively predict brain tau pathology and neurodegeneration in mice subjected to experimental traumatic brain injury.

We have been unable to identify tau seeding activity in mouse serum in the setting of traumatic brain injury, or in the setting of tauopathy that results from overexpression of a mutant tau transgene. For the purposes of this grant, it was impossible for us to move forward because Task 1, despite much effort, failed to produce a trauma-induced mouse tauopathy model.

Moving forward, we are continuing to experiment with methods designed to extract tau seeding activity from mouse serum. We feel this should be feasible based on the ability of others to extract brain tau from serum following peripheral dosing of anti-tau antibody(4).

TASK 3: To test whether antibodies that block tau aggregating activity in cultured cell-based assays also block tau pathology, neurodegeneration and behavioral deficits in mice subjected to experimental traumatic brain injury.

This task was not carried out due to the lack of a suitable mouse model that develops pathological tau assemblies following traumatic injury. It is worth noting that one of the antibodies in question (HJ8.5) is now in Phase II trials for the treatment of Alzheimer's disease and Progressive Supranuclear Palsy. Should these human trials show positive results in Phase III, this antibody may be of use for treatment of individuals with traumatic brain injury and chronic traumatic encephalopathy.

Task 4: To develop an antibody-based assay for tau aggregating activity.

We have successfully isolated various pathological tau assemblies from human brain, which we have used in structural studies to identify critical conformational changes that occur in tau, and lead to its ability to self-assemble. We are using this information to develop new antibodies that will discriminate various forms of tau. So far it has not been possible to find the "perfect" epitope that is present only on pathological tau, and absent in normal tau. However, we have designed epitopes that enable highly efficient immunoprecipitation of pathological tau seeding from brain tissues. This varies with the strain, or conformation of the tau assemblies.

In future work we will continue to engineer tau epitopes for detection of pathological aggregating species. We are optimistic that it will be feasible to detect pathological tau assemblies in biofluids once the appropriate antibodies are created.

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