ESTABLISHING AN ASSAY FOR DETECTING SINGLE TAU FIBRILS

https://neurodegenerationresearch.eu/survey/establishing-an-assay-for-detecting-single-tau-fibrils/

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ESTABLISHING AN ASSAY FOR DETECTING SINGLE TAU FIBRILS

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Research Abstract

? DESCRIPTION (provided by applicant): Currently there are no biomarkers for the earliest preclinical stage of Alzheimer’s disease. This constitutes an important problem because future therapeutic interventions will rely on early diagnosis. Tau fibrils are spreading throughout the brain via transfer from one neuron to another. Unless new methods are developed that detect

these fibrils, the early stages in the pathology of preclinical Alzheimer’s disease will remain largely illusive. The long-term goal is to understand the pathways of Tau propagation and how they can be manipulated for preventive and therapeutic purposes. The objective of this proposal is to use newly developed amplification methodology in conjunction with sequence-based protein design and enzyme-linked immunodetection to detect single Tau fibrils. The central hypothesis is that single Tau fibrils can be detected after repetitive cycles of shearing and growth. This hypothesis has been formulated based on data produced in the applicant’s lab that reveal shear-induced amplification of synthetic and brain-derived Tau fibrils. The rationale for this project is that once single fibril sensitivities are obtained, biofluidics can be tested for A diagnosis, and mechanistic studies into the release of Tau fibrils can be initiated. Supported by strong preliminary data the central hypothesis will be tested by pursuit of the following three specific aims. 1) Suppress self-nucleation of Tau monomers through sequence-guided protein design. Select residues in the hydrophobic core of Tau will be individually substituted to suppress self-nucleation, but not growth. Aggregation will be monitored by fluorescence spectroscopy, sedimentation, and electron microscopy. 2) Develop proteolysis-enhanced immunodetection protocols for distinguishing fibrils from monomers. Proteolysis will be used to completely degrade unfolded Tau monomers. The protease resistant core will be captured by monoclonal antibodies and detected by enzyme-linked immunosorbent assays. 3) Amplify Tau fibrils from Alzheimer’s disease brain tissue. AD brain tissue will serve as a source of authentic Tau fibrils. Amplification of single Tau fibrils will be achieved by repetitive cycles of shearing nd growth. Immunodetection will be used to enhance sensitivity. The research is innovative, because it uses a new approach to detect single Tau fibrils, namely cyclic amplification combined with sequence-guided protein design and immunodetection. The proposed research is significant because the results will provide a robust protocol for amplifying and detecting single Tau fibrils. Such capability has the potential to lead to new assays for early diagnosis of Alzheimer’s disease.

Further information available at:

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