The Role of P-Tau in the Driving of Neurovascular Uncoupling

Lilly O'Shea[1], Alyssa Collins[2], Kierra Eldridge[2], Rose Diaz[2], Margaret Bright[2], Scott Persohn[2], Paul Territo[1,2], and the IU/JAX/PITT MODEL-AD Center[2,3,4,5,6]

[1]Indiana University School of Medicine, Division of Clinical Pharmacology Indianapolis, IN, USA; [2]Stark Neuroscience Research Institute Indianapolis, IN, USA; [3]The Jackson Laboratory Bar Harbor, ME, USA; [4]University of Pittsburgh, PA, USA; [5]Sage Bionetworks Seattle, WA, USA; [6]Emory University Atlanta, GA, USA

Background and Hypothesis: Alzheimer's disease (AD) presently affects more than 50 million people worldwide, with that number projected to rise to more than 150 million by 2050 according to the World Health Organization (WHO). The neuropathologic underpinnings of AD are defined by the accumulation of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein (p-tau). Recent evidence suggests p-tau specifically acts as a catalyst for global cognitive degeneration, implicating the protein in neuronal dysfunction at the synaptic level. A robust correlation has been demonstrated between both the reprogramming of cellular metabolism in favor of glycolytic upregulation as well as mitochondrial instability enhancing the oxidative stress response, thus driving the accumulation of cerebral p-tau. These determinants have been empirically linked to the precursors of endovascular debasement and subsequent neurovascular uncoupling in Aβ mouse models. Prior studies support the position of microglial activation as the precipitating source of the comprehensive FDG-PET signal, with diminished glucose uptake corresponding to a more pronounced neurovascular uncoupling. However, the comprehensive implications of increased p-tau in cerebral metabolic dysfunction (CMET), cerebral blood flow (CBF), and neurovascular coupling (NVC) are not presently well defined. In order to further elucidate the relationship, we hypothesize that aggregates of p-tau will drive progressive neurovascular uncoupling, disrupting CMET and CBF in the PS19 mouse model of AD.

Experimental Design: To establish clinical significance, we obtained 18F-FDG and 64Cu-PTSM PET/CT images and co-registered these to stereotactic brain coordinates to assess neurometabolic and vascular uncoupling. To assess the co-localization of p-tau on specific cell types involved in metabolic and vascular dysregulation, cryoprotected tissues were stained for co-localization of p-tau in neurons (NeuN), astrocytes (GFAP), microglia (IBA1), vascular endothelia (CD3), and mono-carboxylate transporters (MCT2 and MCT4). Immunopathological assays were conducted to assess cellular communication, neuroinflammation, and oxidative stress.

Results: When observing the effects of aging by genotype, B6 control mice exhibited a randomized and dispersed distribution, consistent with the expected physiological variability associated with the normative aging process, while PS19 mice exhibited neuro-metabolic failure, with significant regions including the auditory cortex (dorsal/ventral/medial), caudate putamen (dorsal striatum), cerebellum, dorsal intermediate entorhinal cortex, entorhinal cortex,

fornix, frontal association cortex, medial orbital cortex, perirhinal cortex, secondary motor cortex, temporal association cortex, thalamus, and ventral orbital cortex.

Conclusion: These findings demonstrate a temporally and regionally progressive pattern of p-tau–driven neurovascular uncoupling, originating in the entorhinal cortex and advancing to higher-order cortical regions. Dysfunction in areas governing executive function, emotional regulation, spatial processing, and memory highlights the behavioral consequences of tau pathology and supports the potential for early diagnostic imaging and therapeutic targeting in AD.