New Phospho-Tau Epitopes for Early-Stage AD Diagnosis and as Neuropathological Markers of Pretangle Tau Assemblies in Alzheimer's Disease

Bin Xu[1,2,5], Ling Wu[1,5], Shih-Hsiu J. Wang[3,4,5], Andy Liu[3,5], Hibat Gindeel[2], John F. Ervin[3,5], Nailya Gilyazova[1,5]

[1]Biomanufacturing Research Institute & Technology Enterprise (BRITE), [2]Department of Pharmaceutical Sciences, North Carolina Central University, Durham, NC 27707, USA. Department of [3]Neurology and [4]Pathology, Duke University Medical Center, Durham, NC 27710, USA. [5]Affiliated Member, Duke/UNC Alzheimer's Disease Research Center, Durham, NC 27710, USA.

ABSTRACT

Differential biomarkers for early-stage Alzheimer's disease (AD) diagnosis and neuropathological characterization are urgently needed. From a systematic screen of site-specific phospho-tau antibodies targeting two-dozen phosphorylation sites that showed high frequencies in AD patients, we identified novel epitopes p-tau198, p-tau356, and p-tau422. These new biomarkers were not only highly capable to differentiate AD from cognitively normal (CN) brains, but also discriminate early-stage AD from CN brains with outstanding differentiation capabilities that rival or outcompete p-tau181 and p-tau217. We further developed plasma-based Single Molecule Array (Simoa) homebrew tests that are not only capable of differentiating AD from non-AD cases, but also differentiating MCI due to AD from MCI due to non-AD subjects. We compared all three epitopes with AT8 (p-tau202/205), a reference antibody for AD neuropathological staging, using immunohistochemistry staining of different Braak stages of early AD brains of CA4-CA1 hippocampal areas, entorhinal cortex, superior temporal cortex, and other adjacent areas. We discovered that both p-tau356 and p-tau422 staining are heavily skewed toward early stage prefibrillar tau aggregates (pre-tangles and intermediate tangles), while AT8 and p-tau198 staining are skewed toward mature tangles and dystrophic neurites. We further discovered that p-tau356 epitope as a marker of tau burden in the superior temporal cortex showed significantly better correlation with Braak stages of early-stage AD subjects ($r=0.83$) compared to AT8 ($r=0.67$). In summary, we identified new neuropathological markers that are more sensitive than AT8 for improved detection of earlier pathological processes that define pre-tangles, also new premortem plasma-based biomarkers for early-stage AD diagnosis and differentiation.

Sponsored By: NIH R01AG067607 and R03AG085058, Alzheimer's Association Biomarkers Across Neurodegenerative Diseases Program Award 19-614848, NC Biotechnology Center Translational Research Grant 2023-TRG-0015, Duke/UNC Alzheimer's Disease Research Center (NIH P30AG072958), and Duke Clinical & Translational Science Institute Collaborative Research Award.

Presenter Name and contact information:
Bin Xu, Ph.D., Principal Investigator & Associate Professor of Pharmaceutical Sciences
BRITE Research Institute, North Carolina Central University, Durham, NC 27707
Affiliated Faculty, Duke/UNC Alzheimer's Disease Research Center
Email: bxu@nccu.edu