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【Overview presentation】

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Development of MTBR-tau Fragment Assay Using a Fully Automated Immunoassay System

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Overview presentation	**Background:** The Alzheimer's Association Workgroup has proposed a staging system that facilitates the characterization of disease progression in Alzheimer's disease dementia (AD) based on clinical and biological status determined by biomarkers [1]. While amyloid-β has long been a primary therapeutic target, increasing attention is now being directed toward tau pathology as a critical driver of neurodegeneration in AD. In this context, there is a growing need for reliable tau biomarkers to support patient selection for emerging therapies, monitor treatment response, and evaluate therapeutic efficacy. To address this need, various candidate biomarkers such as the residue 243-containing microtubule-binding region of tau (e.g. MTBR-tau243), phosphorylated tau (e.g. p-tau205), and non-phosphorylated mid-region tau fragments have been proposed. MTBR-tau243 in cerebrospinal fluid (CSF), measured by immunoprecipitation-mass spectrometry (IP-MS), reported to correlate strongly with Tau-PET status and is a promising biomarker for insoluble tau aggregates [2, 3]. To facilitate the widespread adoption of such promising tau biomarkers in routine clinical practice, the development of simple, cost-effective, and fully automated immunoassays represents one potential approach. In this study, we developed a highly sensitive and simple immunoassay for the detection of a novel MTBR-tau fragment using a fully automated immunoassay system. Here, we report the analytical performance of the assay along with a preliminary evaluation of clinical specimens.

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	Methods: Reagent for the detection of the MTBR-tau fragment was developed by selecting antibodies from various original and commercially available candidates based on their sensitivity and specificity. This assay was optimized for application on Automated Immunoassay System HISCL™-5000 (Sysmex Corporation, Japan), which enables highly sensitive testing and provides rapid results within 17 minutes, requiring only 10 – 30 µL of sample. Analytical performance of the assay was evaluated by assessing parameters such as dynamic range, dilution linearity, within-run precision, and spike recovery. For quality control (QC) samples, pooled commercial CSF was diluted to prepare two levels, low and high. To confirm the basic clinical performance of the assay, MTBR-tau fragment levels in commercially available CSF samples were measured and compared between cognitively normal individuals (CN, n=18) and patients with clinically diagnosed AD (n=18). Group differences were assessed using the Mann-Whitney U test. Furthermore, several plasma samples from CN and AD were analyzed to evaluate the potential applicability of the assay to blood-based measurements. **Results:** This highly sensitive assay, requiring only 30 µL of sample per test, was developed with a dynamic range of 0.50 – 54.60 pg/mL. Sample dilutions within this range demonstrated 88 – 100% linearity compared to theoretical values. The assay showed high within-run precision, with coefficient of variation values of 3.7% or less for two QC samples. The spike recovery rate in CSF was 100% relative to the theoretical value. Among the 36 CSF samples, the median (interquartile range) concentrations of the MTBR-tau fragment in the CN group and the AD group were 0.35 (0.27 – 0.66) pg/mL and 4.11 (0.97 – 6.86) pg/mL, respectively. A significant increase in MTBR-tau fragment levels was observed in AD group compared to CN group ($p < 0.01$), with median values indicating an approximately ten-fold difference. Furthermore, fragments were successfully quantified within the assay's dynamic range in plasma samples, and similar to the CSF results, the AD group showed a trend towards higher levels compared to the CN group. **Conclusion:** This newly developed assay achieved high sensitivity with minimal sample volume requirements and can be easily operated on a fully automated platform.

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	It also demonstrated excellent analytical performance, indicating that MTBR-tau fragment concentrations can be reliably measured in clinical samples. MTBR-tau fragment levels measured using this assay were significantly elevated in the CSF AD group, suggesting that our assay may reflect the progression of AD tau pathology. Although the sample size was limited, this assay showed potential for application to plasma-based measurements. Additionally, the implementation of fully automated measurement systems for MTBR-tau fragment in clinical settings may contribute to the appropriate selection of eligible patients for future tau therapies. **References:** 1. Jack CR, et al. *Alzheimer's & Dementia* 2024; 20(8). 2. Horie K, et al. *Brain* 2021; 144(2): 515-527. 3. Horie K, et al. *Nat Med* 2023; 29(8): 1954-1963.
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