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【Overview presentation】

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Validation of highly specific and automated immunoassays for endogenously cleaved MTBR-tau243 in CSF: a comparison with mass spectrometry

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Overview presentation	**Background:** Tau targeting therapies for Alzheimer's disease (AD) have gained increasing attention in recent years, creating a growing need for reliable and pathology specific tau biomarkers to support their development. Among the candidates, endogenously cleaved MTBR-tau243 (eMTBR-tau243), specifically two characteristic fragments: the form cleaved at Val256 (V256) and its deamidated form at Asn255 (V256-dN), is increasingly utilized as a promising biomarker that specifically reflects brain tau pathology (Horie *et al.*, *Nat Med*, 2025). Because these tau fragments share highly similar structures, their detection requires a method with exceptional analytical specificity. Consequently, their measurement has traditionally been limited to immunoprecipitation–mass spectrometry (IP-MS). To facilitate the widespread application of such promising tau biomarkers, we have developed fully automated immunoassays capable of quantifying these specific eMTBR-tau243 fragments. In this study, we validated the analytical specificity of our developed immunoassays in cerebrospinal fluid (CSF) by assessing correlation with our newly established in-house eMTBR-tau243 IP-MS method (reference method). **Methods:** Two immunoassays targeting eMTBR-tau243 fragments (V256 and V256-dN) were developed on the Automated Immunoassay System HISCL™-5000, requiring 30 µL of CSF and a 17-minute assay time. In-house IP-MS

	assays capable of quantifying these eMTBR-tau243 fragments were established based on previous reports. Levels of eMTBR-tau243 fragments in commercially available CSF samples (n=20) from subjects with mild cognitive impairment (MCI) and clinically diagnosed AD dementia were measured by both HISCL and IP-MS assays. The correlation of measurement values obtained by the two assays was evaluated using Spearman's rank correlation coefficient (r_s). **Results:** The developed immunoassays exhibited broad measurement ranges (V256: 0.023 to 40.00 pg/mL; V256-dN: 0.016 to 10.00 pg/mL). Furthermore, they demonstrated high correlation with IP-MS (V256: $r_s = 0.98$, $p < 0.001$; V256-dN: $r_s = 0.95$, $p < 0.001$). **Conclusion:** Our fully automated immunoassays exhibited high concordance with the in-house IP-MS method, demonstrating exceptional specificity for accurate detection of eMTBR-tau243 fragments in the complex CSF matrix. A highly specific and high-throughput eMTBR-tau243 immunoassay on the HISCL may be well-positioned to support efficient and accurate recruitment of appropriate participants for clinical trials of tau-targeting therapies.
Session	Developing Topics: Biomarkers (Sunday-1219)

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