

A Novel CSF eMTBR-tau243 Immunoassay For Detecting AD Tau Pathology And Assessing Etalantug Pharmacodynamics In DIAD



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Introduction

- Insoluble tau aggregates in brain are the pathological hallmark of Alzheimer's Disease (AD) and Positron Emission Tomography (PET) has been used to detect them, but there are challenges in the access and cost
- Recently, tau microtubule-binding region containing residue 243 with the endogenous cleavage at residue 256 (eMTBR-tau243) analyzed by mass spectrometry (MS) emerged as a fluid biomarker that reflects tau tangle pathology¹
- We developed cost-effective and scalable immunoassay to quantify eMTBR-tau243 in human cerebrospinal fluid (CSF) and applied the assay to samples from the clinical study of etalantug, an investigational anti-MTBR-tau antibody, in subjects with dominantly inherited AD (DIAD) (NCT04971733)²
- As eMTBR-tau243, both non-deamidated and deamidated form at residue 255 are known. In this study, we focused on non-deamidated form

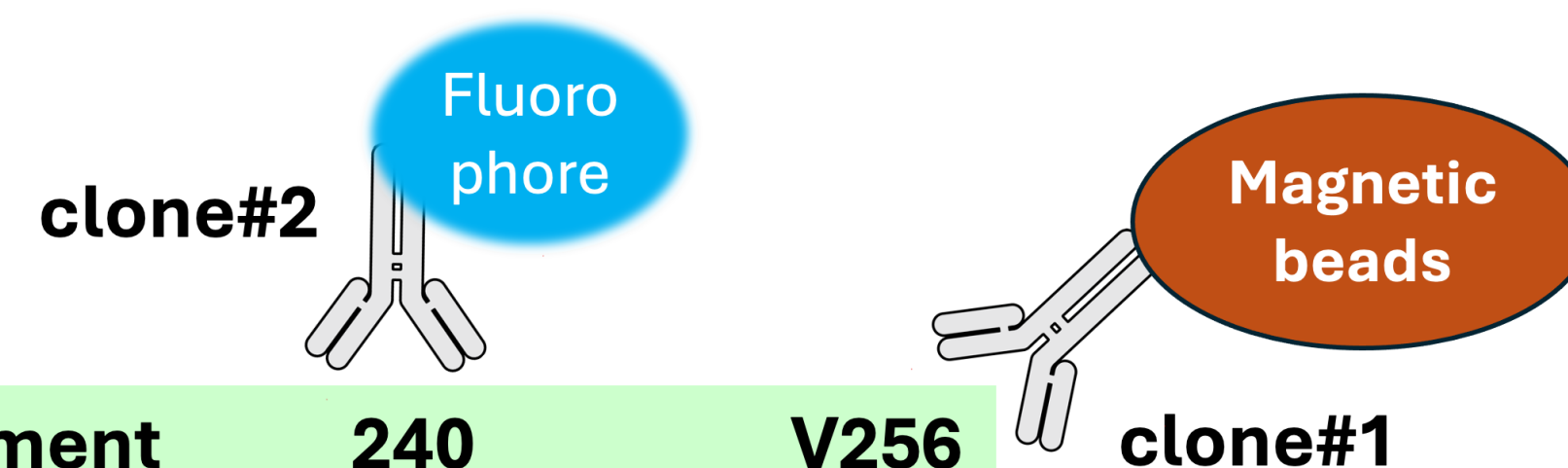
Methods

Generation of monoclonal antibodies

- We generated rabbit monoclonal antibodies against
 - The neo-epitope at the V256 (**clone#1**)
 - The region around amino acid 240 of Tau (**clone#2**)

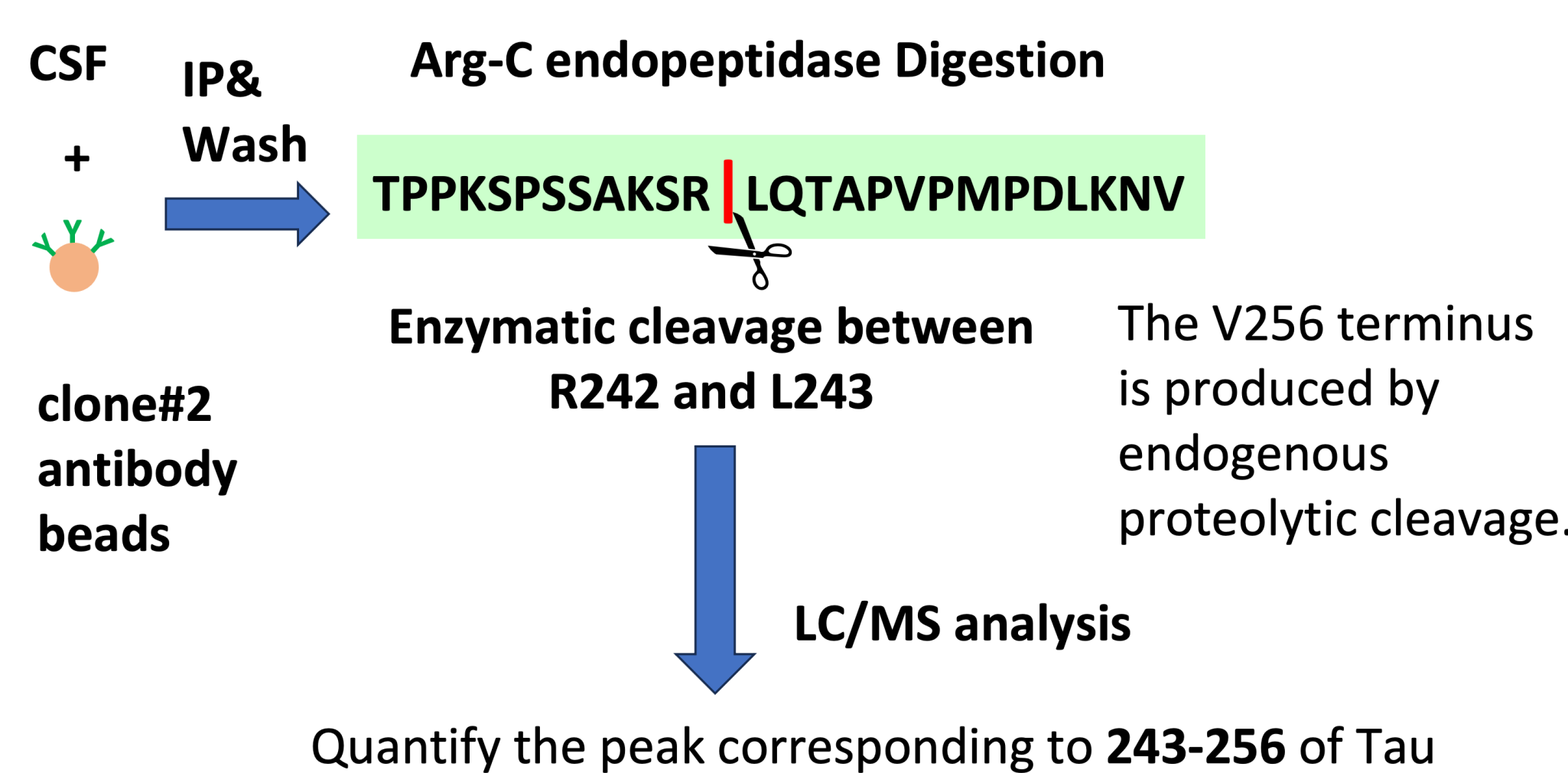
eMTBR-tau243 Immunoassay

- Clone#1 was immobilized to magnetic beads and clone#2 was labeled with fluorescent dye
- Following the previously reported method³, immunocomplex was formed and eluted, and fluorescence was counted by SMCxPRO[®]



MS-based assay

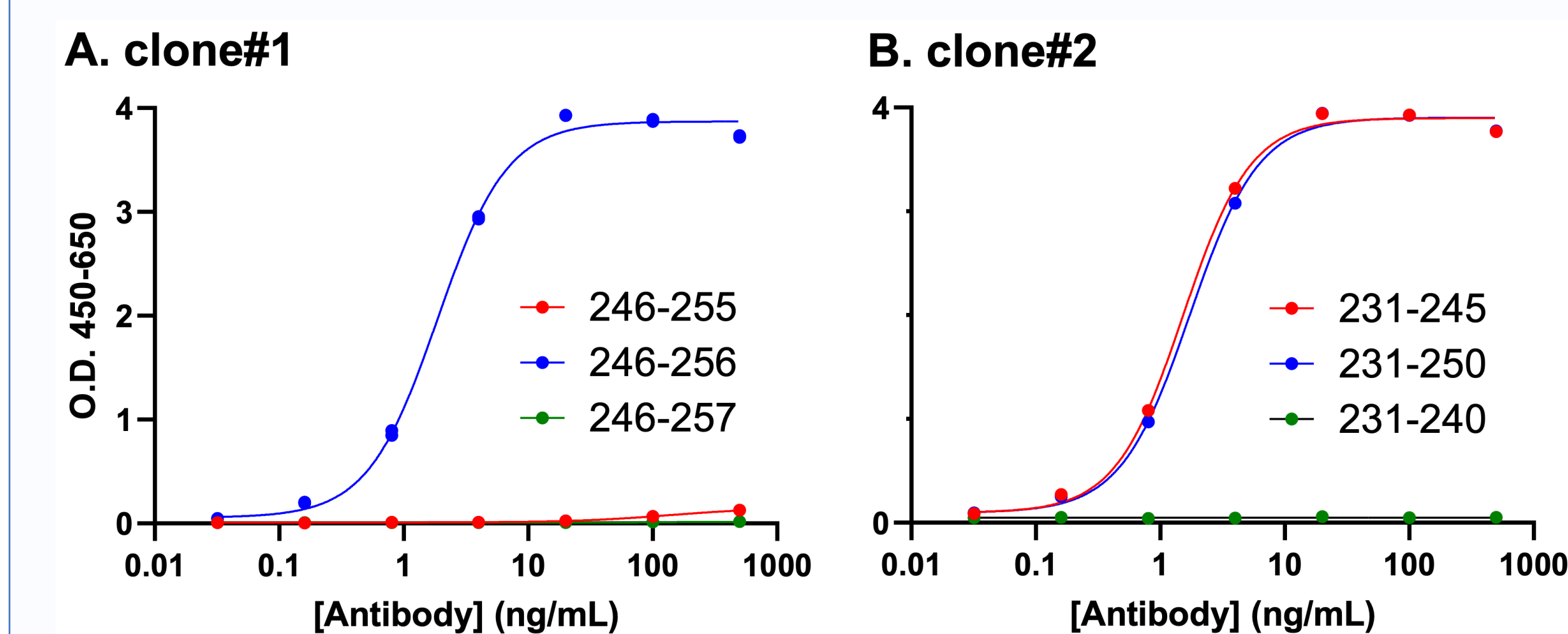
- Following to the original method,¹ MS-based method to evaluate the immunoassay was conducted



Generated antibodies were specific to the neo-epitope at V256 and the region around residue 240

- For generated antibodies, reactivity to synthetic peptides were evaluated by ELISA
- Clone#1 specifically reacted to 246-256, the peptide with V256 terminal
- Clone#2 reacted to 231-250 and 231-245, but not to 231-240, suggesting this clone is specific to the region around amino acid 240

Figure 1. Specificity of the generated antibodies for A.) clone#1 and B.) clone#2.

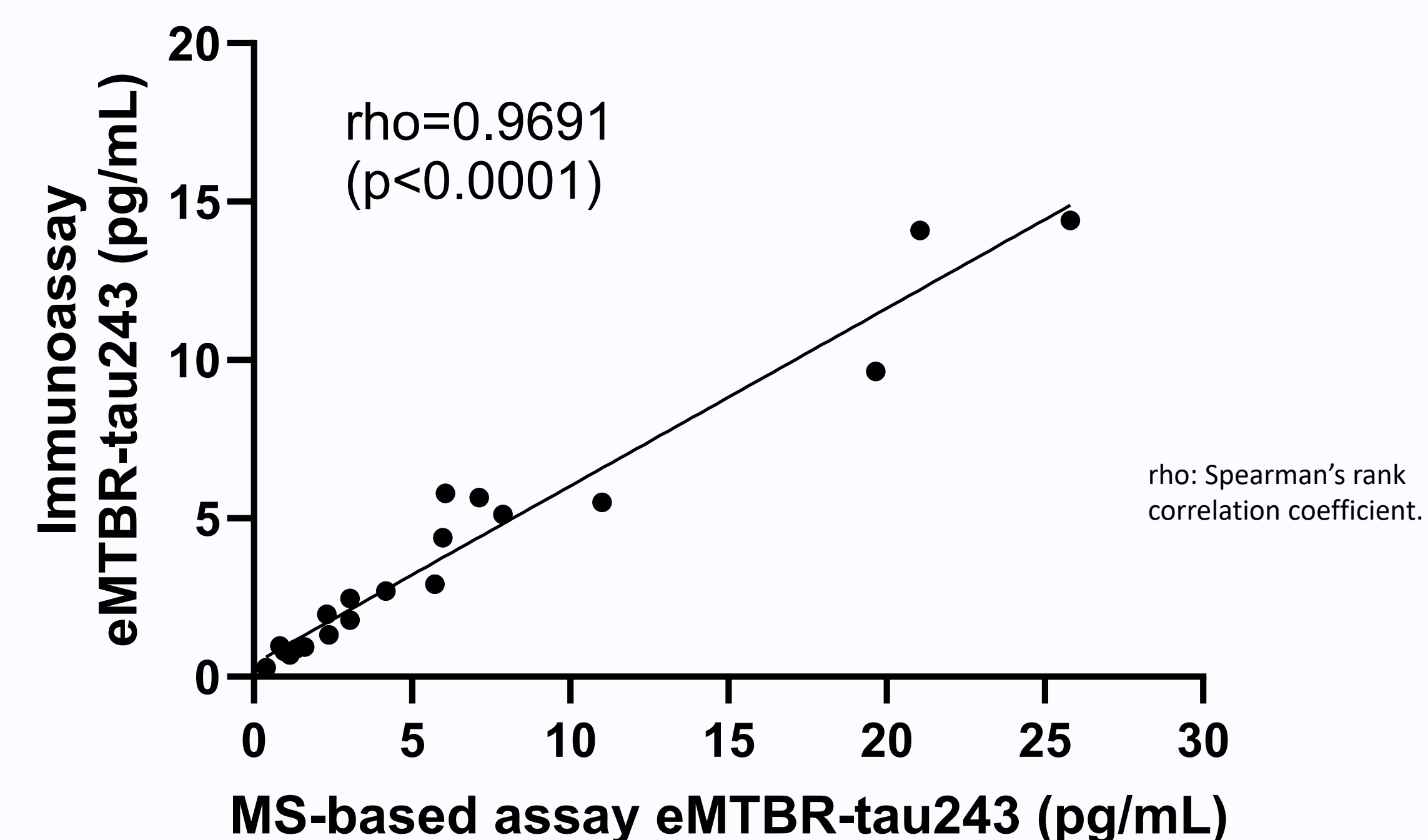


N-terminal biotinylated peptides were coated to streptavidin plate. Each peptide corresponded to partial sequence of 2N4R Tau.

Developed immunoassay was highly correlated with gold standard MS

- To evaluate the developed immunoassay, human CSF (AD N=21) were measured by MS-based method and immunoassay
- Both results were highly correlated, suggesting the appreciable performance of eMTBR-tau243 immunoassay

Figure 2. Correlation between MS-based method and immunoassay.

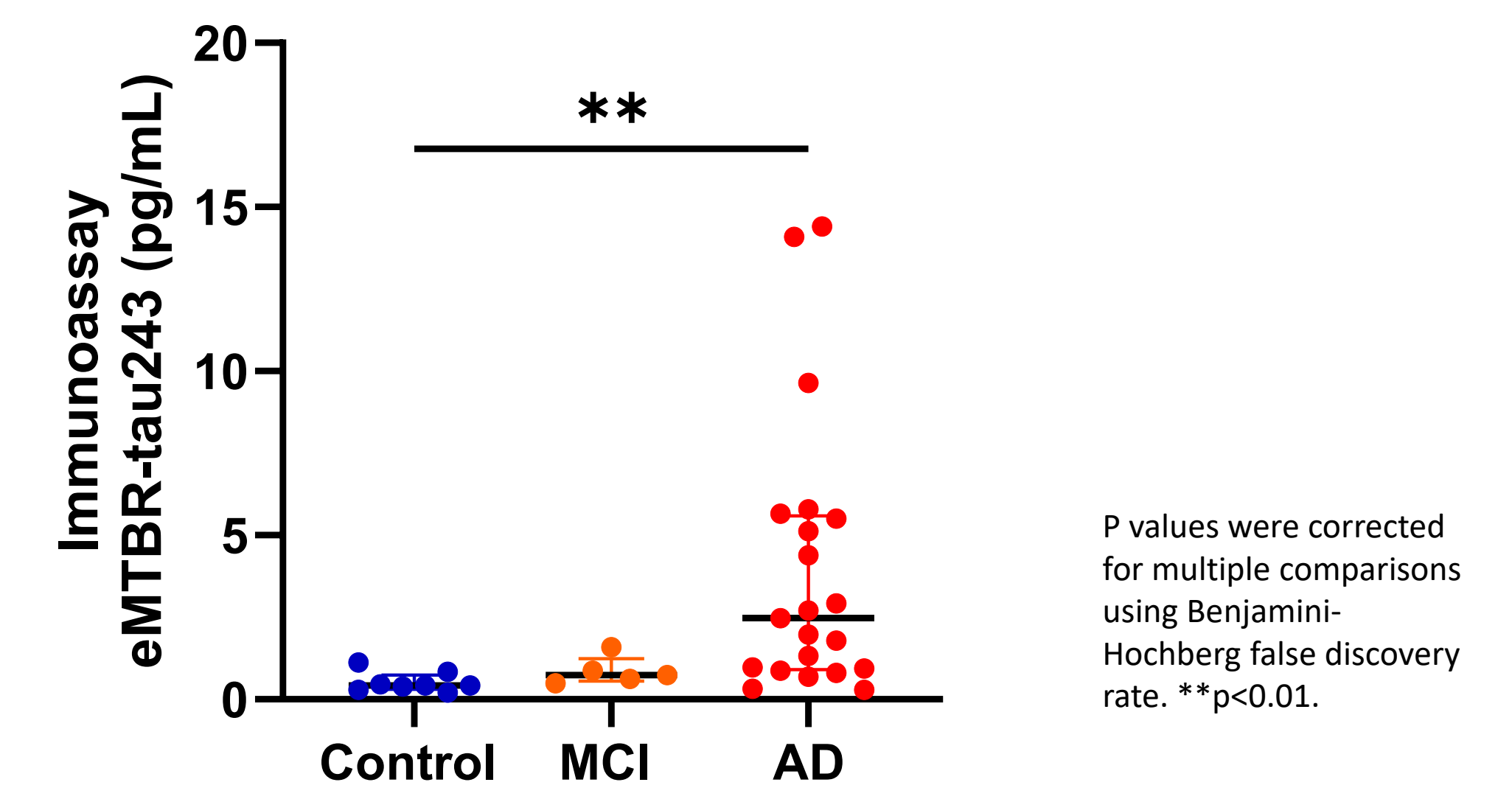


Results

eMTBR-tau243 immunoassay showed clear increase in AD, suggesting its specificity to tau pathology

- Clinically diagnosed CSF (Control N=8, MCI N=5, AD N=21) were measured by eMTBR-tau243 immunoassay
- eMTBR-tau243 levels were significantly higher in AD than the others, suggesting specificity of the immunoassay to tau tangle pathology in AD

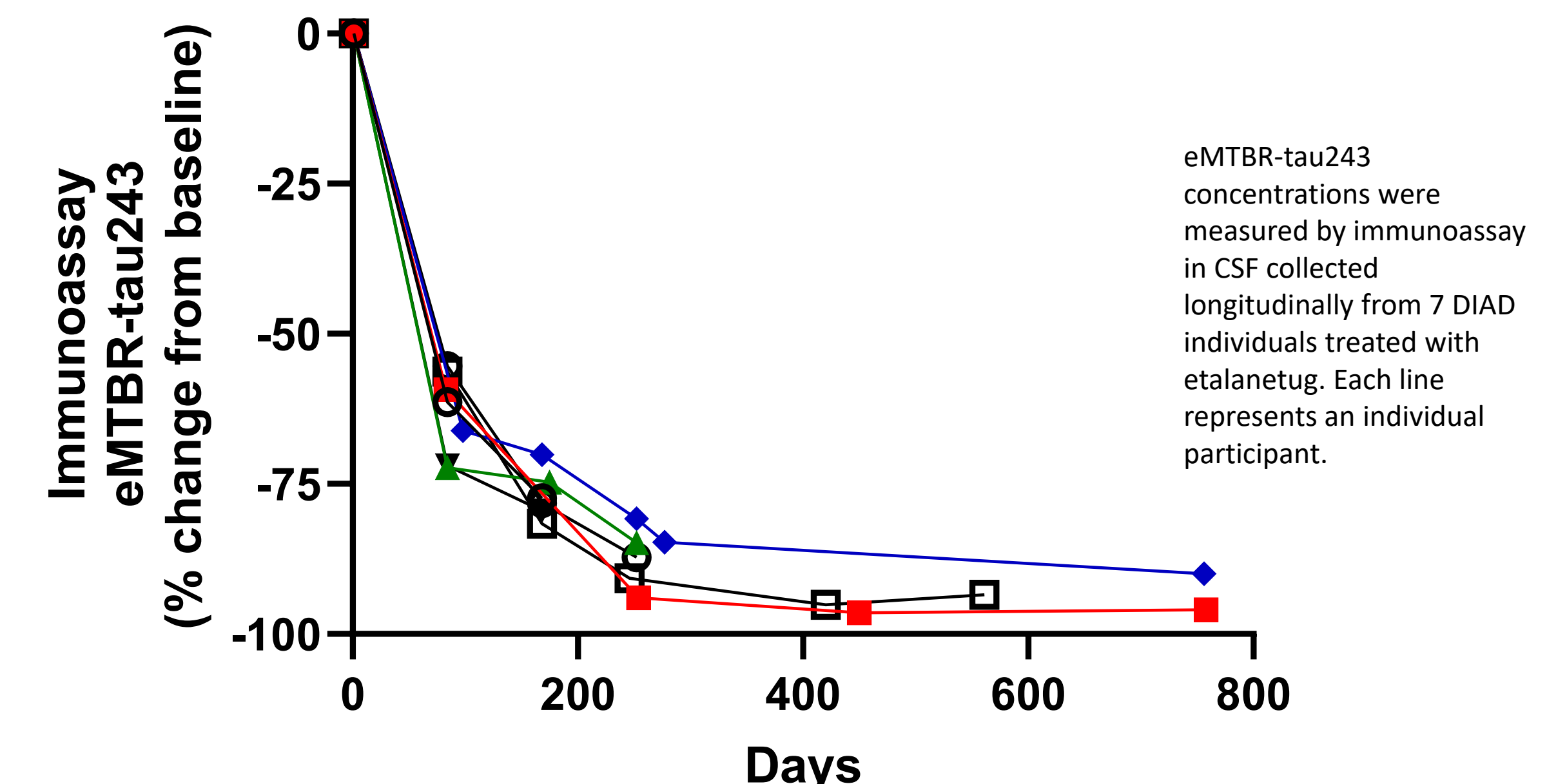
Figure 3. eMTBR-tau243 levels by clinical diagnosis.



Etalantug reduced eMTBR-tau243 (~90%) in CSF from DIAD participants (study 103), which is consistent to the LC/MS results⁴

- CSF collected from etalantug-treated DIAD participants were measured. The presence of etalantug did not interfere was previously demonstrated
- As previously reported⁴ by MS-based method, etalantug reduced CSF eMTBR-tau243 level approximately 90% from baseline, which suggests that the immunoassay can be used to show the pharmacodynamic effects of etalantug

Figure 4. Etalantug reduced CSF eMTBR-tau243 measured by immunoassay.



Conclusions

- A novel immunoassay for CSF eMTBR-tau243 was successfully developed and confirmed to show a clear increase in AD
- The immunoassay showed strong concordance with MS-based method, supporting its analytical robustness
- The application in the DIAD clinical study of etalantug further demonstrated its capability for assessing pharmacodynamic effects in future tau-targeting clinical trials

References

1. Horie K, et al. Nat Med. 2025;31:2044. 2. Andreozzi E, et al. Alzheimers Res Ther. 2026;18:87. 3. Noguchi-Shinohara M, et al. Ann Neurol. 2025;5:993. 4. Wildsmith K, et al. presentation at CTAD2025.

Acknowledgments/Disclosures

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