EV-bound proteins in blood as a robust biomarker for accurate classification of Tau tangles in the brain

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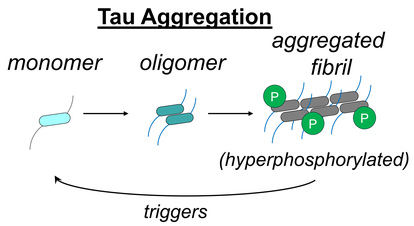
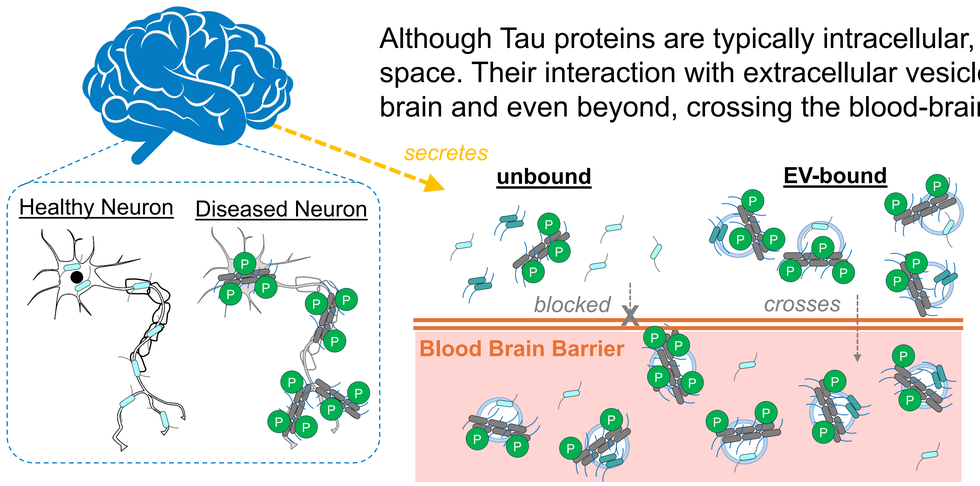
Introduction

Alzheimer's disease is marked by the accumulation of misfolded proteins in the brain, notably Beta-Amyloid and Tau, leading to cognitive decline. It is believed that these two types of protein aggregates may interact synergistically to promote neuronal dysfunction and neurodegeneration in Alzheimer's disease[1]. Tau normally supports neuronal structure, but in Alzheimer's, it becomes hyperphosphorylated, misfolding and forming tangles within neurons, disrupting their function and contributing to their degeneration.





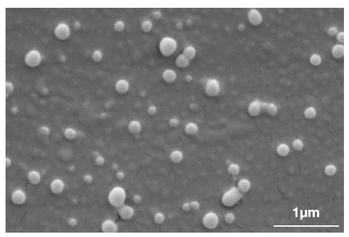
Although Tau proteins are typically intracellular, they can be released into the extracellular space. Their interaction with extracellular vesicles (EVs), facilitates their transport within the brain and even beyond, crossing the blood-brain barrier into the circulation[2,3].

By measuring proteins associated with Tau pathophysiology that are bound to brain derived EVs found in blood, we have developed a blood biomarker signature that better reflects the brain pathology compared to the same soluble, unbound proteins.

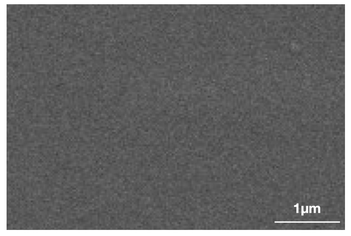
Methods

In collaboration with the Australian Imaging, Biomarker & Lifestyle (AIBL) Study, we collected blood samples from 10 Tau-PET positive participants who had previously undergone cognitive assessments and blood from 22 age-matched healthy control individuals from 4 different sites (UK, USA, Singapore, and Australia)

Plasma was directly measured (without pre-processing to isolate EVs) at Sunbird Bio using our proprietary assays to distinguish between the different EV-bound and soluble forms of Tau. Scanning Electron Microscopy images of the molecules measured by the different assays in blood are shown below:



EV-bound Tau assay



Soluble Tau assay

Results

A signature composed of unbound soluble Tau and phosphorylated Tau (pTau) was unable to classify Tau-PET positive samples in this cohort (AUC: 0.53) (**Fig. 1**)

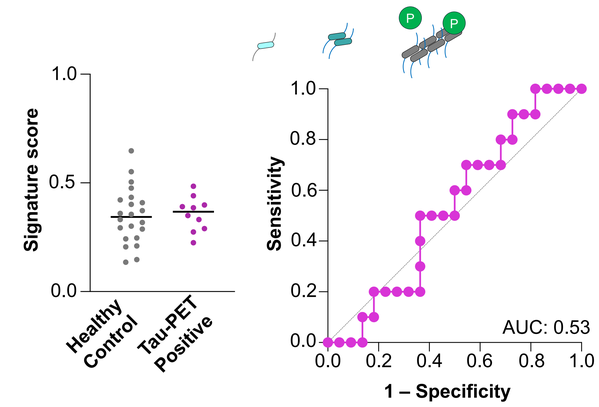


Figure 1: Signature of soluble Tau & pTau
Using a combination of assays measuring soluble Tau and pTau, we built a logistic regression classifier using LOOCV. Predictions of the LOOCV were collated and assessed for classification accuracy.

Results - continued

A signature composed of brain EV bound Tau, was able to accurately classify Tau-PET positive samples (AUC: 0.93) (**Fig. 2**)

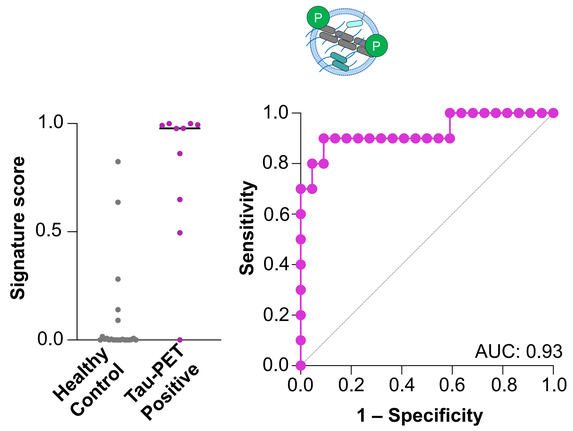


Figure 2: Signature of brain EV bound Tau
Using a combination of assays measuring Tau bound to a series of brain EV subpopulations in the blood, we built a logistic regression classifier using LOOCV. Predictions of the LOOCV were collated and assessed for classification accuracy.

A signature composed of brain EV bound pTau (pTau), was able to accurately classify Tau-PET positive samples (AUC: 0.90) (**Fig. 3**)

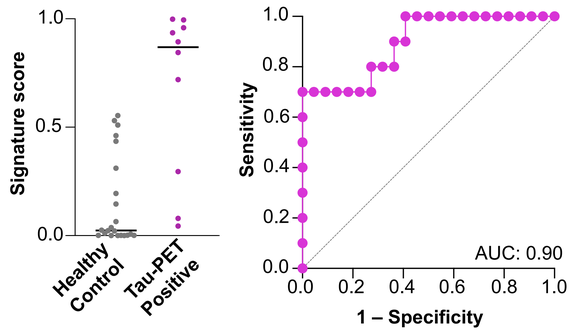


Figure 3: Signature of brain EV bound pTau
Using a combination of assays measuring pTau bound to a series of brain EV subpopulations in the blood, we built a logistic regression classifier using LOOCV. Predictions of the LOOCV were collated and assessed for classification accuracy.

Conclusion

Preliminary findings in a small clinical cohort suggest that our blood-biomarker signatures, consisting of various forms of Tau bound to specific types of brain-derived EVs, hold promise for accurately detecting Tau aggregation in the brain. We plan to run a larger clinical study to validate these blood biomarker signatures.

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[2] Ruan Z, Pathak D, Venkatesan Kalavai S, Yoshii-Kitahara A, Muraoka S, Bhatt N, Takamatsu-Yukawa K, Hu J, Wang Y, Hersh S, Ericsson M, Gorantla S, Gendelman HE, Kayed R, Ikezu S, Luebke JI, Ikezu T. Alzheimer's disease brain-derived extracellular vesicles spread tau pathology in interneurons. Brain. 2021 Feb 12;144(1):288-309. doi: 10.1093/brain/awaa376.
[3] Fowler SL, Behr TS, Turkes E, Cauhy PM, Foiani MS, Schaler A, Crowley G, Bez S, Ficulle E, Tsefou E, O'Brien DP, Fischer R, Geary B, Gaur P, Miller C, D'Acunzo P, Levy E, Duff KE, Ryskeldi-Falcon B. Tau filaments are tethered within brain extracellular vesicles in Alzheimer's disease. bioRxiv [Preprint]. 2023 Apr 30:2023.04.30.537820. doi: 10.1101/2023.04.30.537820.

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