Letter to the Editor in Reply to Correspondence from Pappolla and Sambamurti

We thank Professors Pappolla and Sambamurti for their correspondence and are grateful for their welcoming of the technical advance presented in our study.

We agree that previous works, particularly animal models, are crucial and welcome the authors highlighting their contribution. We agree that it is important to acknowledge earlier findings. However, there is a large body of literature to survey and in our brief report we sought to cite a variety of key background studies within the space afforded. We regret to have not been able to include references to their articles and hope this correspondence helps give their work due prominence (1, 2).

We sought to focus on direct evidence from human samples, hence in our discussion we actively drew attention to the histological samples reported previously by Nauen et al (3), highlighting respective novelties (amyloid staining of cells in resected lymph nodes) and our findings (fluid biomarkers detectable in fine needle aspirate fluid phase). Thus, to clarify and defend the statement they highlight regarding neurodegenerative biomarkers, this refers to the specific contemporary fluid biomarker panel and detection method utilised in the study, including, but not restricted to, $A\beta_{40}$ and $A\beta_{42}$. Indeed, as we discuss, while these peptides were detectable in the cervical lymph node sample supernatant and elevated compared to paired plasma, this was less striking than for pTau181, which in addition showed a change over age in the limited sample series available.

Overall, as we discussed, these clinically-utilised neurodegenerative biomarkers, and ever-expanding proteomics panels, now need considerable further exploration. We reported our initial exploration to help promote this clinical-research opportunity to the field in a timely manner, which as noted by Professors Pappolla and Sambamurti's correspondence, it appears to have done. Clearly, larger well-characterised cohorts across the spectrum of ageing and neurodegenerative dementias, featuring paired cervical lymph node samples at multiple levels together with CSF and non-cervical lymph nodes are needed to clarify these relationships further in people. We anticipate this being an international collaborative and multidisciplinary effort. We look forward to the emerging literature further unveiling this exciting frontier.

Yours faithfully,

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2. Pappolla MA, Matsubara E, Vidal R, Pacheco-Quinto J, Poeggeler B, Zagorski M, et al. Melatonin Treatment Enhances Abeta Lymphatic Clearance in a Transgenic Mouse Model of Amyloidosis. Curr Alzheimer Res. 2018;15(7):637–42.

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Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Competing interests statement

AAD reports no competing interests.

SRI has received honoraria and research support from UCB, Immunovant, MedImmun, Roche, Janssen, Cerebral therapeutics, ADC therapeutics, Brain, CSL Behring, and ONO Pharma; has licensed royalties on patent application WO/2010/046716; and has filed two other patents (WO2019211633 and US-2021-0071249-A1, Patent Cooperation Treaty application WO202189788A1; and PCT/GB2022/050614 and WO202189788A1). The remaining authors report no financial relationships with commercial interests

Declaration of Authorship

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