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Editorial: Brain-penetrant antibodies for Alzheimer's disease: The next generation?

With the emergence of disease modifying anti-Aβ monoclonal antibody treatments for Alzheimer's disease (AD) and their arrival in the clinic, focus has turned to the refinement of these treatments. Only a very small percentage (<1 %) of anti-Aβ monoclonal antibodies enter the brain where they bind to aggregated amyloid species. This limited entry poses a major challenge in developing effective antibody-based therapies, as it necessitates large administered doses to achieve effective brain concentrations. The ability to decrease doses would likely provide a critical reduction in the major toxicities of these treatments: amyloid-related imaging abnormalities (ARIA), including ARIA-E (edema or effusion) and ARIA-H (hemorrhagic events). The ARIA risk contributed to the European Medicines Agency's (EMA) decision to approve Lecanemab for treatment only in patients who are not Apolipoprotein E4 homozygotes, as these individuals are at significantly increased risk of developing both ARIA-E and ARIA-H and ARIA. This decision underscored that the needs of significant numbers of persons living with AD are unmet by current treatments.

In this issue, Sehlin et al. provide a comprehensive review of bispecific brain-penetrant antibodies, with a focus on those being developed for AD, particularly anti-Aβ monoclonal antibodies [1]. The review centers on the transferrin receptor 1 (TfR1) as a shuttle across the blood-brain barrier (BBB)—the delivery of protein drugs to the brain may be enhanced if the drug is modified to include a TfR1-binding domain. The concept of Aβ/TfR1 bispecific antibodies might serve as the foundation for improved AD immunotherapy, because a larger treatment effect could be obtained from higher brain concentrations, with a reduced risk of side effects due to lower peripheral drug concentrations.

Apart from higher brain concentrations, this review emphasizes the importance of more uniform brain concentrations. The preclinical images presented by Sehlin et al. [1] in their Fig 3 provide a striking contrast of the brain distribution of regular IgG vs. bispecific antibodies. In panel A, a control IgG was primarily localized to the brain surface, corresponding to leptomeningeal tissue and associated blood vessels, whereas a bispecific Antibody Transport Vehicle (ATV) exhibited widespread distribution throughout the brain [2]. In panel B, in an AD mouse model, the distribution of RmAb158 (murine version of Lecanemab) was mainly restricted to central brain regions and appeared as hotspots, probably corresponding to large blood vessels, whereas bispecific RmAb158-scFv8D3 was widely distributed throughout the brain, overlapping regions with Aβ pathology [3].

Bispecific anti-Aβ antibodies may thus enable the rapid clearance of a larger pool of aggregated Aβ, and more uniform brain delivery may also yield a more favorable safety profile. As the authors note, conventional antibodies are thought to cross the BBB principally via perivascular transport along large blood vessels rather than through the capillary network. This route of delivery may result in high local antibody concentrations at sites of vascular Aβ deposits, increasing the risk of hemorrhages. Preclinical studies suggest that bispecific antibodies are less likely to accumulate at these sites, which may confer a lower risk for ARIA.

With regard to the translation of bispecific anti-Aβ antibodies to human AD, encouraging reports are already emerging for the prototype Trontinemab. Sehlin et al. cite early results presented from an ongoing Phase 2 study at scientific meetings (CTAD conference, Madrid 2024). These data highlight the superiority of Trontinemab in reducing brain amyloid as evaluated by PET, compared to the conventional approved antibodies Lecanemab and Donanemab. At a significantly lower dose of 3.6 mg/kg administered once per month, Trontinemab reduced brain amyloid to normal levels (below the 24 centiloid threshold) in 81 % of participants by 7 months (additional data following this review from AD/PD conference, Vienna 2025). By comparison, Lecanemab and Donanemab, administered at doses of approximately 10 mg/kg, required 12 to 18 months to achieve comparable reductions [4,5]. Importantly, no data have thus far been reported for cognitive or functional effects of Trontinemab treatment.

The authors report comparatively little about the safety data from the Trontinemab presentations. Nevertheless, the early blinded safety results are already quite striking. Among 76 participants who have received 1.8 mg/kg Trontinemab or placebo, and 38 who have received 3.6 mg/kg or placebo for 28 weeks (4:1 active/placebo ratio) only three mild cases of ARIA-E and five cases of ARIA-H have been reported (AD/PD conference, Vienna 2025). Because the ongoing Phase 2 study remains blinded, ARIA frequencies come from the combined placebo and active groups from each cohort. Thus far, three ARIA-E cases and four of five ARIA-H cases occurred in the 1.8 mg/kg cohort, with only one ARIA-H case in the 3.6 mg/kg cohort (CTAD conference, Madrid 2024; AD/PD conference, Vienna 2025).

In addition to Aβ, other AD pathologies, including tau in the form of neurofibrillary tangles, may also be targeted by bispecific antibodies. Unlike amyloid plaques, tau aggregates are primarily intracellular and thus potentially more difficult to access. As the authors note, since TfR1 is also expressed by neurons, it may facilitate antibody transport across the neuronal cell membrane to enable the direct targeting of intracellular tau. However, the leading current strategy for tau immunotherapy is instead focused on prevention of tau propagation and spreading in the

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brain by clearing extracellular tau aggregates using anti-microtubule binding region (MTBR) tau antibodies. This strategy may also benefit from tau-TfR1 bispecific antibodies, as diffusible tau aggregates are present in the brain at much lower concentrations than e.g. Aβ aggregates and may require particularly high concentrations of the antibody.

Bispecific brain-penetrant antibodies have the possibility of revolutionizing not only the therapeutics of AD, but also some of the diagnostic imaging techniques. PET imaging of amyloid has been instrumental in improving the clinical diagnosis of AD and in establishing that anti-Aβ antibodies significantly remove brain amyloid. However, current PET radioligands bind to insoluble (fibrillar) Aβ deposits, which are primarily present in the dense core of amyloid plaques [6]. They do not visualize soluble aggregated forms of Aβ, which may accumulate around plaques and represent an important target for therapeutic anti-Aβ antibodies. Thus, the very pool of Aβ that some antibodies may fail to target is also unimaged by current PET radioligands, providing an incomplete picture of Aβ clearance. This limitation should dictate caution in using PET centiloid thresholds for defining therapeutic goals and in using amyloid PET as a surrogate endpoint for the accelerated approval of therapeutic antibodies targeting Aβ in AD.

As Sehlin et al. underscore, a critical innovation in amyloid PET imaging could follow from PET radioligands based on bispecific antibodies. Conventional antibodies are poor candidates for PET tracers, given their low and slow brain delivery. Bispecific antibodies, conversely, exhibit rapid brain entry and have been successfully used in preclinical models to measure brain Aβ. Despite their rapid brain delivery, bispecific antibodies have other pharmacokinetic characteristics that make their use in PET imaging challenging—most notably, elimination half-lives of several hours. This delayed clearance necessitates radiolabeling with radionuclides that have longer decay half-lives than carbon-11 and fluorine-18 and thus would confer increased radiation burden for patients. Whether the successes from preclinical models will translate to immunoPET methodologies for human AD remains to be seen.

In their thoughtful review, Sehlin et al. are still more forward-looking on a number of topics. They delineate other possible techniques for receptor-mediated transcytosis, apart from TfR1, including CD98 and insulin receptors. Looking beyond the monoclonal antibodies directed at Aβ aggregates, they discuss several possible alternative cargo molecules such as neprilysin and antisense oligonucleotides (ASOs). Finally, they preview novel strategies to extend the brain residence time of protein-based therapeutics e.g., by attaching an additional high-affinity antibody domain that targets an abundant brain protein, thereby prolonging drug exposure at the target site.

CRediT authorship contribution statement

C.H. van Dyck: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

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