Differentiation of PMN310 from other amyloid-beta-directed antibodies: Ability to selectively target toxic brain oligomers despite competing monomers and plaque

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Objective

Compare PMN310 to other Abeta-directed antibodies for selectivity and ability to avoid plaque and to maintain interaction with toxic oligomers in the presence of competing monomers.

Methods

Surface plasmon resonance was used to assess the binding of multiple Abeta-directed antibodies (PMN310, donanemab, aducanumab, lecanemab, crenezumab, solanezumab, gantenerumab) to a toxic oligomer-enriched low molecular weight fraction of soluble brain extract from AD patients, and to maintain interaction with toxic oligomers in the presence of competing monomers. Binding to Abeta plaque was examined by immunohistochemistry on AD brain sections.

Results & Conclusions

1. PMN310 was raised against a conformational epitope computationally predicted to be present on misfolded, toxic Ab oligomers, distinct from monomers or fibrils.

2. PMN310 showed strong binding to a toxic oligomer-enriched fraction from AD brain and, compared to other Abeta-directed antibodies, was the least impacted by monomer competition in retaining binding to the toxic oligomers.

3. Antibodies that were outcompeted by pre-exposure to monomers showed no clinical benefit in pivotal trials while antibodies that were less impacted by monomer competition produced positive clinical data.

4. PMN310 did not react with plaque or vascular deposits in AD brain, suggesting that it may carry a reduced risk of ARIA which has been observed with plaque-binding antibodies.

5. The greater selectivity of PMN310 for toxic oligomers may translate into greater clinical benefit and a potentially improved safety profile.

References


1. Specific targeting of toxic Ab oligomers for increased efficacy and improved safety profile

2. ProMIS computational platform vs. conventional immunization allowed for the generation of PMN310 selective for toxic Ab oligomers

3. PMN310 targets a conformational epitope present on Ab oligomers, not monomers

4. PMN310 shows strong ex vivo target engagement with toxic oligomers in Alzheimer’s brain extract

5. Clinical efficacy of Ab antibodies correlates with ability to avoid monomer competition and retain binding to AD brain toxic oligomers

6. PMN310 does not bind plaque, expected to avoid ARIA-E

7. Importance of specific targeting of toxic Ab oligomers

PMN310 selects synthetic IgG oligomers vs. monomers

Surface plasmon resonance (SPR) was used to measure the binding of immobilized PMN310, or a human IgG1 isotype control (huIgG1), to synthetic Ab oligomers (Y)

Abbreviations: Aβ, amyloid-beta; Ab, antibody; AD, Alzheimer’s disease; ARIA, adverse reaction to immunotherapy; SPR, surface plasmon resonance; HMW, high molecular weight; Conventional, conventional immunization; ProMIS, ProMIS Neurosciences; P0214, ProMIS Neurosciences.

Note: HMW = high molecular weight