Distinguishing between amyloid-beta-directed antibodies: Ability of PMN310 to target toxic oligomers despite competing species

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Background

A large body of evidence indicates that the most pathogenic species of Abeta (Aβ) in Alzheimer's disease (AD) consist of soluble toxic oligomers as opposed to insoluble fibrils and monomers. The ability of a therapeutic antibody to target toxic Aβ oligomers without being diverted by binding to competing non-toxic species is expected to result in greater efficacy, as supported by clinical results to date. As a next generation antibody, PMN310 is a therapeutic candidate designed to more selectively target toxic oligomers. Avoiding interaction with plaque and vascular deposits has the additional advantage of potentially decreasing the incidence of amyloid-related imaging abnormalities (ARIA). In this study, PMN310 was compared to other Aβ antibodies for selectivity and ability to maintain interaction with toxic oligomers in the presence of competing monomers.

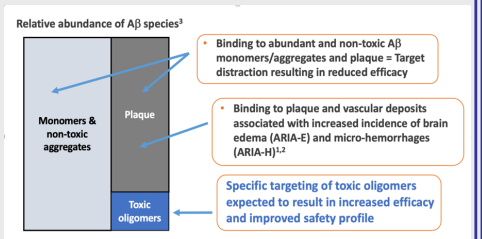
Results

- PMN310 was raised against a conformational epitope computationally predicted to be present on misfolded, toxic Aβ oligomers, distinct from monomers or fibrils;
- PMN310 showed selective binding to toxic oligomers and, compared to other Aβ-directed antibodies, was among the least impacted by excess monomer competition in binding to synthetic oligomers or naturally occurring toxic oligomers in AD brain extract;
- In contrast to other Aβ-directed antibodies, PMN310 additionally avoided interaction with plaque and vascular deposits;
- The greater selectivity of PMN310 for toxic oligomers may translate into greater clinical benefit and a potentially reduced risk of ARIA.

References

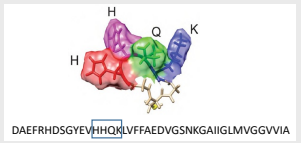
1: Sevigny et al, Nature 2016; 2: Shankar et al, Nature Medicine 2008; 3: Goure et al, Alz Res & Ther 2014; 4: Gibbs et al, Scientific Reports 2019; 5: Cleary et al, Nat Neurosci. 2005; 6: Reed et al, Neurobiol Aging 2011; 7: Yang et el, J Neurosci. 2017; 8: Sperling et al, Alzheimer's and Dementia 2011

Importance of specific targeting of toxic Aβ oligomers



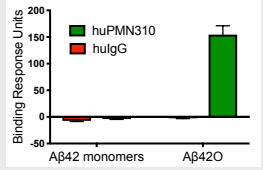
PMN310 targets conformational epitope on Aβ oligomers

Conformational epitope of PMN310



A scaffolded cyclic peptide mimicking the conformation of an epitope computationally predicted to be exposed in Aβ oligomer, distinct from monomer or fibril was used for immunization, leading to the generation of PMN310[4].

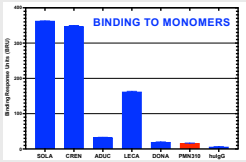
Selectivity of PMN310 for Aβ oligomers *vs.* monomers



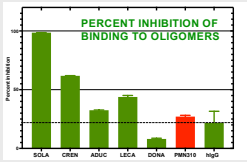
Surface plasmon resonance (SPR) was used to measure the binding of immobilized PMN310, or a human IgG control (huIgG), to Aβ monomers or oligomers

PMN310 targeting of Aβ oligomers is minimally impacted by monomer competition

Aβ-directed antibodies show varying degrees of binding to non-toxic Aβ monomers



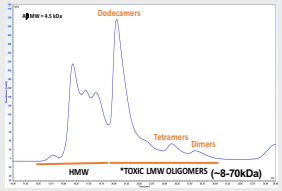
Binding to monomers results in reduced interaction with toxic, synthetic Aβ oligomers



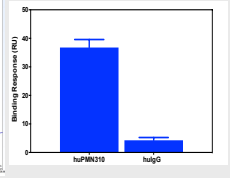
SPR was used to measure the binding of immobilized antibodies to monomers alone and to oligomers +/- pre-exposure to monomers. Percent inhibition = [(Oligomer binding response units (BRU) without monomers) – (Oligomer BRU with monomer pre-exposure)] / (Oligomer BRU without monomers) X 100
SOLA: solanezumab, CREN: crenezumab, ADUC: aducanumab, LECA: lecanemab, DONA: donanemab, huIgG or hIgG: human IgG control.

PMN310 binds to the toxic oligomer-enriched low molecular fraction of Alzheimer's brain extract

SEC fractionation of AD soluble brain extract – the low molecular weight (LMW) fraction is enriched for toxic oligomers*



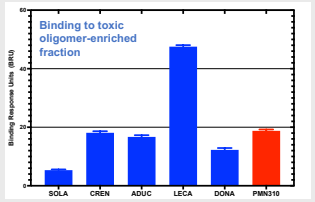
High binding to toxic oligomer-enriched LMW fraction of soluble AD brain extract by PMN310



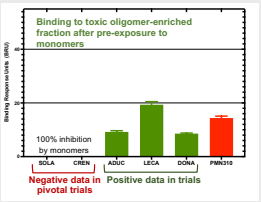
SPR was used to measure binding of immobilized PMN310 to brain extract.
*Toxic as assessed by inhibition of long-term potentiation[2], induction of cognitive deficit in rats[5,6], activation of microglia and decrease in neuronal β-adrenergic receptors[7].
SEC: size exclusion chromatography.

Positive clinical data correlate with the ability of Aβ-directed antibodies to retain binding to toxic oligomers in AD brain extract in the face of monomer competition – PMN310 is minimally impacted by monomers

Aβ-directed antibodies show varying degrees of binding to toxic oligomers in AD brain extract



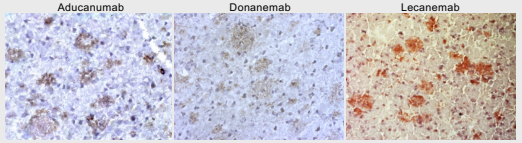
Ability of Aβ-directed antibodies to overcome monomer competition correlates with positive clinical trial data



SPR was used to measure the binding of immobilized antibodies to the LMW, toxic oligomer-enriched fraction of AD brain extract +/- pre-exposure to monomers. SOLA: solanezumab, CREN: crenezumab, ADUC: aducanumab, LECA: lecanemab, DONA: donanemab.

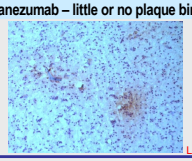
Unlike other Aβ-directed antibodies, PMN310 does not bind to plaque or vascular deposits in AD brain, which could potentially lead to a reduced risk of ARIA-E[8]

Plaque-binding antibodies associated with ARIA-E

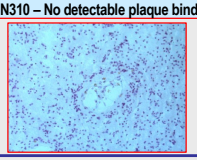


- Fresh frozen AD brain sections were incubated with test antibody followed by detection with secondary HRP-conjugated rabbit anti-human IgG;
- ARIA-E: Amyloid Related Imaging Abnormality with Edema.

Solanezumab – little or no plaque binding



PMN310 – No detectable plaque binding



Low incidence of ARIA-E