P0214

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, with and without pre-exposure to competing monomers. Binding to Abeta plaque was examined by immunohistochemistry on AD brain sections.

Results & Conclusions

- **PMN310 was raised against a conformational epitope computationally predicted to be present on misfolded, toxic Aβ oligomers, distinct from monomers or fibrils**
- **PMN310 showed strong binding to a toxic oligomer-enriched fraction from AD brain and, compared to other Aβ-directed antibodies, was the least impacted by monomer competition in retaining binding to the toxic oligomers**
- **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**
- **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**
- **The greater selectivity of PMN310 for toxic oligomers may translate into greater clinical benefit and a potentially improved safety profile**

References

1: Goure et al, 2014 Alz Res & Ther;
2: Gibbs et al, 2019, Scientific Reports;
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4: Shankar et al, 2008 Nat. Med.;
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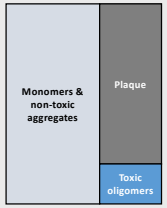
6: Reed et al, 2011 Neurobiol Aging.;
7: Sperling RA et al, 2011, Alzheimer's and Dementia;
8: Budd Haeberlein S et al, 2022, J Prev Alz Di;
9: Mintun MA et al, 2021, NEJM;
10: Swanson CJ et al, 2021, Alzheimer's Research and Therapy;
11: https://www.roche.com/media/releases/med-cor-2022-11-14;
12: Carlson C et al, 2016, Alzheimer's and Dementia;
13: Ostrowitzki S et al, 2022, JAMA Neurol.

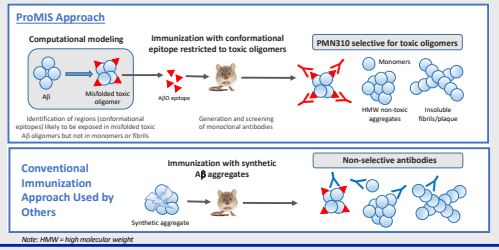
1. Specific targeting of toxic Aβ oligomers for increased efficacy and improved safety profile



The Challenge

- Aβ oligomers are a major driver of Alzheimer's disease but are much less abundant than other forms of Aβ (monomers, non-toxic aggregates, plaque)
- Antibodies that bind monomers are directed away from the toxic oligomer target, reducing efficacy
- Antibodies that bind plaque are associated with an increased risk of brain edema and microhemorrhages (ARIA-E and ARIA-H)

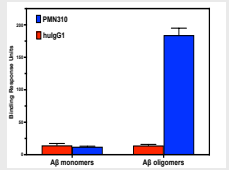
2. ProMIS computational platform *vs.* conventional immunization allowed for the generation of PMN310 selective for toxic Aβ oligomers



Note: HMW = high molecular weight

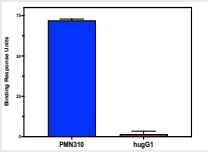
3. PMN310 targets a conformational epitope present on Aβ oligomers, not monomers

PMN310 selectively binds synthetic Aβ oligomers *vs.* monomers



Surface plasmon resonance (SPR) was used to measure the binding of immobilized PMN310, or a human IgG1 isotype control (hulgG1), to synthetic Aβ monomers or oligomers

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



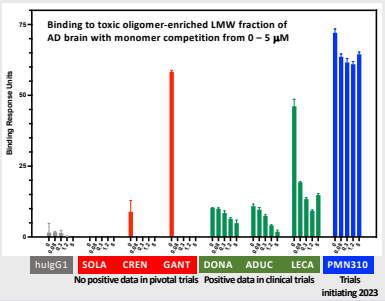
SPR was used to measure the binding of immobilized PMN310, or a human IgG1 isotype control (hulgG1), to the LMW fraction of soluble AD brain extract

High binding of PMN310 to the toxic oligomer-enriched low molecular weight (LMW) fraction of soluble AD brain extract

- PMN310 shows strong binding by SPR to LMW brain extract, enriched for toxic oligomers[2]
- Binding was observed in > 20 brains tested suggesting that PMN310 targets an Aβ oligomer epitope widely shared across patients
- AD soluble brain extract fractionated by molecular weight by size-exclusion chromatography[3]
- Low molecular weight fraction (8 kDa – 70 kDa) found to contain the most toxic oligomers*

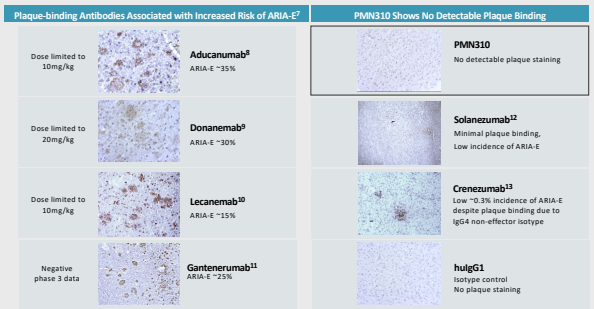
**Toxic as assessed by inhibition of long-term potentiation (LTP)[1]; induction of cognitive deficit in rats[5, 6], and decrease in neuronal β2-adrenergic receptors and activation of microglia[3].*

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

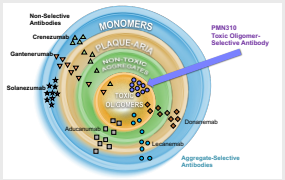


- Antibodies that failed in the clinic have toxic oligomer binding negated by monomer exposure
- Antibodies with positive clinical trial data are more resistant to monomer competition and retain significant binding to toxic oligomers
- **PMN310 targeting of toxic Aβ oligomers was the least impacted by monomer competition**
- *In vivo*, plaque binding (not captured in this assay) will result in additional target distraction for plaque-reactive antibodies

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



7. Importance of specific targeting of toxic Aβ oligomers



	Non-Selective Antibodies	Aggregate-Selective Antibodies	ProMIS Neurosciences
Drug	crenezumab, gantenerumab, solanezumab	aducanumab, lecanemab, donanemab	**PMN310**
Mechanism	Bind abundant non-toxic monomers/aggregates and are diverted away from the toxic oligomer target	Target oligomers more effectively but incur increased risk of ARIA associated with plaque binding	Specific targeting of toxic oligomers expected to result in increased efficacy and improved safety
Clinical Benefit	None	Modest	Potentially High