Selective targeting and protection against toxic amyloid-beta oligomers by PMN310, a monoclonal antibody rationally designed for greater therapeutic potency in Alzheimer's disease

Neil Cashman[1,2], Ebrima Gibbs[2], Judith Silverman[2*], Beibei Zhao[1], Juliane Coutts[2], Ian Mackenzie[2], Xubiao Peng[2#], Steven Plotkin[2], Johanne Kaplan[1]
[1]ProMIS Neurosciences, Cambridge, USA; [2]University of British Columbia, Vancouver, Canada

Background

A large body of evidence indicates that the most pathogenic species of amyloid-beta (Aβ) in Alzheimer's disease (AD) consists of soluble toxic oligomers (AβO) as opposed to insoluble fibrils and monomers. Clinical results to date indicate that non-selective antibodies that bind Aβ monomers, oligomers and plaque fail to provide a therapeutic benefit. Partially selective antibodies that bind AβO and plaque have shown improved success but are associated with dose-limiting adverse events (amyloid-related imaging abnormalities, ARIA). These findings suggest that antibodies capable of selectively neutralizing toxic AβO may achieve improved efficacy and safety. Monoclonal antibody PMN310 was raised against a conformational epitope predicted by computational modeling to be exposed on toxic AβO but not monomers or fibrils. A summary of the selectivity and protective activity of PMN310 against toxic AβO *in vitro* and *in vivo* is presented.

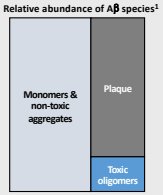
Methods

The binding selectivity of PMN310 was characterized and compared to that of other Aβ-directed antibodies by surface plasmon resonance (SPR) and immunohistochemistry (IHC). Its ability to neutralize the propagation and toxicity of AβO was assessed in vitro in a thioflavin-T propagation assay and in cultures of primary rodent neurons, respectively. In vivo protective activity was tested in wild-type mice injected intracerebroventricularly (ICV) with AβO and in the APP/L transgenic mouse model of AD.

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 selective binding to oligomers, not monomers, and strong binding to a toxic oligomer-enriched fraction from AD brain
- PMN310 protected against the pathogenic activity of Aβ oligomers *in vitro*, and preserved memory function in two rodent models of AD
- PMN310 targeting of toxic Aβ oligomers was minimally impacted by monomer competition. Antibodies that were outcompeted by pre-exposure to monomers showed no clinical benefit in phase 2/3 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, avoiding diversion away from toxic oligomers and suggesting that it may reduce the risk of ARIA 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

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

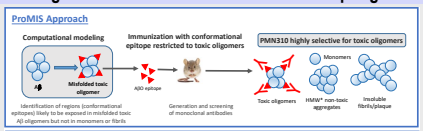


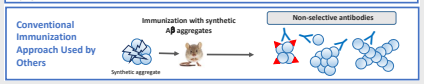
[1]Goure et al, Alz Res & Ther, 2014

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)

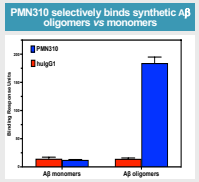
2. ProMIS computational platform *vs* conventional immunization allowed for the generation of PMN310 selective for toxic Aβ oligomers

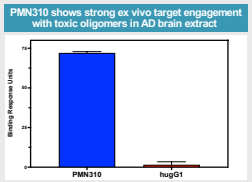




*HMW = High molecular weight

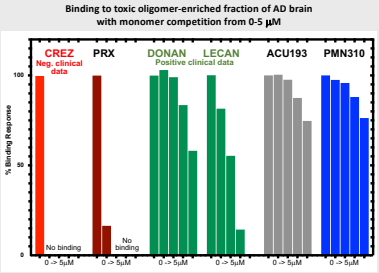
3. PMN310 targets a conformational epitope present on Aβ oligomers, not monomers





Surface plasmon resonance (SPR) was used to measure the binding of immobilized PMN310, or a human IgG1 isotype control (huIgG1), to synthetic Aβ monomers or oligomers, and to the toxic oligomer-enriched low molecular weight fraction of soluble AD brain extract (~8-70 kDa).

4. In a side-by-side comparison of Aβ antibodies, PMN310 binding to AD brain toxic oligomers was minimally impacted by monomer competition, a potential correlate of clinical efficacy

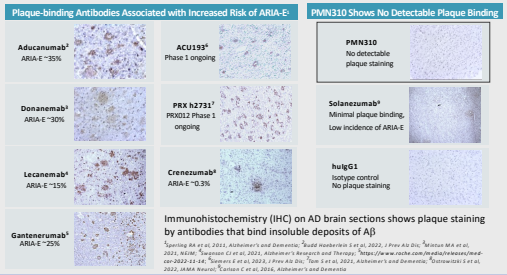


- Monomer concentrations: 0, 0.08, 0.3, 1.25, 5 μM
- CREZ: crenezumab, PRX: Prothena PRX h2371, DONAN: donanemab, LECAN: lecanemab. All comparator antibodies are biosimilars.
- Percent binding response: [(Binding response units (BRU) with monomers) / (BRU without monomers)] X 100

- Antibodies with positive clinical trial data (donanemab, lecanemab, aducanumab*) resisted monomer competition, retaining binding to toxic oligomers
- **PMN310 targeting of toxic Aβ oligomers was minimally impacted by monomer competition.** Similar pattern with ACU193
- Antibodies with negative clinical data (crenezumab, solanezumab*, gantenerumab*) did not bind toxic oligomers in the face of monomer competition. Also observed with PRX h2371.
- ***In vivo*, plaque binding (not captured in this assay) will result in additional target distraction for all antibodies except PMN310**

*Not shown here: solanezumab, gantenerumab sensitive to monomer competition; aducanumab more resistant

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



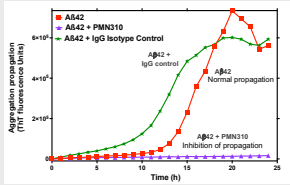
Immunohistochemistry (IHC) on AD brain sections shows plaque staining by antibodies that bind insoluble deposits of Aβ

[1]Sperling RA et al, 2011, Alzheimer's and Dementia; [2]Budd Haeberlein S et al, 2022, J Prev Alz Dis; [3]Ketton MA et al, 2021, NEJM; [4]Swanson CJ et al, 2021, Alzheimer's Research and Therapy; [5]https://www.roche.com/media/releases/med-cor-2022-14.htt; [6]Sevigny J et al, 2024, J Prev Alz Dis; [7]Sim J et al, 2021, Alzheimer's and Dementia; [8]Ostrowitzki S et al, 2022, JAMA Neurol; [9]Cartoon C et al, 2016, Alzheimer's and Dementia

6. PMN310 inhibits *in vitro* propagation and toxicity of Aβ oligomers

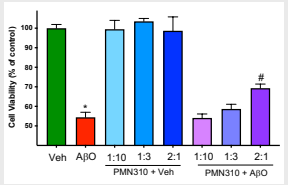
Complete inhibition of aggregation propagation

(Thioflavin-based assay)



Dose-dependent inhibition of Aβ oligomer toxicity

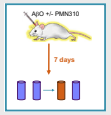
(Primary mouse cortical neurons)

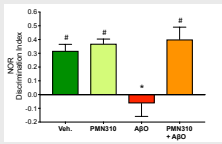


*Veh *vs* AβO, $p<0.0001$
#AβO *vs* PMN310 + AβO, $p=0.0112$

7. PMN310 preserves memory and learning in two AD mouse models

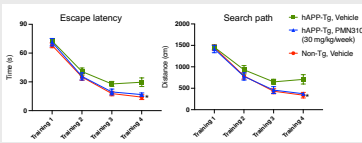
PMN310 prevents short-term memory loss caused by toxic oligomers in a novel object recognition (NOR) assay

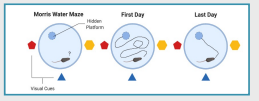




Discrimination index = (Time exploring new object – time exploring familiar object) / total exploration time.
Gibbs et al, 2019, Scientific Reports

PMN310 delivered systemically corrects the cognitive defect of hAPP/L transgenic mice in the Morris Water Maze task





*Veh *vs* AβO, $p<0.0001$; #AβO *vs* PMN310 + AβO, $p=0.0112$

[*]Current address: Bill & Melinda Gates Foundation, Seattle, USA; [#]Current address: Beijing Institute of Technology, Beijing, China