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ProMIS™ Neurosciences

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

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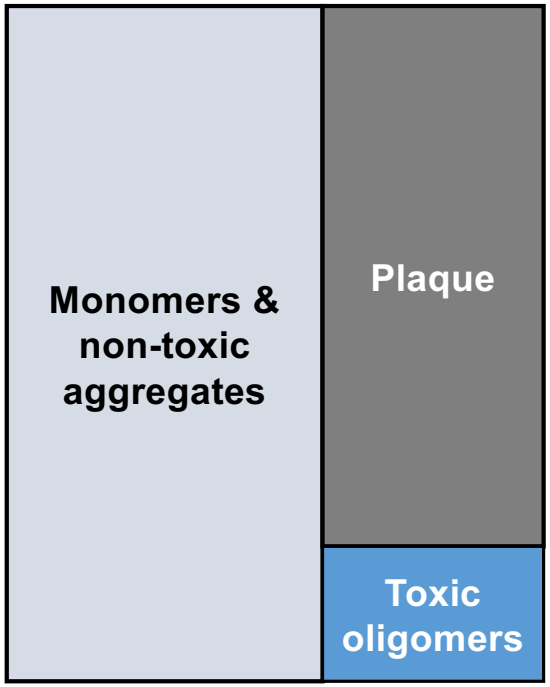
Disclosure

Employee of ProMIS Neurosciences

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

Relative abundance of Aβ species[1]



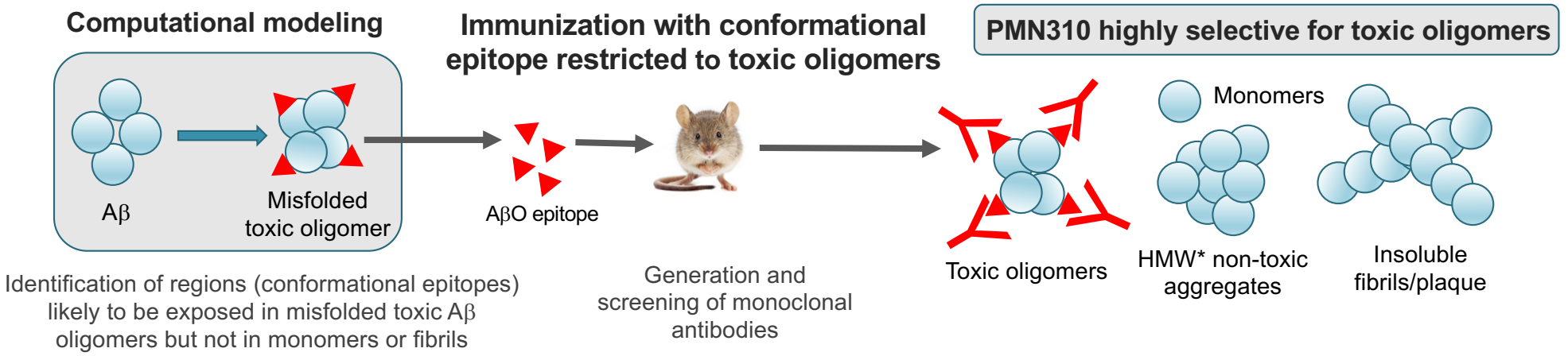
[1]Goure et al, Alz Res & Ther, 2014

The Challenge

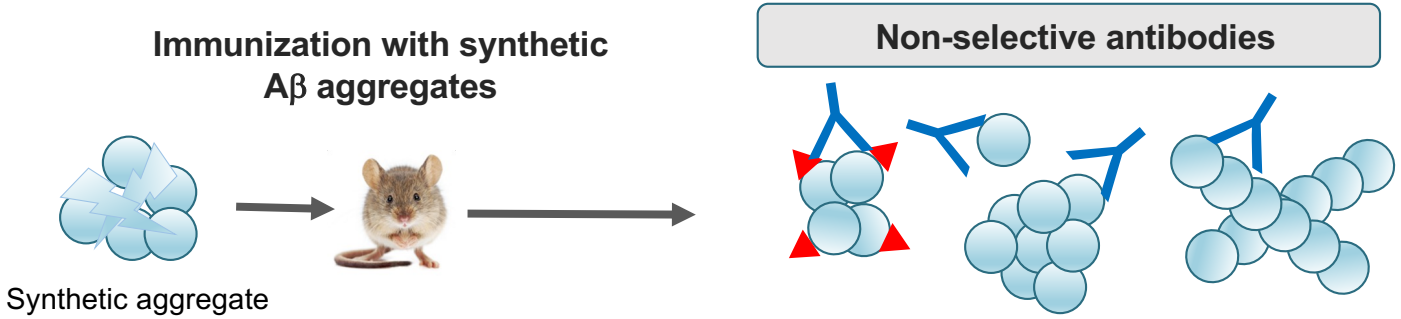
- **Aβ oligomers are a major driver of Alzheimer's disease but are much less abundant than other forms of Aβ (monomers, non-toxic aggregates, plaque)**
- **Antibodies that bind monomers are directed away from the toxic oligomer target, reducing efficacy**
- **Antibodies that bind plaque are associated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

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

ProMIS Approach



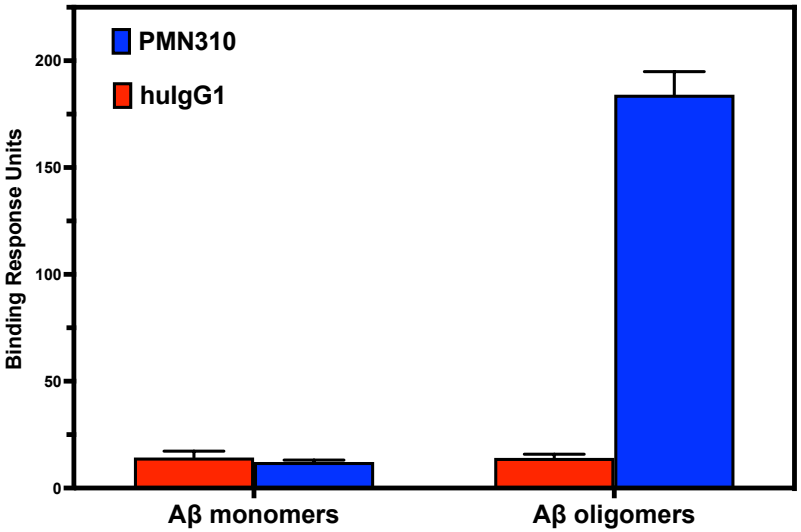
Conventional Immunization Approach Used by Others



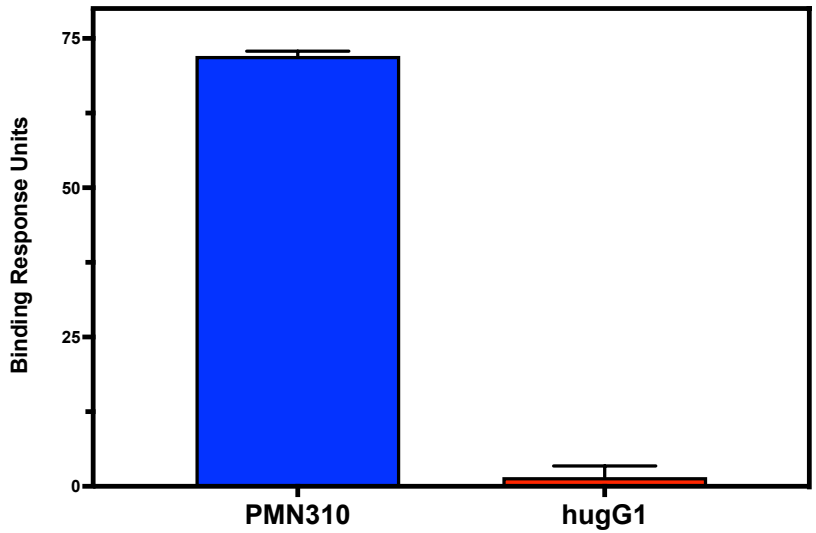
*HMW = High molecular weight

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

PMN310 selectively binds synthetic Aβ oligomers vs monomers

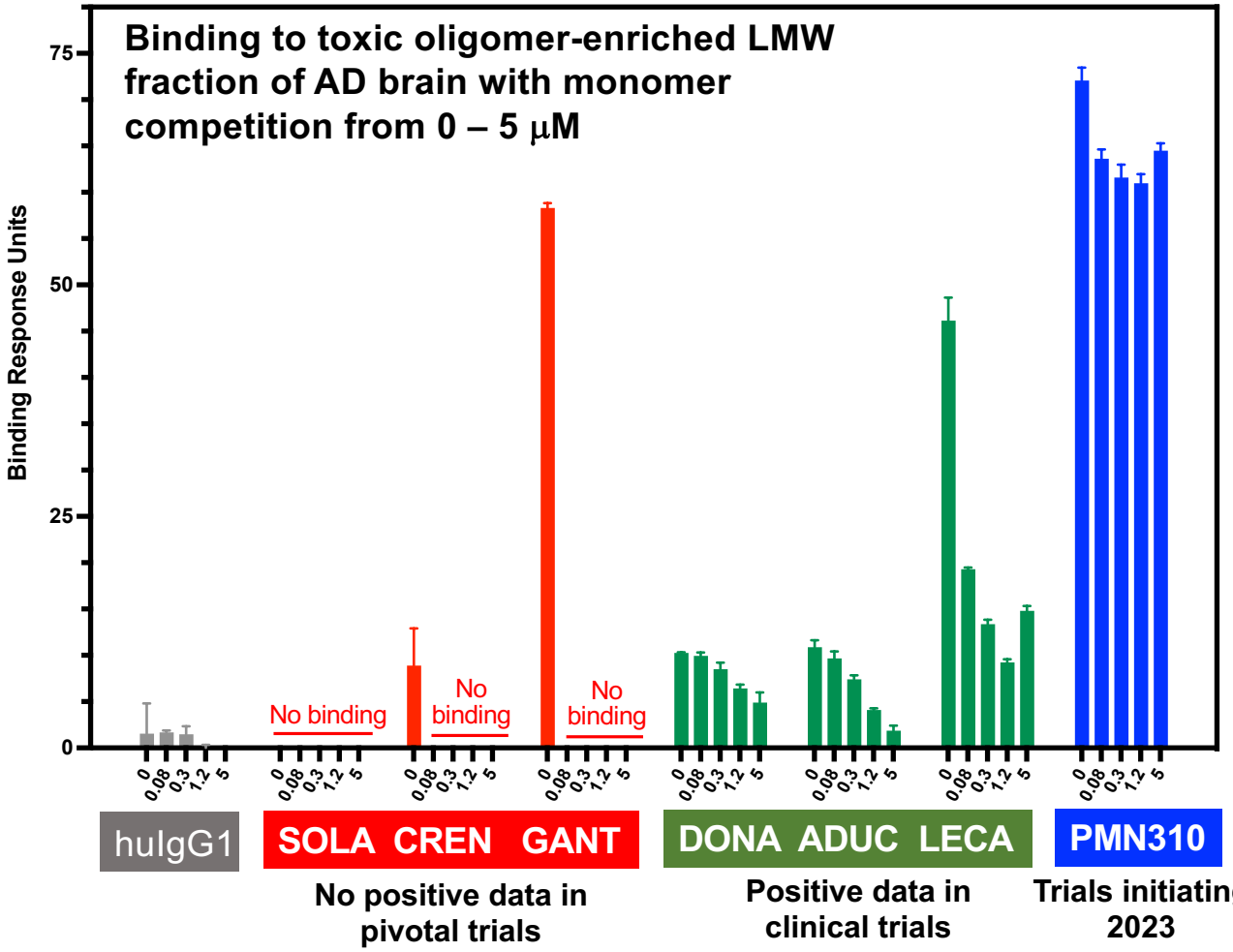


PMN310 shows strong ex vivo target engagement with toxic oligomers in Alzheimer's brain extract



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)

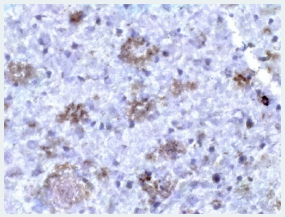
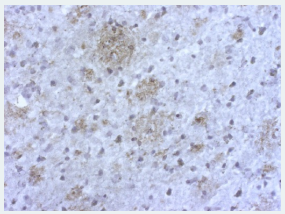
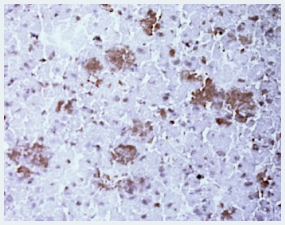
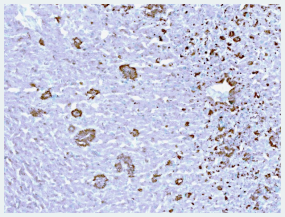
In a side-by-side comparison of Aβ antibodies, PMN310 binding to AD brain toxic oligomers was the least impacted by monomer competition, a potential correlate of clinical efficacy



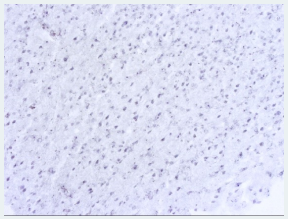
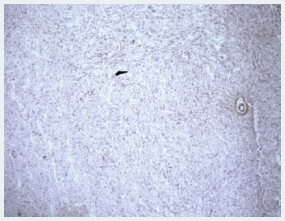
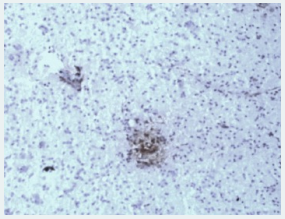
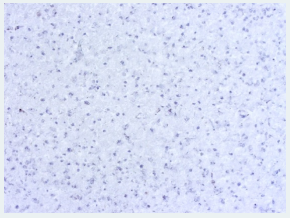
- Antibodies that failed in the clinic had toxic oligomer binding negated by monomer exposure
- Antibodies with positive clinical trial data were more resistant to monomer competition and retained significant binding to toxic oligomers
- **PMN310 targeting of toxic Aβ oligomers was the least impacted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

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

Plaque-binding Antibodies Associated with Increased Risk of ARIA-E[1]

Dose limited to 10mg/kg		**Aducanumab[2]** ARIA-E ~35%
Dose limited to 20mg/kg		**Donanemab[3]** ARIA-E ~30%
Dose limited to 10mg/kg		**Lecanemab[4]** ARIA-E ~15%
Negative phase 3 data		**Gantenerumab[5]** ARIA-E ~25%

PMN310 Shows No Detectable Plaque Binding

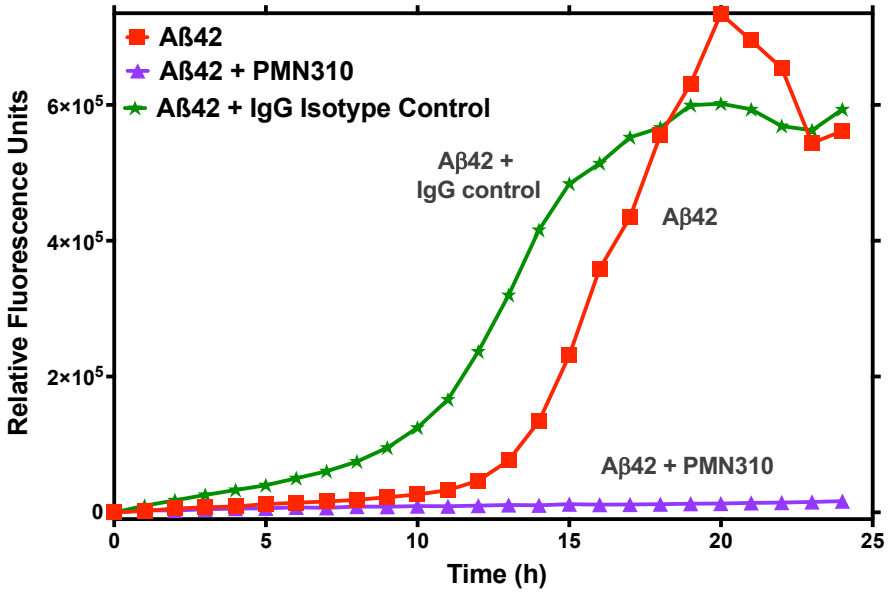
	**PMN310** No detectable plaque staining
	**Solanezumab[6]** Minimal plaque binding, Low incidence of ARIA-E
	**Crenezumab[7]** ARIA-E ~0.3%
	**huIgG1** Isotype control No plaque staining

[1]Sperling RA et al, 2011, Alzheimer's and Dementia; [2]Budd Haeberlein S et al, 2022, J Prev Alz Dis; [3]Mintun 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-2022-11-14; [6]Carlson C et al, 2016, Alzheimer's and Dementia; [7]Ostrowitzki S et al, 2022, JAMA Neurol

PMN310 inhibits in vitro propagation and toxicity of Aβ oligomers

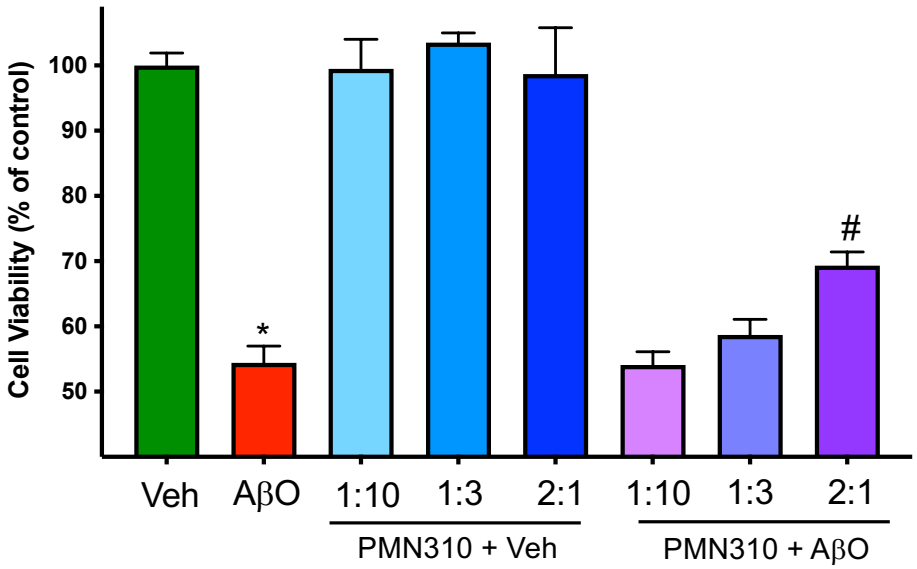
Complete inhibition of aggregation propagation

(Thioflavin-based assay)



Dose-dependent inhibition of Aβ oligomer toxicity

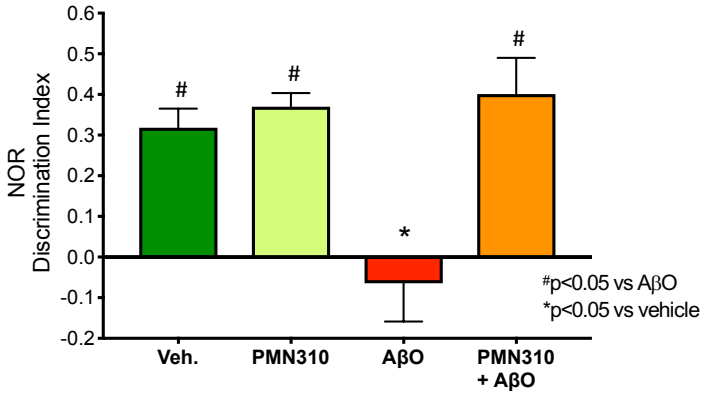
(Primary mouse cortical neurons)

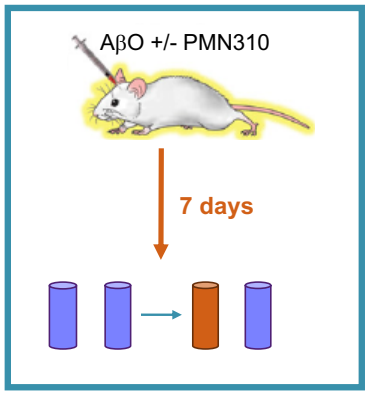


*Veh vs AβO, p<0.0001
#AβO vs PMN310 + AβO, p=0.0112

PMN310 preserves memory and learning in two AD mouse models

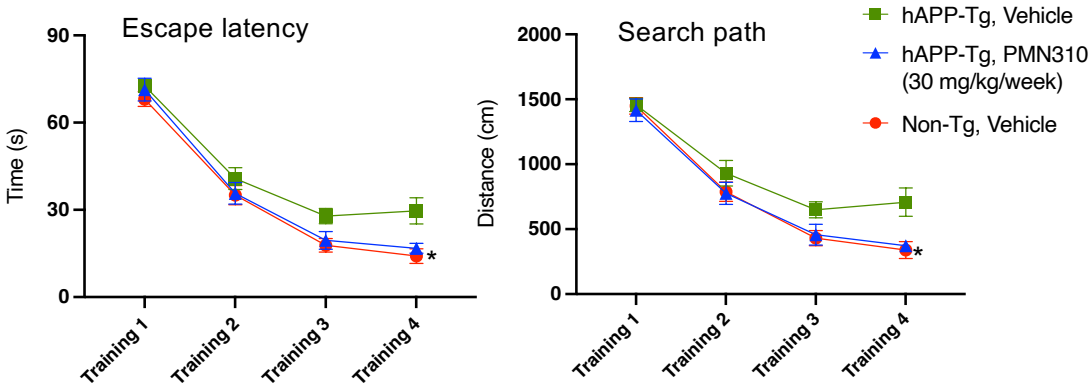
PMN310 prevents short-term memory loss caused by toxic oligomers in a novel object recognition (NOR) assay



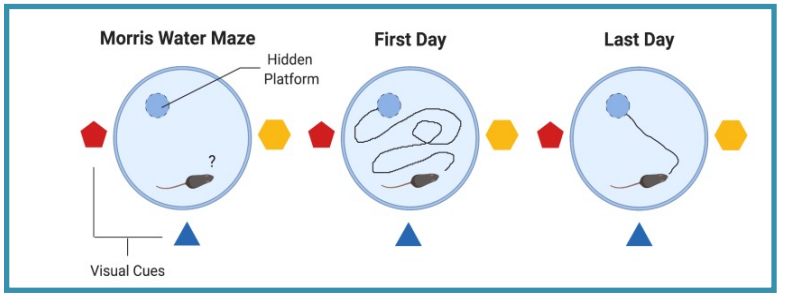


Gibbs et al, 2019, Scientific Reports; Discrimination index = (Time exploring new object – time exploring familiar object) / total exploration time.

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



*p<0.05 vs vehicle-treated hAPP-Tg for both vehicle-treated non-Tg and PMN310-treated Tg mice



Summary and Conclusion

- 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
- Compared to other Aβ-directed antibodies, PMN310 targeting of toxic Aβ oligomers was the least 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, 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