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

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

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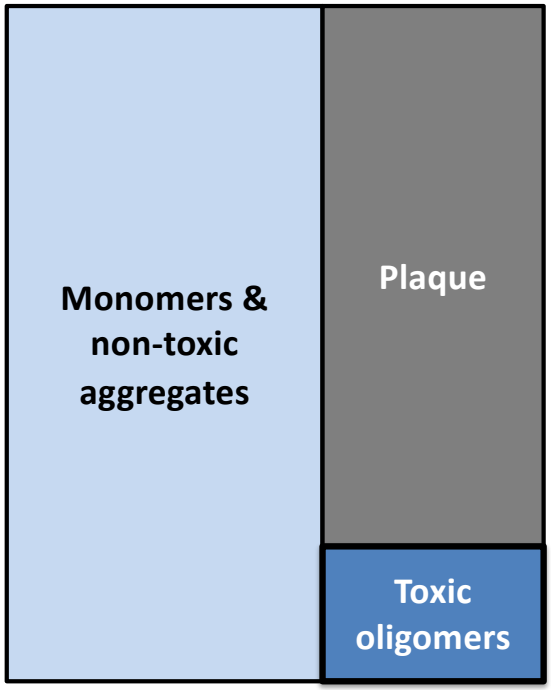
Relative abundance of Aβ species[1]



[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

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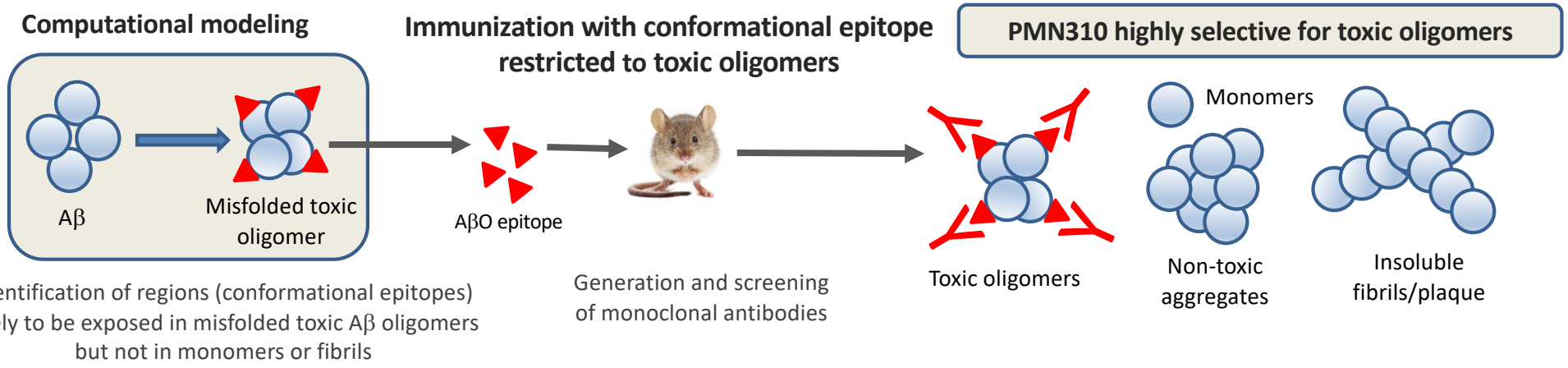
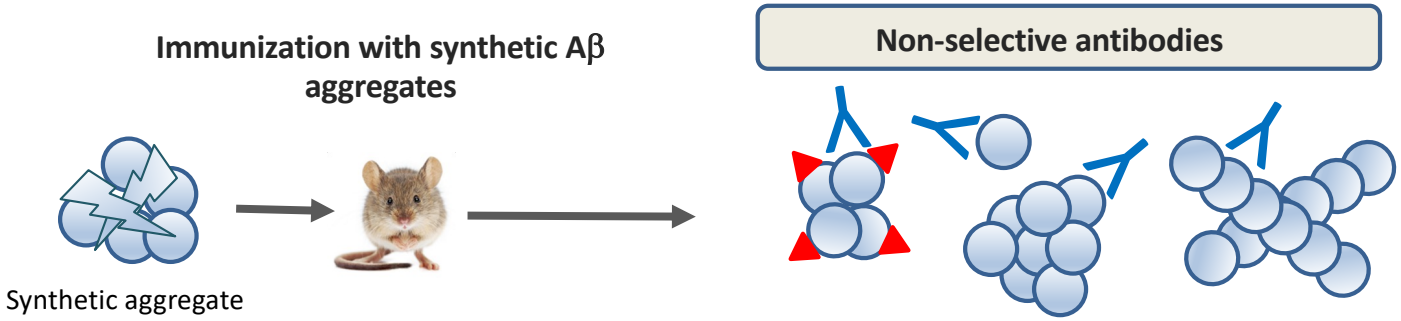
ProMIS Approach



Conventional Immunization Approach Used by Others



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

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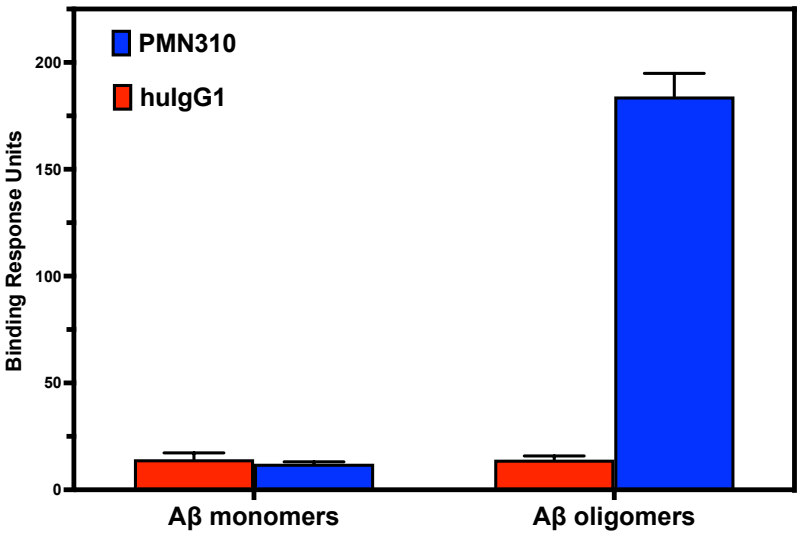
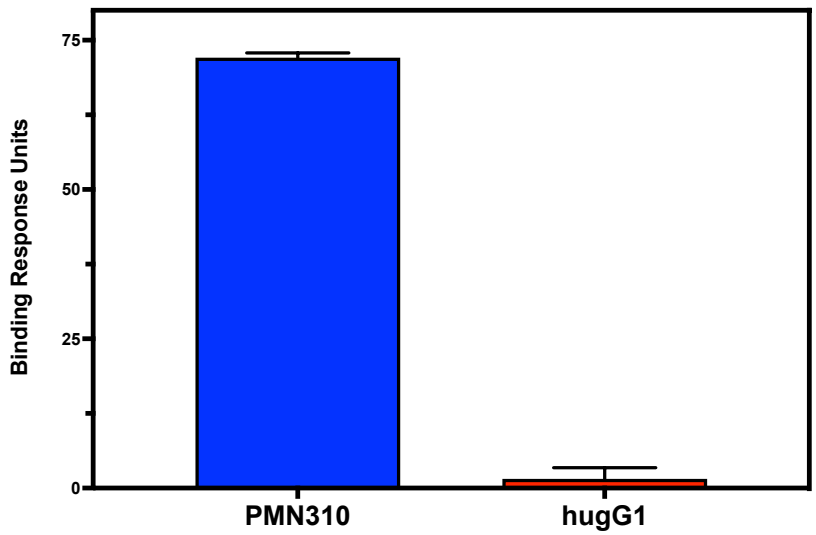
PMN310 selectively binds synthetic Aβ oligomers vs monomers



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)

PMN310 binding to toxic oligomers is minimally impacted by monomer competition, a potential correlate of clinical efficacy

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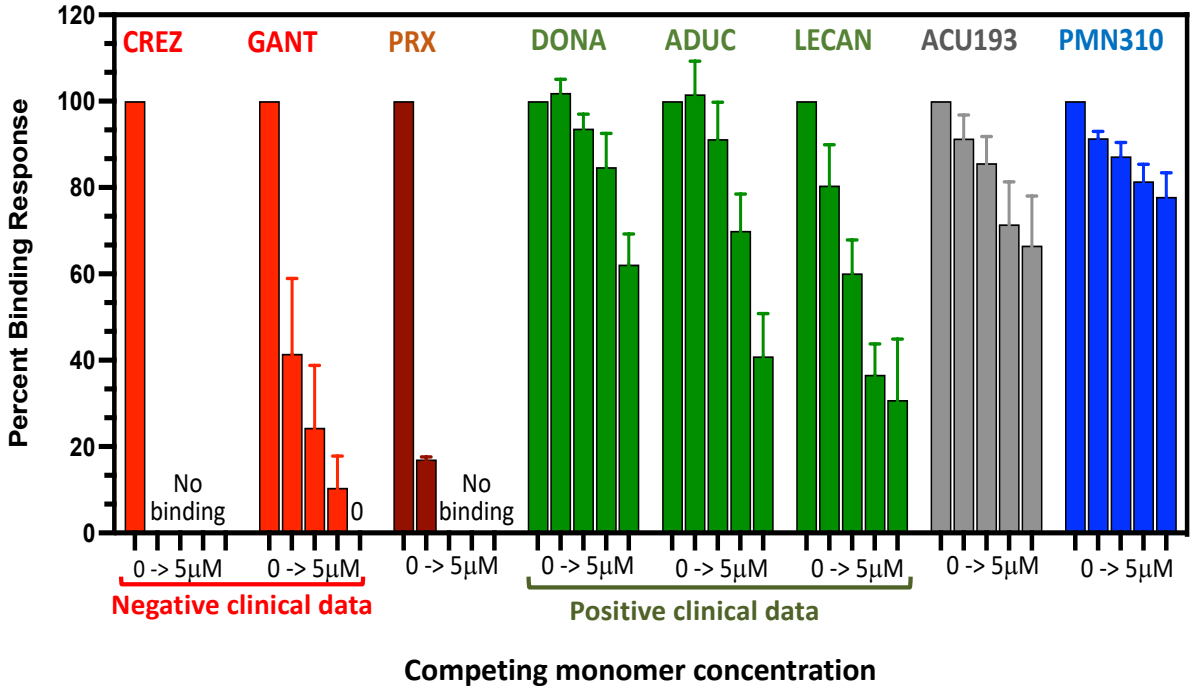
Binding to toxic oligomer-enriched fraction of AD brain with monomer competition from 0-5 μM



- Antibodies that failed in the clinic had toxic oligomer binding abrogated 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

SPR measurement of immobilized antibody binding to the LMW fraction of soluble AD brain extract after pre-exposure to monomer concentration ranging from 0 (100% binding), 0.08, 0.3, 1.25, and 5 μM. Percent binding response was calculated as: [(BRU) with monomers) / (BRU without monomers)] X100. Mean + SEM of combined data from 6 independent studies.

Ability to overcome monomer competition for binding to Aβ oligomers correlates with cognitive benefit in Phase 3, pivotal trials

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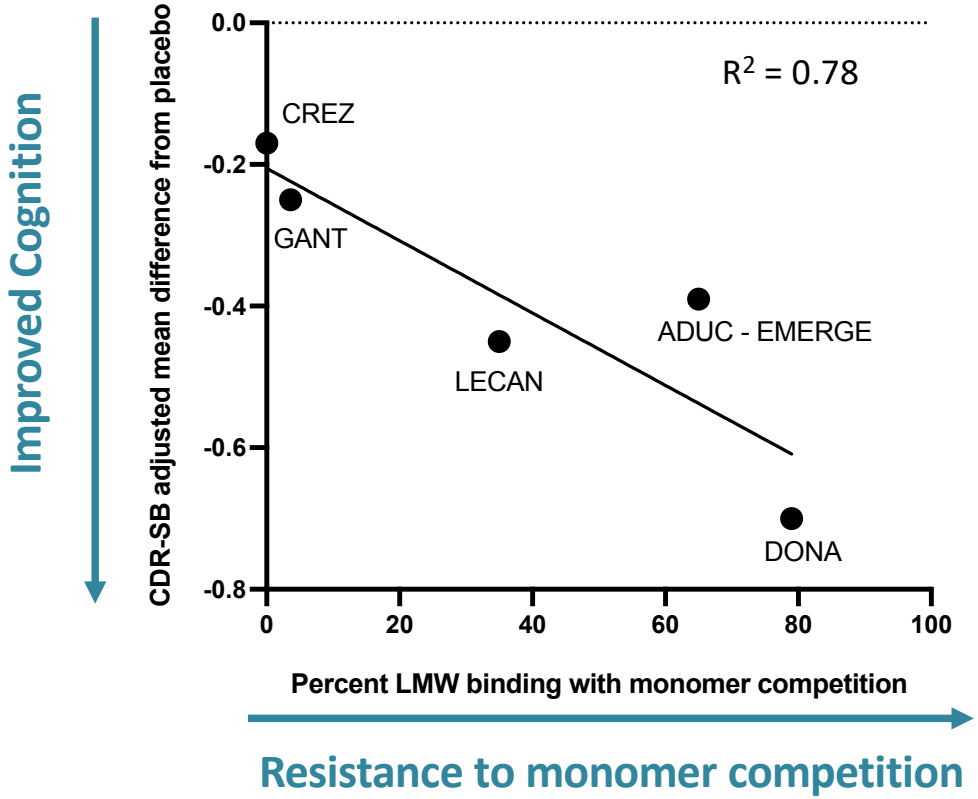

PMN310 inhibits in vitro propagation and toxicity of Aβ oligomers

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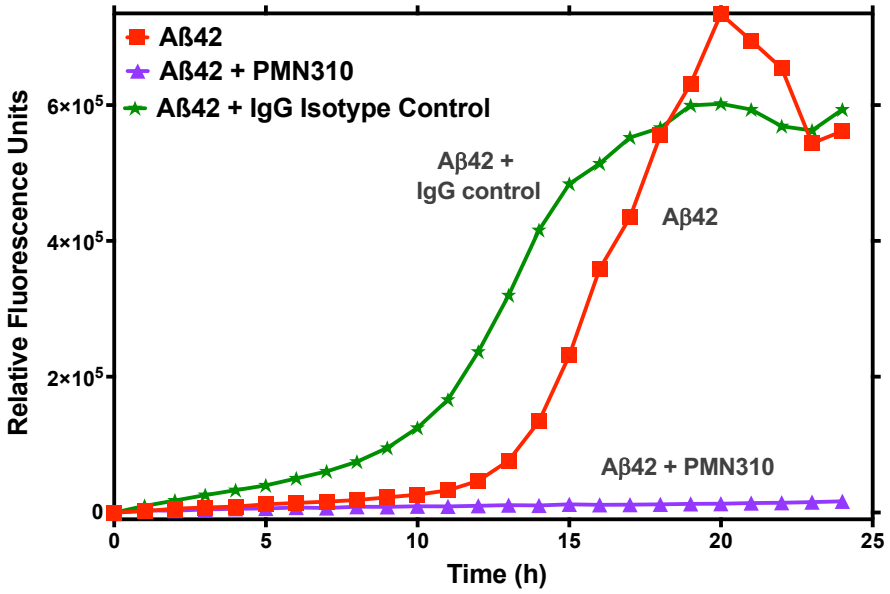
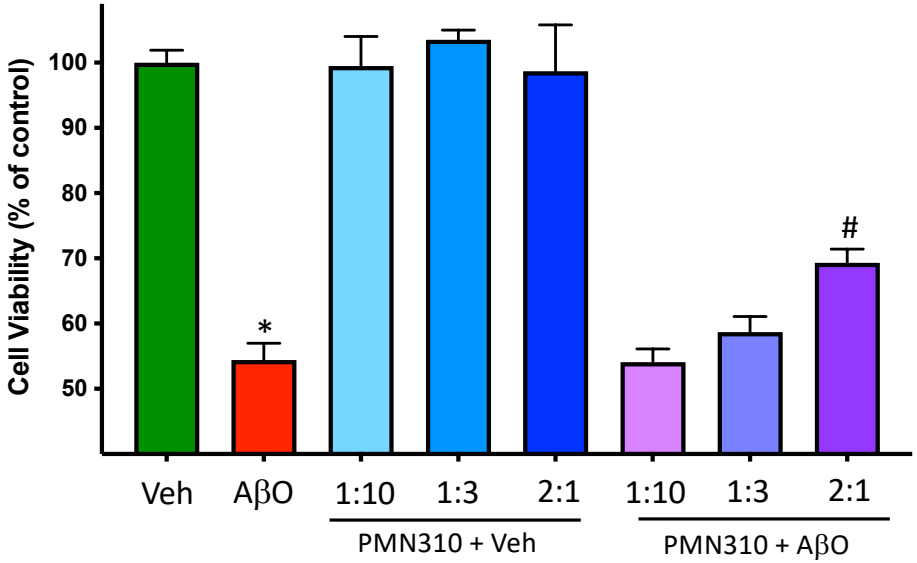
Complete inhibition of aggregation propagation

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

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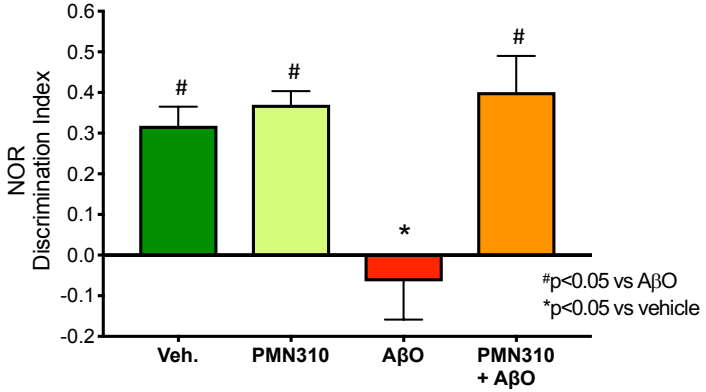
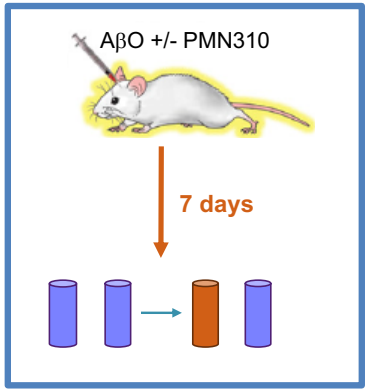
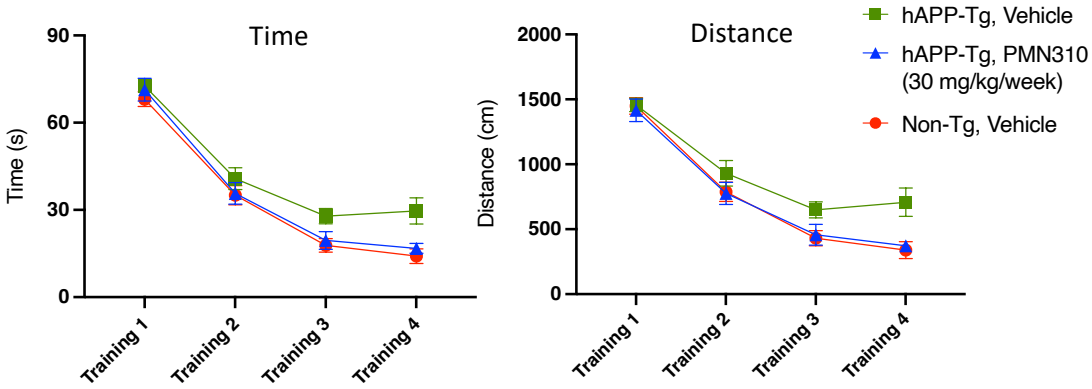
PMN310 prevents short-term memory loss caused by toxic oligomers in a novel object recognition (NOR) assay



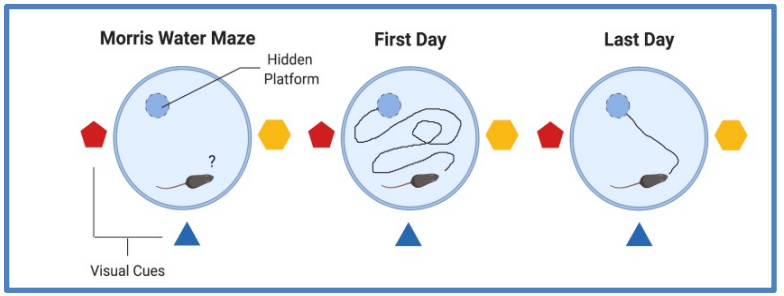


Gibbs et al, 2019, Scientific Reports; Discrimination index = (Time exploring new object – time exploring familiar object) / total exploration time.

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



PMN310 does not bind plaque, expected to avoid ARIA

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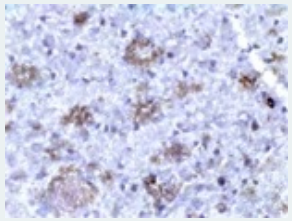
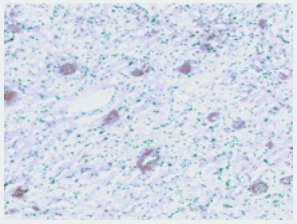
Plaque-binding antibodies associated with increased risk of ARIA-E

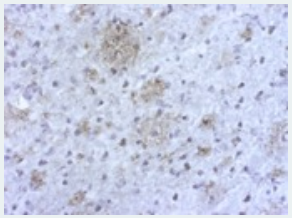
Aducanumab
ARIA-E ~35%



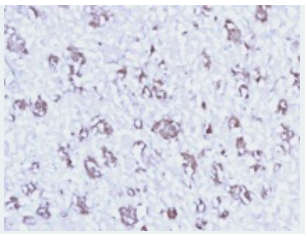
ACU193
Phase 1 – ARIA-E 21.4% at top dose



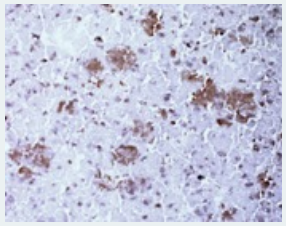
Donanemab
ARIA-E ~30%



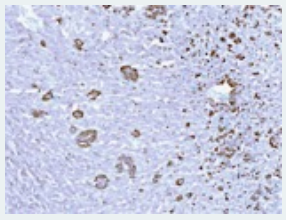
PRX h2731
PRX012 Phase 1 ongoing



Lecanemab
ARIA-E ~15%

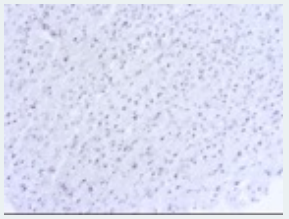


Gantenerumab
ARIA-E ~25%



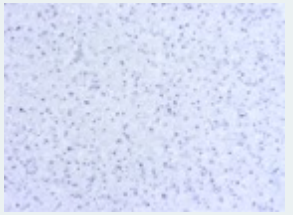
PMN310 shows no detectable plaque binding

PMN310
No detectable plaque staining
Expected efficacy without ARIA-E



Solanezumab
Minimal plaque binding - Low incidence of ARIA-E
Targets monomers – No efficacy

huIgG1
Negative control
No plaque staining



Reported ARIA rates: Sperling RA et al, 2011, Alzheimer's and Dementia; Budd Haeberlein S et al, 2022, J Prev Alz Dis; Mintun MA et al, 2021, NEJM; Swanson CJ et al, 2021, Alzheimer's Research and Therapy; https://www.roche.com/media/releases/med-cor-2022-11-14; Siemers E et al, 2023, J Prev Alz Dis; Tam S et al, 2021, Alzheimer's and Dementia; Ostrowitzki S et al, 2022, JAMA Neurol
Scale bars = 50 μm

High dose treatment with PMN310 does not cause microhemorrhages (ARIA-H) in AD mice

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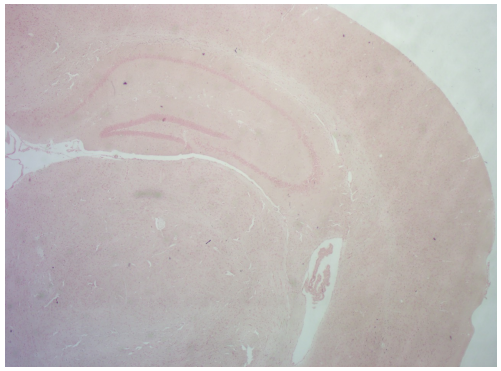
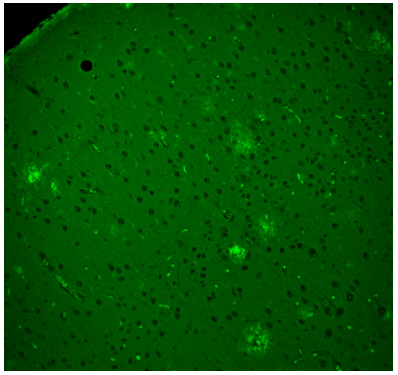
PMN310 - 800 mg/kg/week for 26 weeks

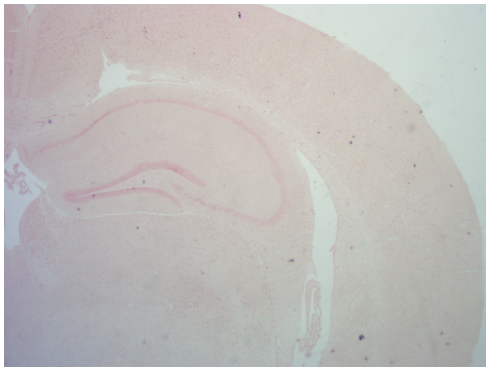
Vehicle control

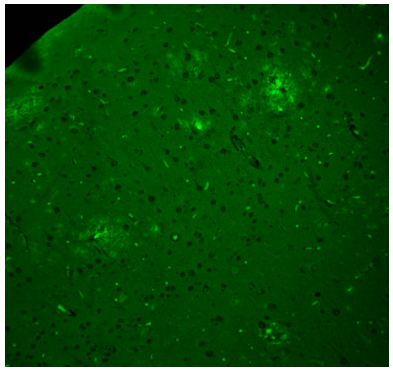


Perls' stain – No microhemorrhage



Amylo-Glo – Plaque present





- Transgenic *B6.Cg-App*$^{tm1.1Dnli}$*/J* mice dosed weekly for 26 weeks with murine version of PMN310 (800 mg/kg) or with vehicle (placebo)
- Brain sections from 29 vehicle control mice and 29 PMN310-treated mice were examined

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 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 and did not trigger microhemorrhages in an AD mouse model, 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
- Phase 1a trial in normal human volunteers completed. Initiation of Phase 1b in AD patients planned for 2024.

Acknowledgments

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