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JULY 27-31 > TORONTO, CANADA, AND ONLINE

Protein misfolding-specific epitope identification for passive and active immunotherapy of neurodegeneration

Dr. Neil Cashman

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Dr Cashman is Co-Founder and Chief Scientific Officer of ProMIS Neurosciences

ProMIS Neurosciences Inc. is a **clinical stage** biotech company focused on developing novel therapies for **neurodegenerative diseases**

Leveraging its **proprietary, AI-based platform, EpiSelect™**, to engineer disease specific antibodies that selectively bind to toxic misfolded proteins to **slow or halt disease progression**, with minimal off-target effects

ProMIS™ Neurosciences

Lead candidate (PMN310) is a humanized mAb selectively targeting toxic Aβ oligomers driving **Alzheimer's Disease**; Ph1b POC study ongoing**, interim data expected 1H26, top-line data expected 2H26**

PMN310 is designed to be **differentiated** in its ability to selectively target only the toxic oligomers, avoiding plaque, potentially **reducing or eliminating ARIA liability; FDA Fast Track designation** granted for treatment of Alzheimer's disease

Multiple preclinical pipeline candidates in neurodegenerative diseases, including **ALS, FTD, MSA, PD, and Aβ and α-synuclein vaccines;** additional co-development opportunities available leveraging EpiSelect™ platform

ALS: Amyotrophic lateral sclerosis, FTD: Frontotemporal dementia, MSA: Multiple system atrophy

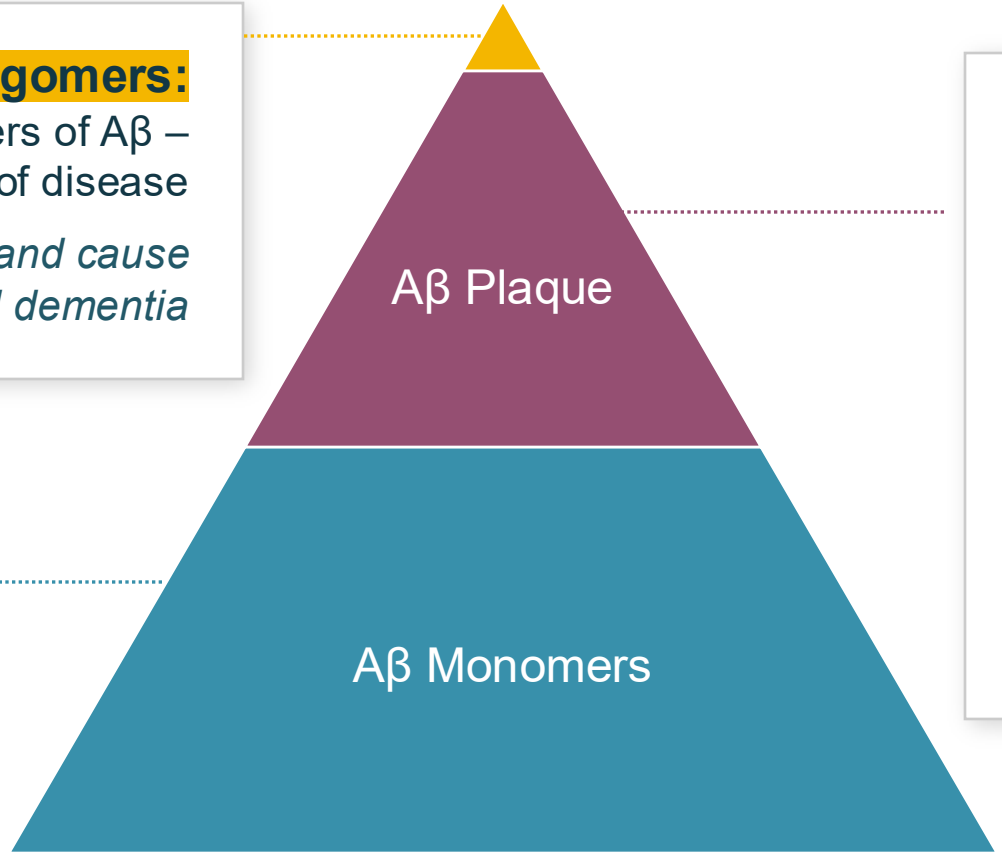
Amyloid-beta protein exists in different forms and different concentrations

Highly toxic Aβ Oligomers:
Small, soluble clusters of Aβ – Main driver of disease

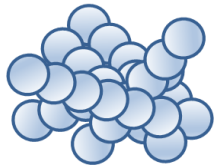
Damage the brain cells and cause cognitive decline and dementia

Aβ Monomers:
Abundant, produced over lifetime

Have a beneficial biologic role



Aβ Plaque:
Large, insoluble aggregates of Aβ



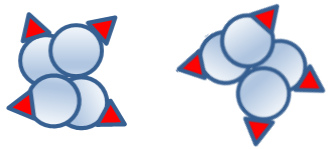
Form in spaces between nerve cells in the brain

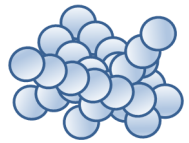
- Hallmark of Alzheimer's disease; can cause neuroinflammation but not a primary driver of disease
- Antibody binding to plaque is associated with increased risk of **ARIA**

ESTIMATED RELATIVE ABUNDANCE OF Aβ SPECIES

Goure et al, 2014, *Alz Res & Ther*

Importance of selectivity for toxic amyloid-β oligomers (AβOs)





Monomers	Oligomers	Plaque
Abundant, produced over lifetime *Have a beneficial biologic role*	Small, soluble clusters of Aβ – Main driver of disease *Damage the brain cells and cause cognitive decline and dementia*	Large, insoluble aggregates of Aβ *Form in spaces between nerve cells in the brain*

	Clinical Benefit
solanezumab	None
gantenerumab	None
crenezumab	None
lecanemab	Modest
aducanumab	Modest
donanemab	Modest
Ideal Specificity?	**Potentially high**

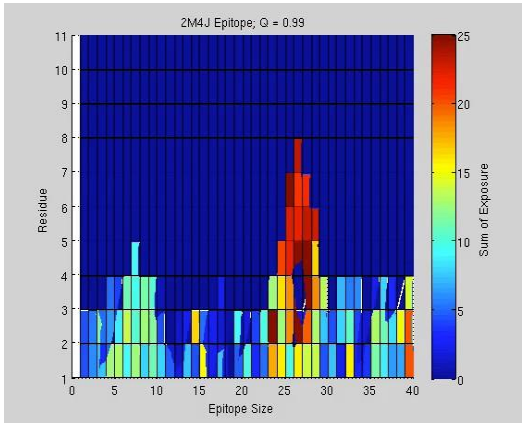
Note: No head-to-head clinical studies have been conducted

The ProMIS Platform: EpiSelect™

EpiSelect™ is a patented target discovery platform that applies a proprietary thermodynamic, computational algorithm to predict disease-specific epitopes on the molecular surface of misfolded proteins

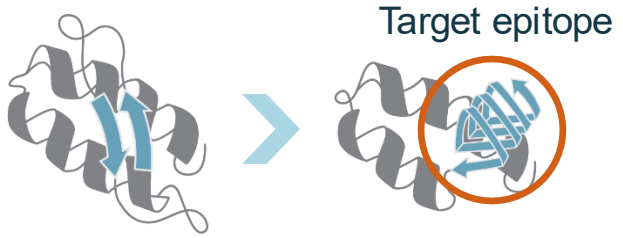
Can potentially be applied across a range of neurodegenerative diseases and other therapeutic areas given the broad presence of naturally occurring misfolded proteins causing debilitating disease

Computational Modeling



Proprietary algorithms are used to identify the parts of a protein that are likely to become exposed and misfolded

Predictive Analysis



Normal protein

Toxic misfolded protein

Protein structures are analyzed, allowing the platform to predict which regions are likely to misfold and form toxic aggregates

Target Epitope Construct

Target epitope construct

Conformational epitope is replicated as a cyclic peptide

Reference: *Collective Coordinates applied to SOD1*: Peng X, Cashman NR & Plotkin SS, J Phys Chem, 2018.
EpiSelect™ was formerly named Collective Coordinates.

The ProMIS Platform: EpiSelect™

Selective Antibody Development Driven by EpiSelect™

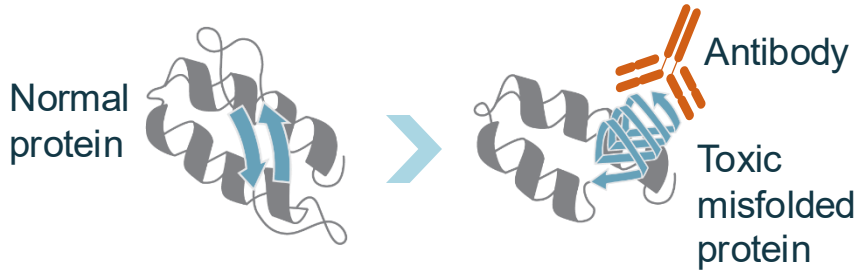
EpiSelect™ output enables efficient generation of selective antibodies that strongly bind disease-associated epitopes

Epitope Construct & Antibody Candidate Generation

Humanized IgG1 monoclonal antibodies with high effector function

Antibodies screened for selective neutralization of toxic misfolded form creating potential to slow or halt disease progression

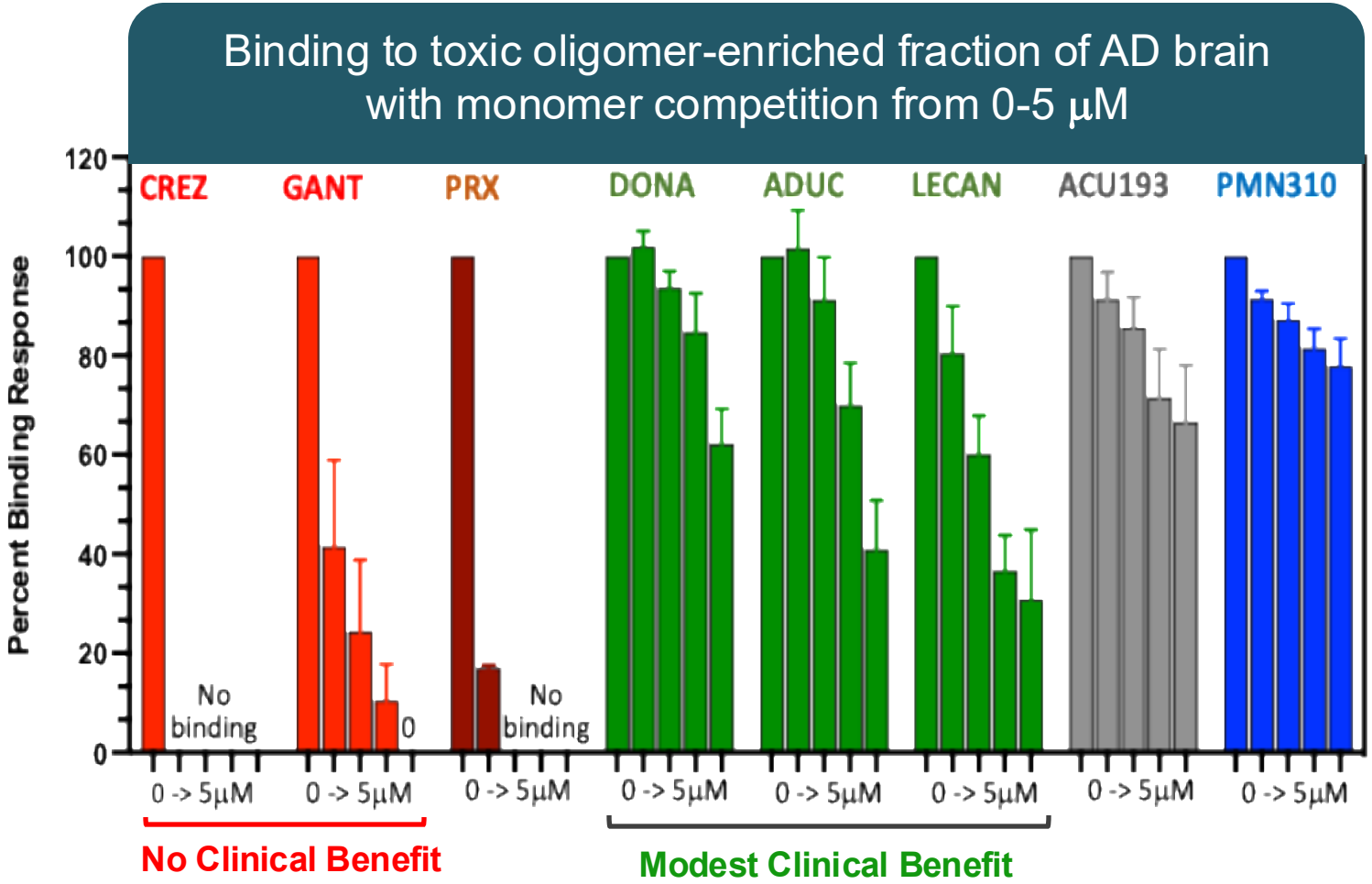
Screening for selectivity and protective activity



Potential to eliminate disease-causing toxic proteins without affecting the normal protein

PMN310 – Demonstrated best-in-class resistance to Aβ monomer competition

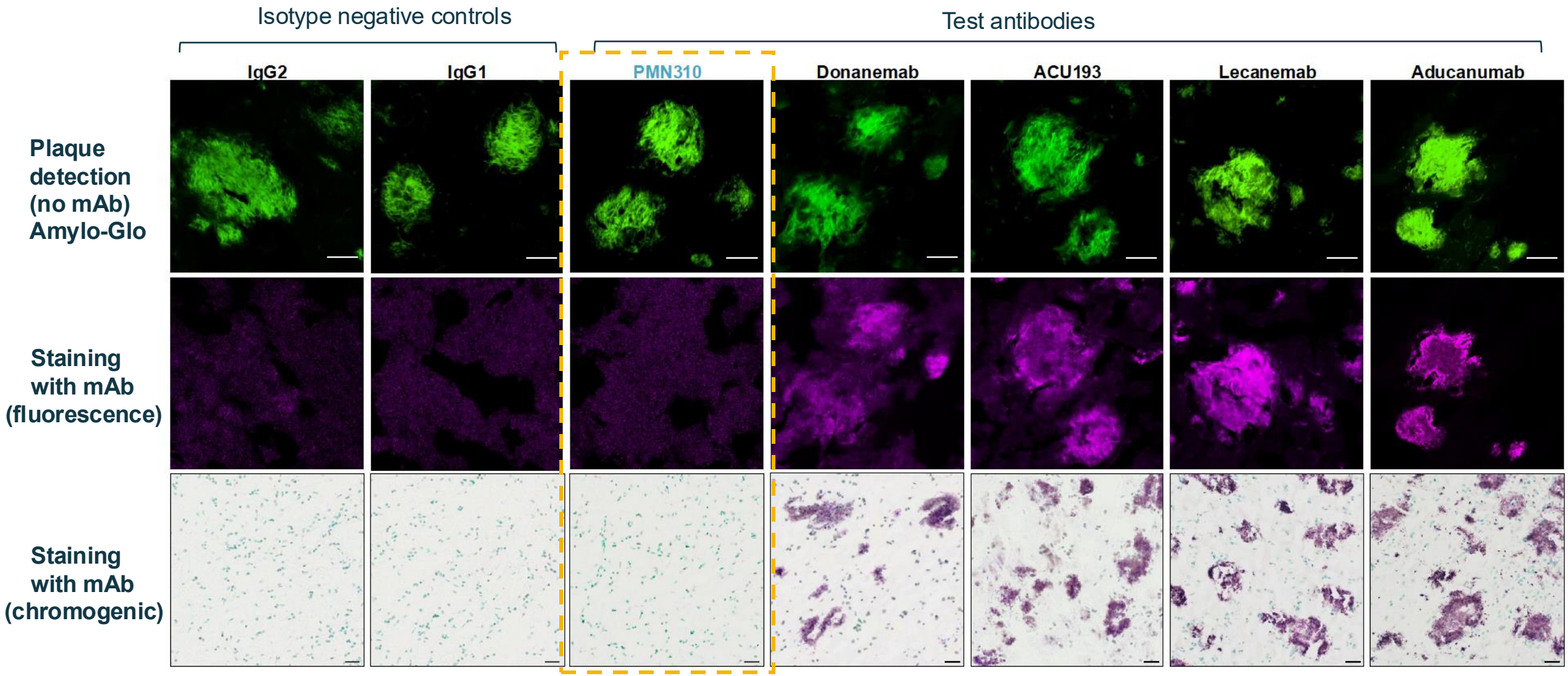
- Antibodies that failed in the clinic had toxic oligomer binding abrogated by monomer exposure
- Antibodies with positive clinical trial data were more resistant to monomer competition and retained significant binding to toxic oligomers
- **PMN310 targeting of toxic Aβ oligomers least impacted by monomer competition to date**



CREZ: crenezumab; **GANT**: gantenerumab; **PRX**: Prothena; **DONA**: donanemab; **ADUC**: aducanumab; **LECAN**: lecanemab; **ACU193**: Acumen mAb

Kaplan et al, 2024, *bioRxiv*, https://www.biorxiv.org/content/10.1101/2024.04.20.590412v2

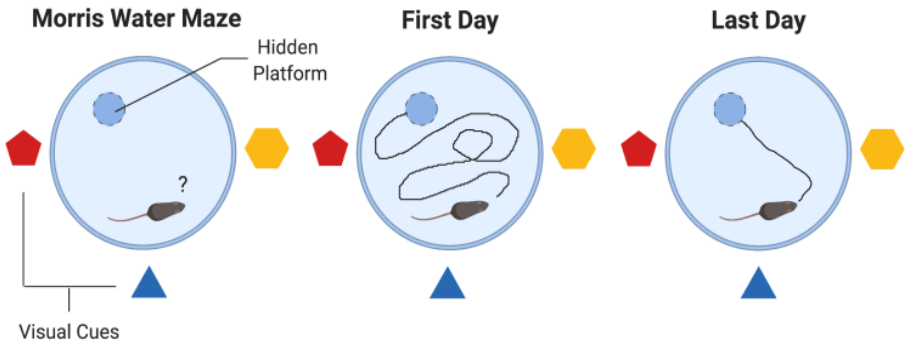
Quantitative immunofluorescence indicates PMN310 as the only antibody Tx with no plaque binding



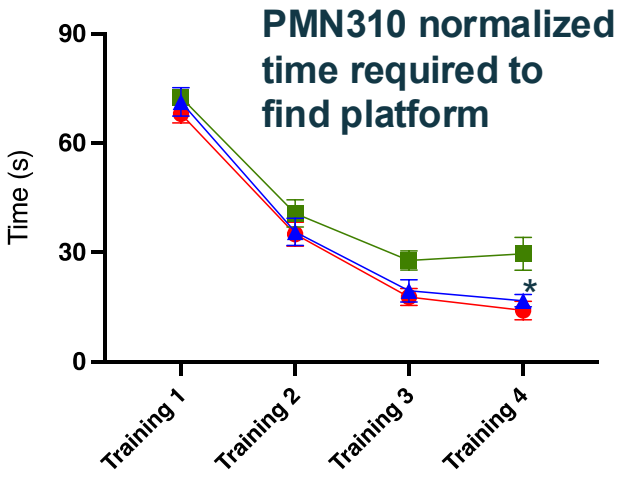
Staining conducted using 1.0 µg/ml concentration of each antibody; similar results achieved at 0.1 and 0.3 µg/ml of each antibody and quantification of plaque stain fluorescent intensity across concentrations can be provided upon request

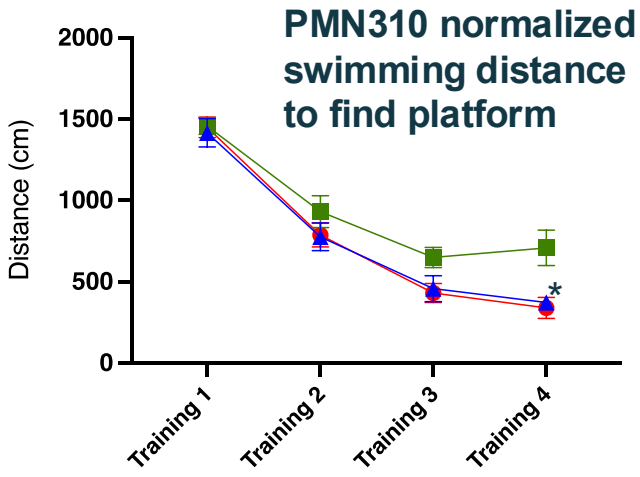
PMN310 preserves memory and learning in AD mouse model

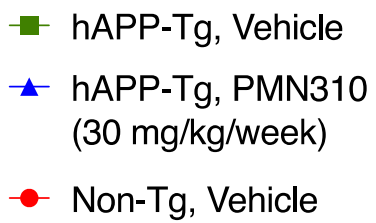
PMN310 delivered systemically corrected the cognitive defect of hAPP/L transgenic mice in the Morris Water Maze task



- **Morris Water Maze test:** Over successive training days, mice learn and remember where a hidden platform is located in a pool of water, reducing the time and swimming distance required to reach the platform.
- Mice transgenic for human APP-L have cognitive deficits and do not perform as well (more time, longer swimming distance needed)







Transgenic AD mice treated with PMN310 were completely protected and performed as well as normal mice.

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

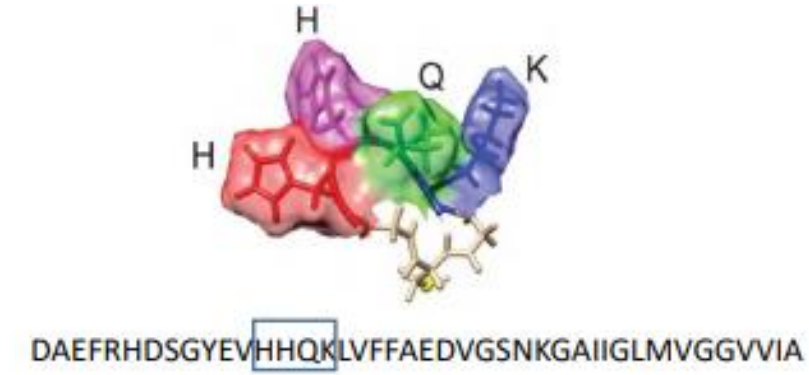
Kaplan et al, 2024, *bioRxiv*, https://www.biorxiv.org/content/10.1101/2024.04.20.590412v2

PMN310 Is Differentiated From other AD Antibody Therapies

Potential for Improved Efficacy

- Designed to selectively target **toxic oligomers that drive disease**
- **No sink effect** from off-target binding to plaque or monomers
- **Lower doses required** to achieve and sustain efficacy

Conformational epitope of PMN310



Potential for Improved Safety

- Avoidance of plaque expected to carry a **reduced risk of ARIA**
- No impact on efficacy anticipated since **elimination of plaque is not required** for significant clinical benefit

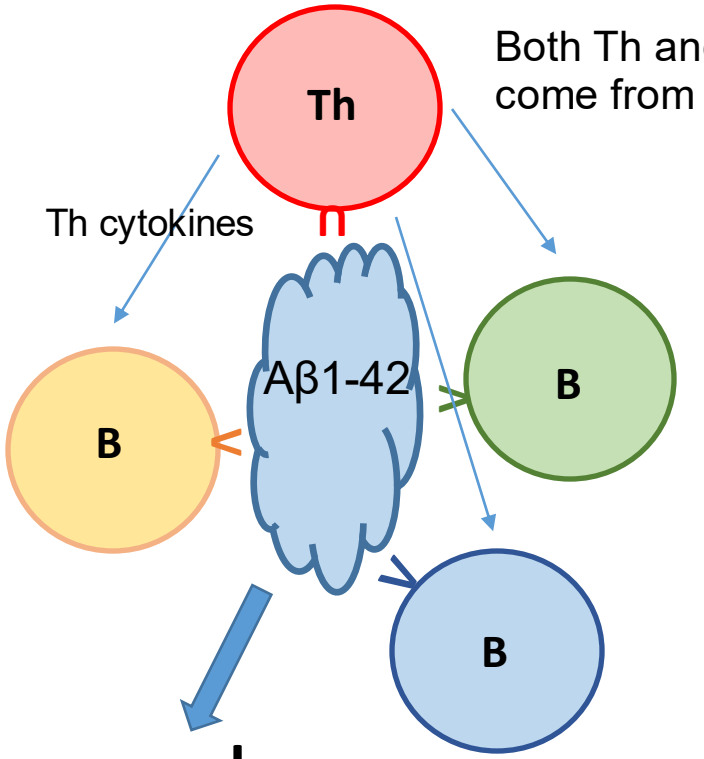
Potential for Improved Compliance

- **Monthly dosing** (half life in CNS = 27 days)
- Currently IV
- **Potential for SC dosing** if able to maximize efficacy at lower doses, given no sink effect (entire dose delivered to clinically relevant target - oligomers)

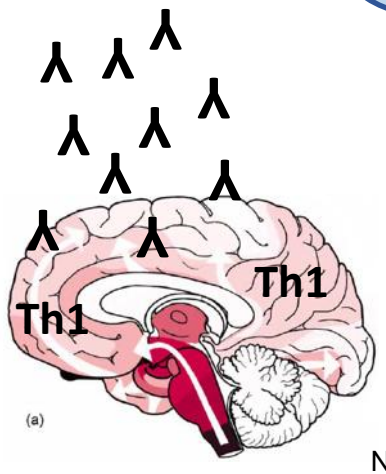
Expected to yield **more favorable benefit:risk profile** than recently approved amyloid-β disease modifying therapies (DMTs)*

* No head-to-head clinical studies have been conducted to date.

First generation Aβ vaccine (Elan)



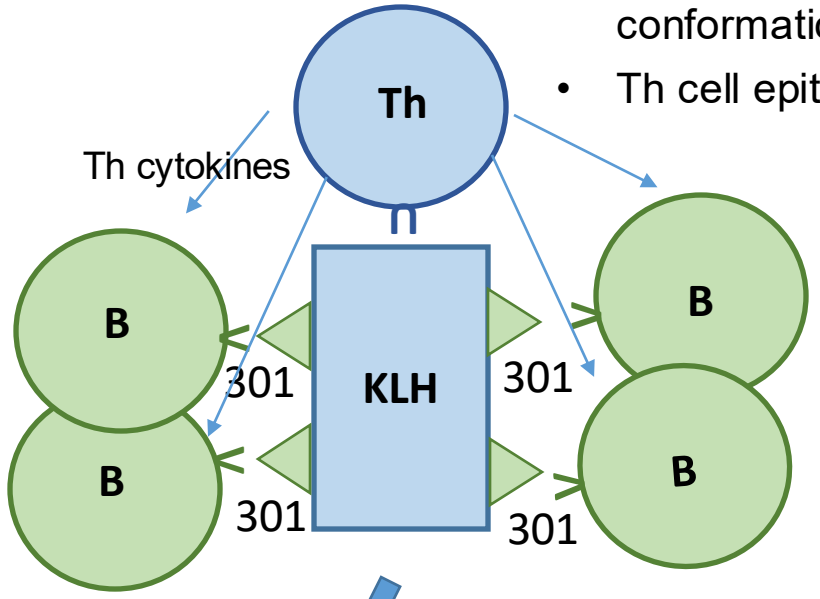
Both Th and B cell epitopes come from Aβ protein

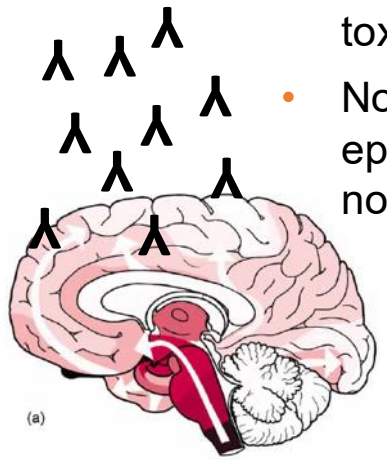


- Aβ B cell epitopes -> Non-selective antibody response to all forms of Aβ
- Aβ T helper epitopes -> Th1-driven meningoencephalitis upon recognition of epitope in the brain

Second generation ProMIS Aβ vaccine

- B cell epitope: ProMIS Aβ conformational peptide
- Th cell epitopes from KLH





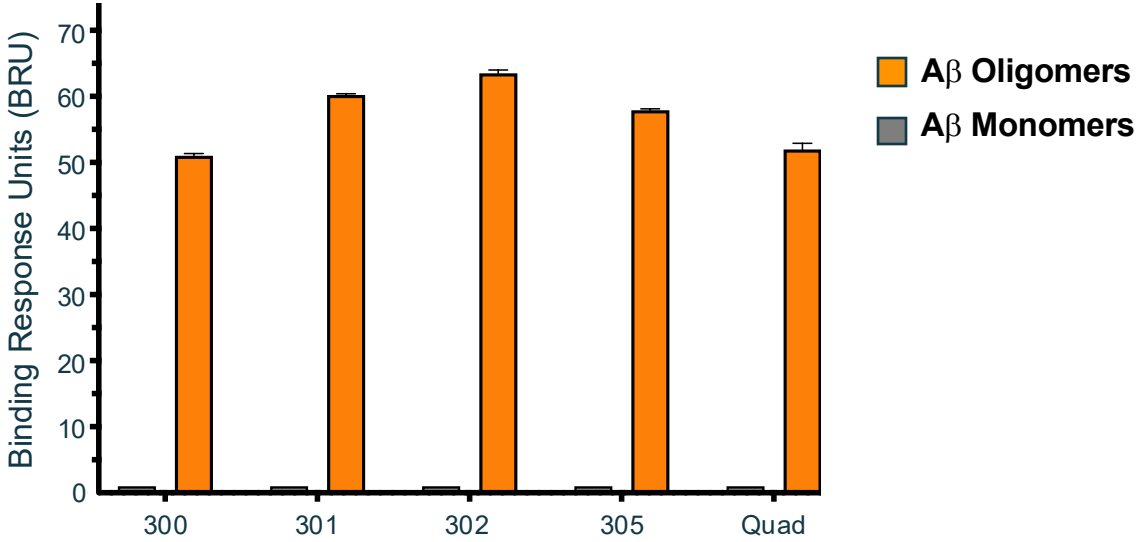
- Aβ conformational B cell epitope -> Antibody response selective for toxic Aβ oligomers
- No Aβ Th epitopes – KLH T helper epitopes not present in the brain, no meningoencephalitis

Note: T helper epitopes are presented on the surface of antigen-presenting cells in association with MHC Class II after uptake and processing of the vaccine. B cell epitopes in the vaccine are presented directly to B cells.

PMN311: Positive early results presented at AAIC 2024

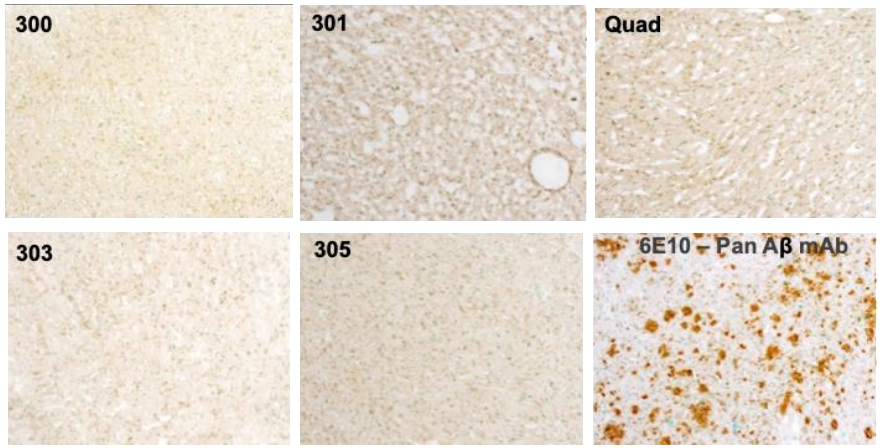
- Testing of 15 possible combinations of 1 to 4 conformational Aβ oligomer epitopes in mouse vaccination studies led to the selection of PMN311 as the lead vaccine candidate for further development.
- PMN311 is composed of a single epitope, the target of PMN310. It elicited maximal antibody binding to a toxic oligomer-enriched low molecular weight fraction of soluble AD brain extracts.
  No advantage of combination with additional epitopes.

Antibodies in immune sera bind Aβ oligomers and not monomers by surface plasmon resonance (SPR)



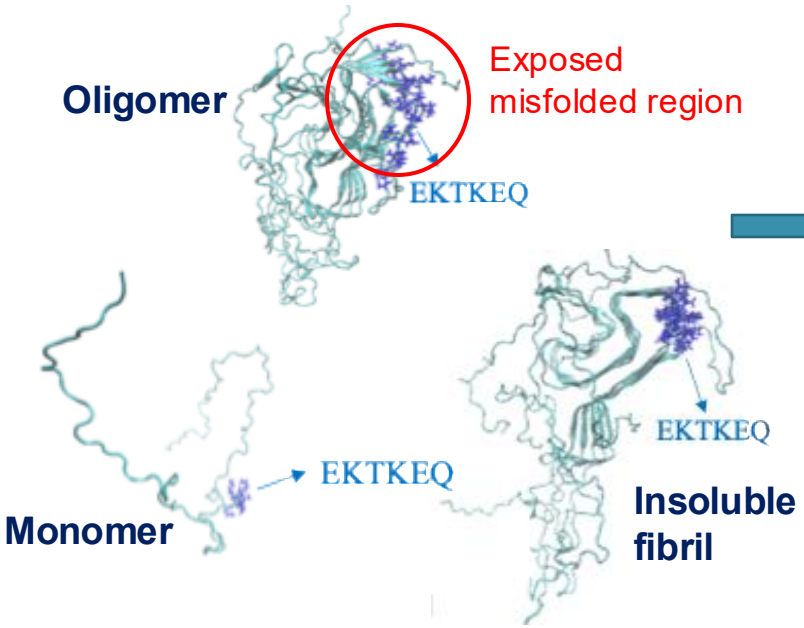
The antibodies induced by conformational AβO epitopes do not bind plaque in AD brain

> Oligomer-selective antibody response



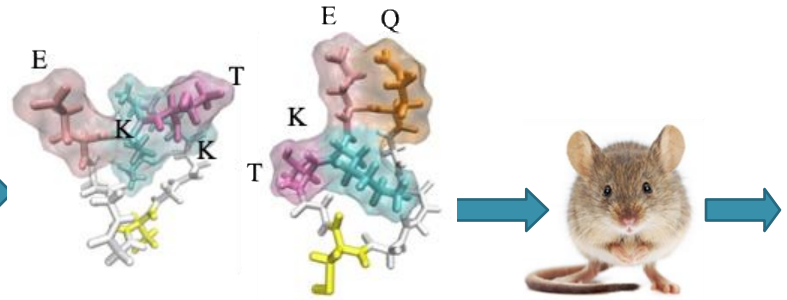
ProMIS platform applied to alpha-synuclein vaccine design

Computational Modeling



Identification of regions (conformational epitopes) likely to be exposed in toxic ASyn oligomers and small seeding fibrils but not in monomers or insoluble fibrils (Lewy bodies)

Vaccination with conformational alpha-synuclein epitopes

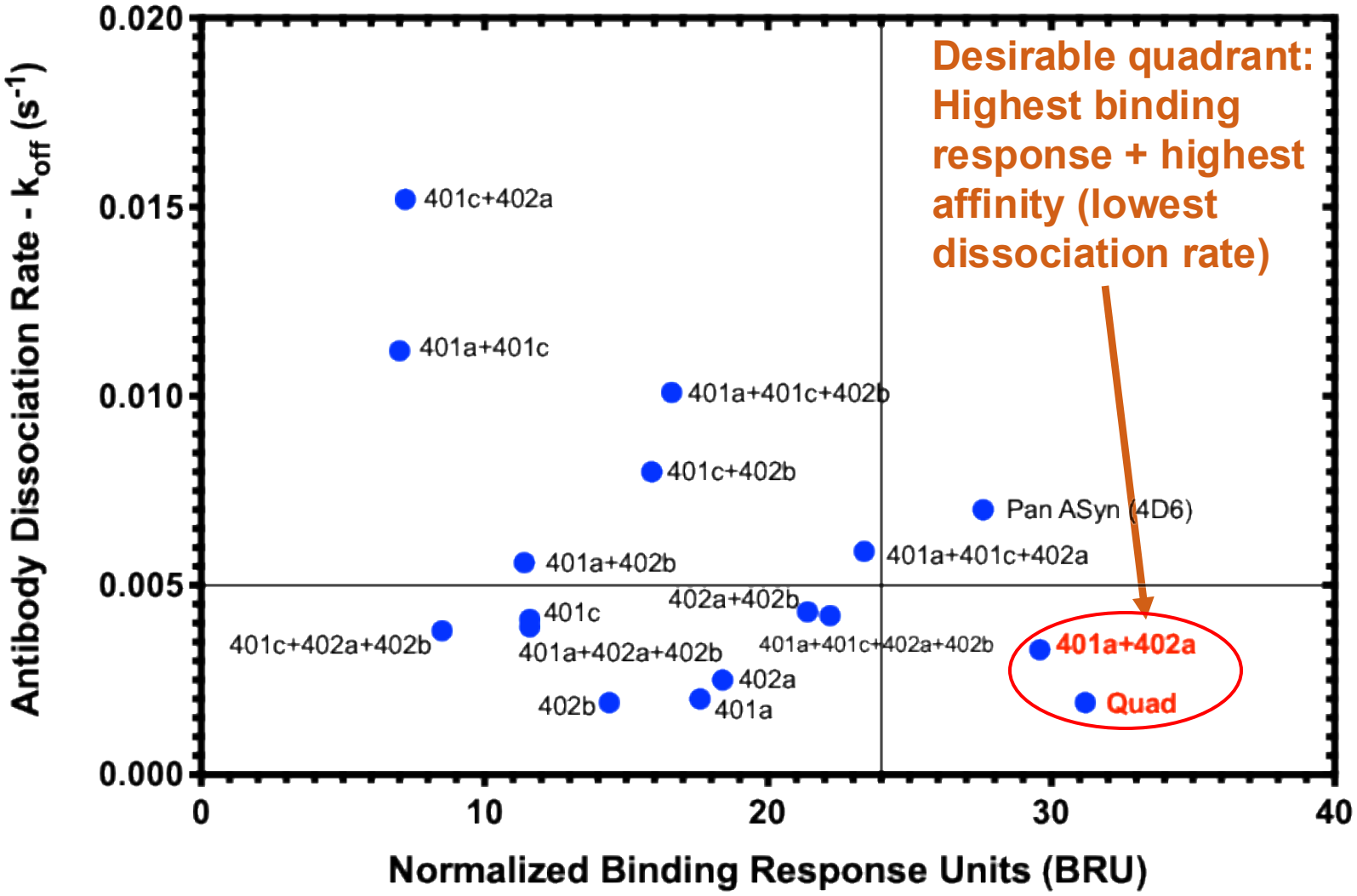


- Conformation of exposed, misfolded epitopes reproduced with cyclized peptides
- Coupled to KLH for T cell help
- QS-21 adjuvant

Read-outs

- ELISA IgG titers
- Selectivity profile
  - Pathogenic alpha-synuclein vs monomers (SPR)
  - Lewy bodies/neurites (IHC)
- Selection of optimal vaccine design
  - Reactivity of immune IgG with soluble toxic species from dementia with Lewy bodies (DLB) brains (SPR)

Maximal reactivity and highest affinity for DLB brain oligomers with immune IgG elicited by vaccination with two select conformational epitopes or a combination of all four

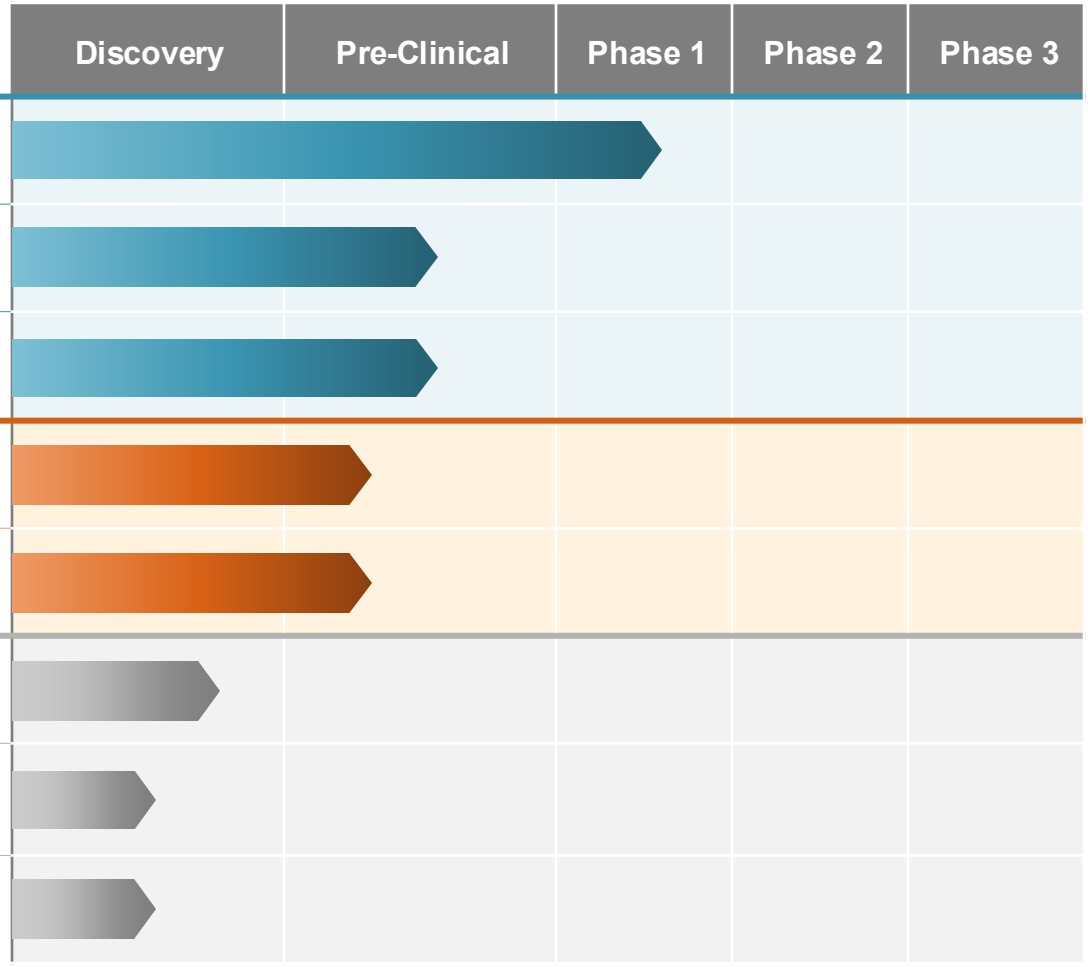


Active Immunotherapy Summary

- Vaccination with conformational B cell epitopes elicited antibodies with the desired selectivity for pathogenic AβOs and ASyn.
- The advantage of this approach, as opposed to inducing pan-Aβeta and pan-ASyn reactivity, is the potential to preserve normal Aβeta and ASyn function(s), and minimize the diversion of active antibody by the more abundant non-toxic forms of AβO and ASyn in blood and CNS.
- For AβO vaccine, lack of ARIA is anticipated.

The EpiSelect™ Platform generates a robust pipeline for targeting toxic misfolded proteins in neurodegenerative diseases

	Product Candidate	Target Protein	Disease Indication(s)
ANTIBODY	PMN310	Amyloid-Beta	AD
	PMN267	TDP-43	ALS
	PMN442	Alpha-Synuclein	MSA[1]
VACCINE	PMN440	Alpha-Synuclein Vaccine	Multiple synucleinopathies
	PMN311	Amyloid-Beta Vaccine	Alzheimer's Prevention
DISCOVERY		Tau	Alzheimer's[2], FTLD, PSP, CBD
		RACK1	ALS[2], HD
		DISC1+Interactome	Schizophrenia



[1] The company plans to investigate additional synucleinopathies, including PD: Parkinson's disease and dementia with Lewy bodies [2]Initial indication AD: Alzheimer's disease, ALS: Amyotrophic lateral sclerosis, MSA: Multiple system atrophy, HD: Huntington's disease, FTLD: Frontotemporal lobar degeneration, PSP: Progressive supranuclear palsy, CBD: Corticobasal degeneration

ProMIS™ Neurosciences

ProMIS Neurosciences
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-Scott Napper (U Saskatchewan)

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