ProMIS™ Neurosciences

ProMIS Neurosciences Overview
Targeting misfolded proteins in neurodegenerative diseases

NASDAQ ticker: PMN
Toronto Stock Exchange (TSX) ticker: PMN.TO
September 12, 2022

Forward looking statement: safe harbor

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Developing the next generation of neurodegenerative treatments

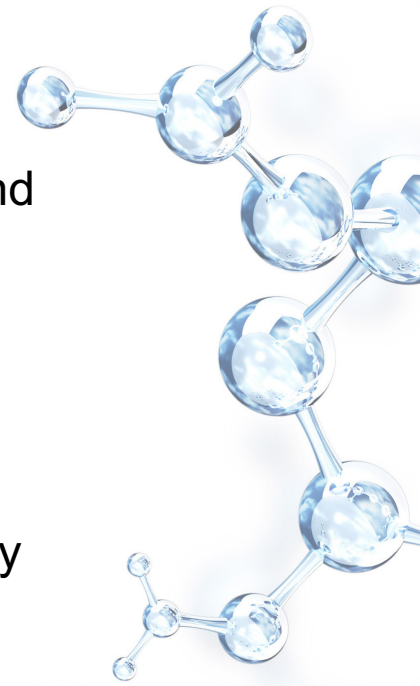
Current therapeutic approaches leave significant unmet need for highly selective, precision treatments

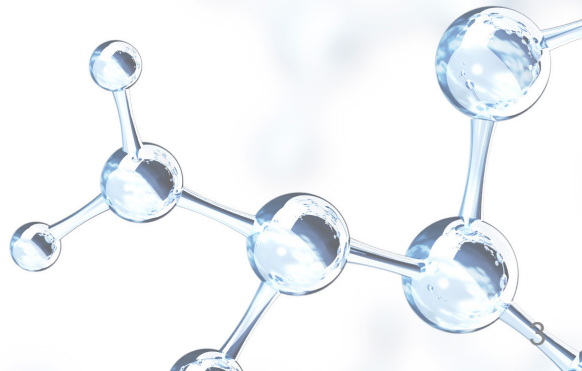
ProMIS' differentiated computational platform at the cross-section of science: biology and physics

Pipeline of highly selective antibodies for toxic misfolded proteins implicated in a wide range of neurodegenerative disorders

Lead program, PMN310 selectively targeting toxic, misfolded amyloid-beta on track for IND by year end

Leveraging of serum-based biomarkers designed to provide rapid insight into potential clinical benefits for all programs





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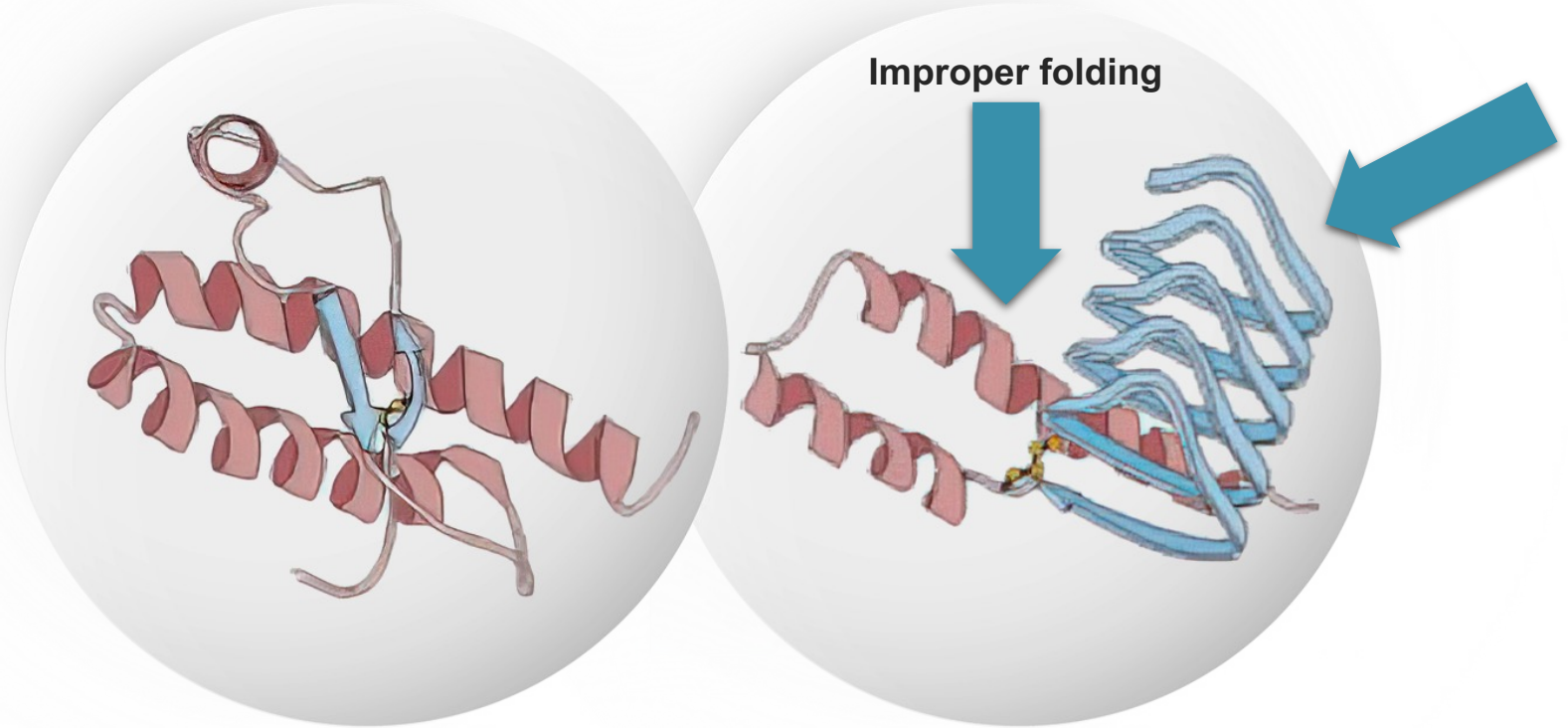
Unique computational platform designed to selectively target misfolded proteins: ProMIS differentiator



Normal protein
folds into a specific shape to perform its physiologic function

Toxic Form: Improper folding
exposes toxic portions of the protein in a particular shape or conformation

Conformational Epitope predicted by ProMIS platform

ProMIS platform is designed to predict conformational epitopes only exposed on toxic misfolded proteins

Immunizations with those epitopes has led to selective antibodies with a 100% success rate so far, providing the basis for strong IP applications

Misfolding specific epitopes promote prion-like propagation, contributing to disease pathology (AAIC, 2021)

Image adapted from
Racaniello V et al, virology.ws, 2016

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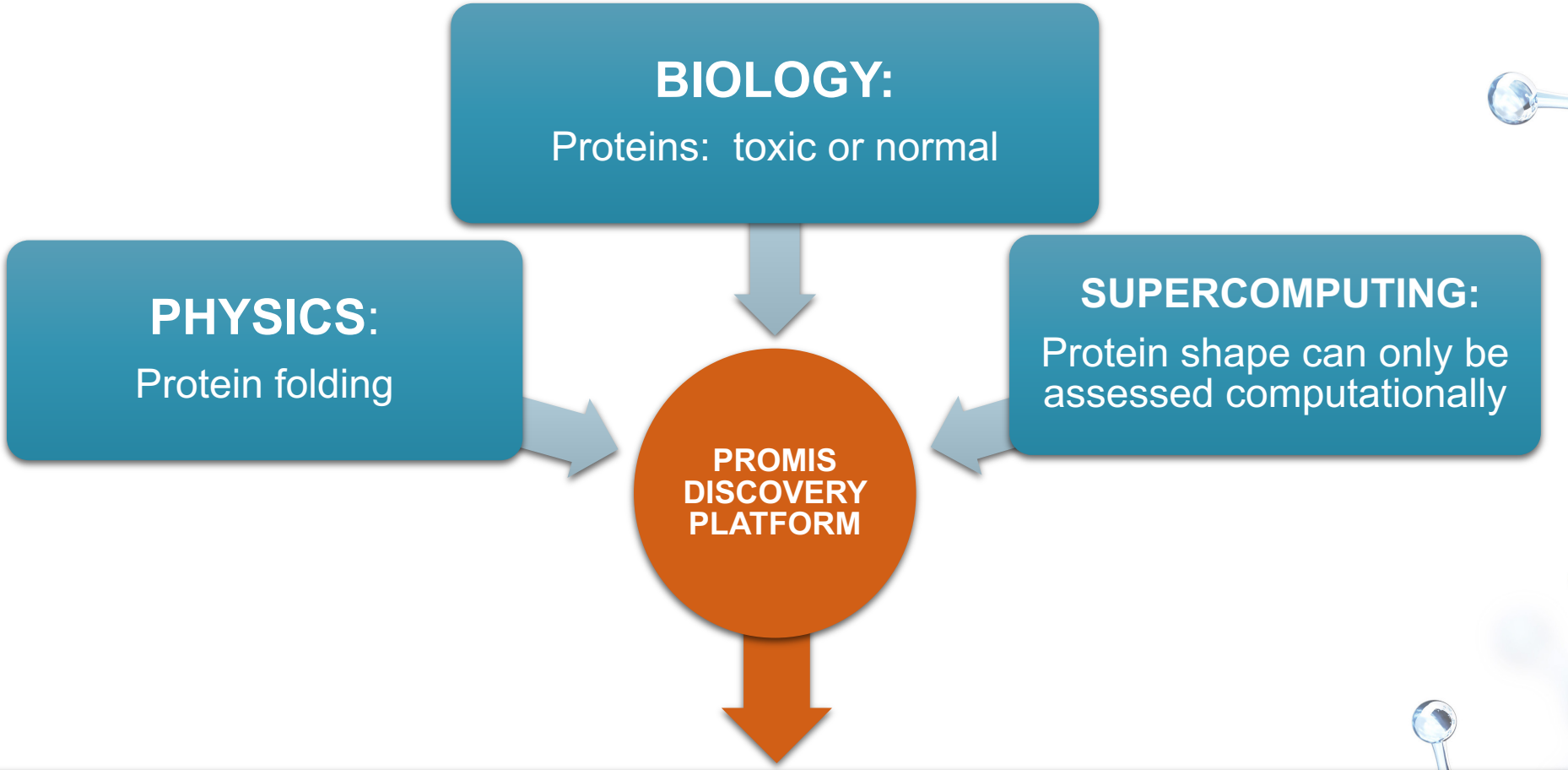
ProMIS Discovery Platform:
Physics + Biology + Supercomputing = Differentiation



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ProMIS platform has generated a robust pipeline of selective antibody product candidates for toxic misfolded proteins

Product Candidate	Target Protein	Disease Indication	Discovery	Pre-Clinical	Phase 1	Phase 2	Phase 3
PMN310	Amyloid-Beta	AD					
PMN267	TDP-43	ALS					
PMN442	Alpha-Synucelin[1]	MSA					
Discovery	RACK1	ALS[2], HD					
Discovery	TAU	Alzheimer's[2], FTLD, PSP, BCD					
Discovery	SOD1	ALS					
Discovery	DISC1+Interactome	Schizophrenla					
Discovery	Amyloid Vaccine	Alzheimer's Prevention					

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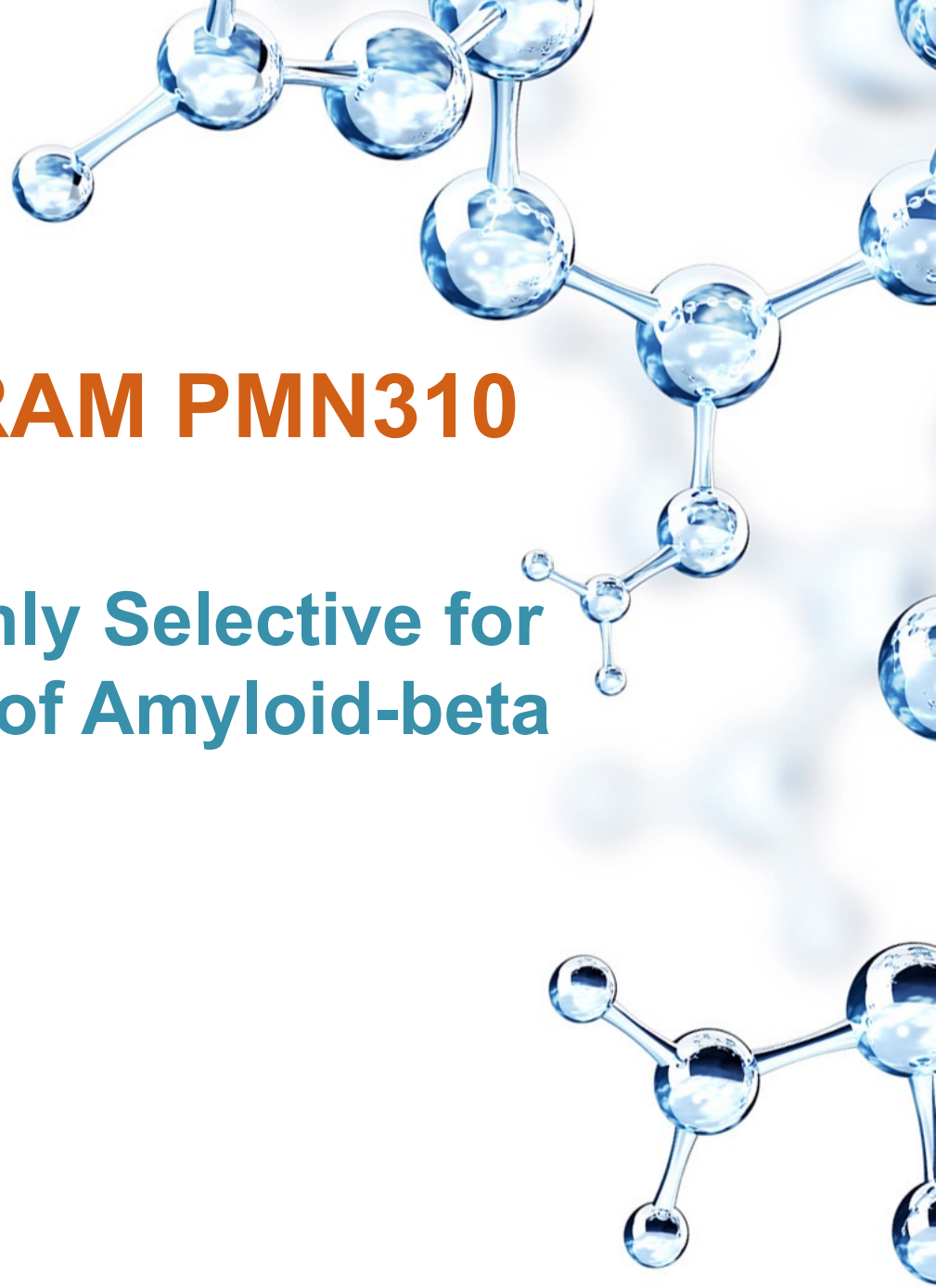
[1] The company plans to investigate additional synucleinopathies, including PD and DLB
[2] Initial indication

PROMIS LEAD PROGRAM PMN310

Differentiated Antibody Highly Selective for Misfolded, Toxic Oligomers of Amyloid-beta



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Alzheimer's Disease: Significant unmet need

- Fifth leading cause of death in the U.S., by far the fastest growing
  - 145% growth since 2000
- An average lifespan of 10 years following diagnosis
- One third of all seniors will die with some form of dementia
- 9.5M people in the U.S. with MCI (mild cognitive impairment) or AD
  - AD projected to from 4.5M now to 12.7M by 2050
- 33% prevalence over age 85
- Estimated $592B cost in 2022
  - $321B direct medical cost
  - $271B unpaid family/friends caregiver
- Very high prevalence of Alzheimer's in Down Syndrome, at an earlier age
  - Three copies of chromosome 21 leads to **excess production of amyloid-beta**
  - AD the leading cause of death in Down Syndrome

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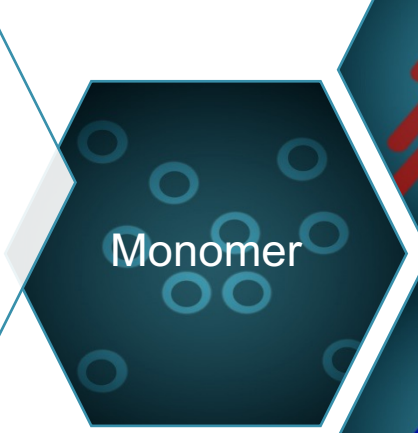
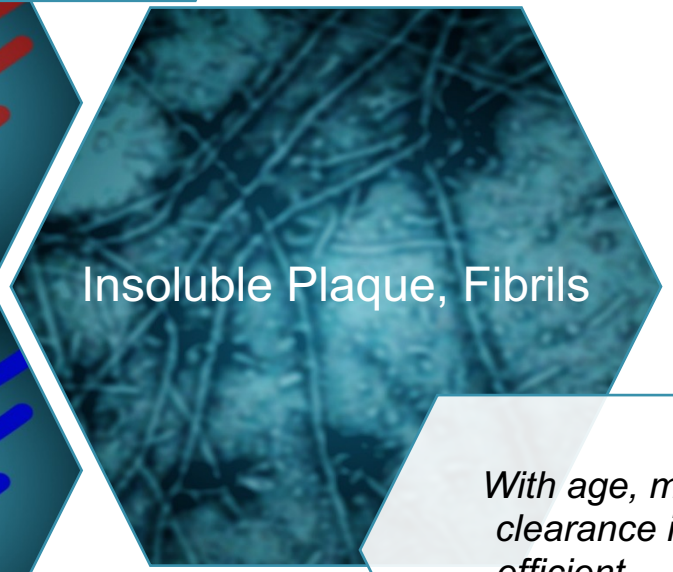
Source: Alzheimer's Association, Johns Hopkins Medicine

Targeting toxic oligomers: When amyloid monomer production exceeds clearance, toxic oligomers of amyloid can form

Toxic Oligomers *are the misfolded, propagating disease drivers*

Monomer*, produced during an entire lifetime, has a biologic role*





With age, microglial (immune system) clearance in the brain becomes less efficient….aggregates build up…the preconditions for disease

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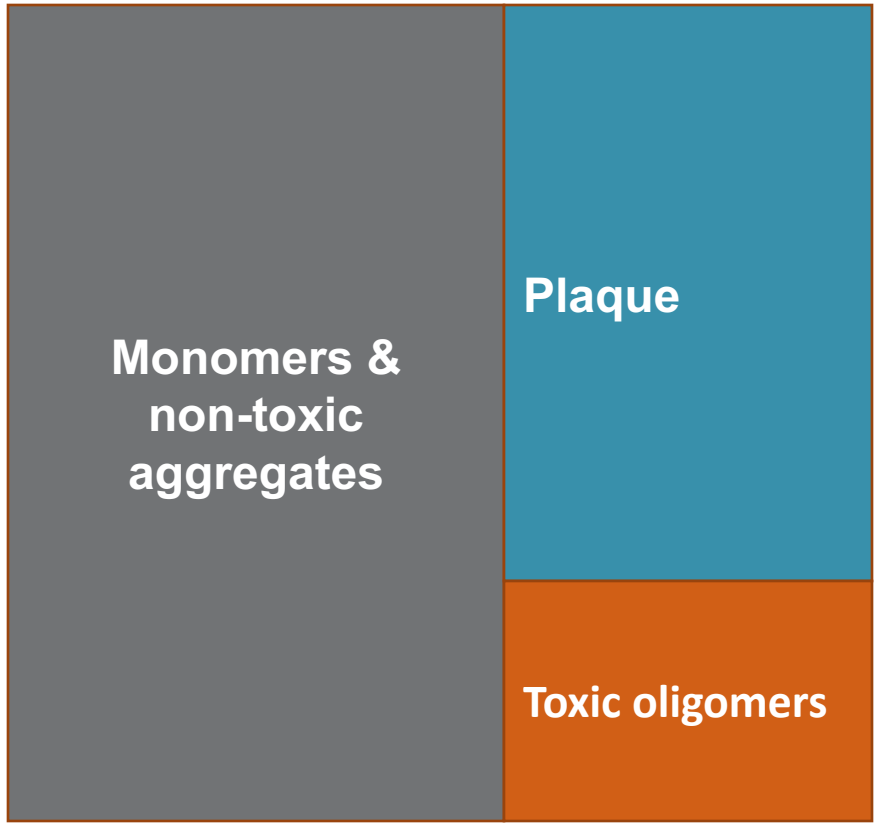
Importance of specific targeting of toxic Aβ oligomers



Relative abundance of Aβ species[3]

Binding to abundant and non-toxic Aβ monomers/aggregates and plaque = Target distraction resulting in reduced efficacy

Binding to plaque and vascular deposits associated with increased incidence of brain edema (ARIA-E) and micro-hemorrhages (ARIA-H)[1,2]

Specific targeting of toxic oligomers expected to result in increased efficacy and improved safety profile

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[1]Sevigny et al, Nature 2016;
[2]Shankar et al, Nature Medicine 2008;
[3]Goure et al, Alz Res & Ther, 2014

PMN310 is a differentiated next generation antibody product candidate in Alzheimer's disease

Failures	First Generation	Next Generation
All BACE inhibitors (monomer) Non-selective antibodies Monomer-targeted antibodies **Failures:** **Crenezumab, solanezumab**	Aduhelm (Biogen, Accelerated approval) Lecanemab (Eisai, Positive Ph2) Donanemab (Lilly, Positive Ph2) • **All showed dose-response curve** • **Treatment gap observations suggest oligomer is key target, not plaque**	**PMN310 – Differentiated** • **High selectivity for toxic oligomers** • **Effector Function (IgG1)** • **Potential subcutaneous delivery**

Eisai Pivotal Trial Readout Q4 2022

Lilly Pivotal Trial Readout ~Q2 2023

PMN310 Clinical data starting in 2023

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Alzheimer's disease: soluble toxic Amyloid-beta oligomers – not plaque or monomers – are the most neuropathogenic Aβ species

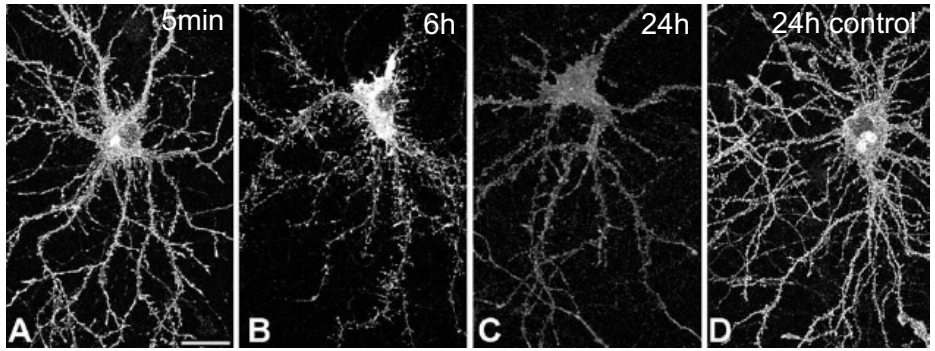
Synapse abnormalities and memory impairment correlate poorly with plaque burden in human and mouse AD[1,2]

Aβ monomers and Aβ insoluble fibrils (plaque) have little or no demonstrable toxicity in vitro or in vivo[3-5]

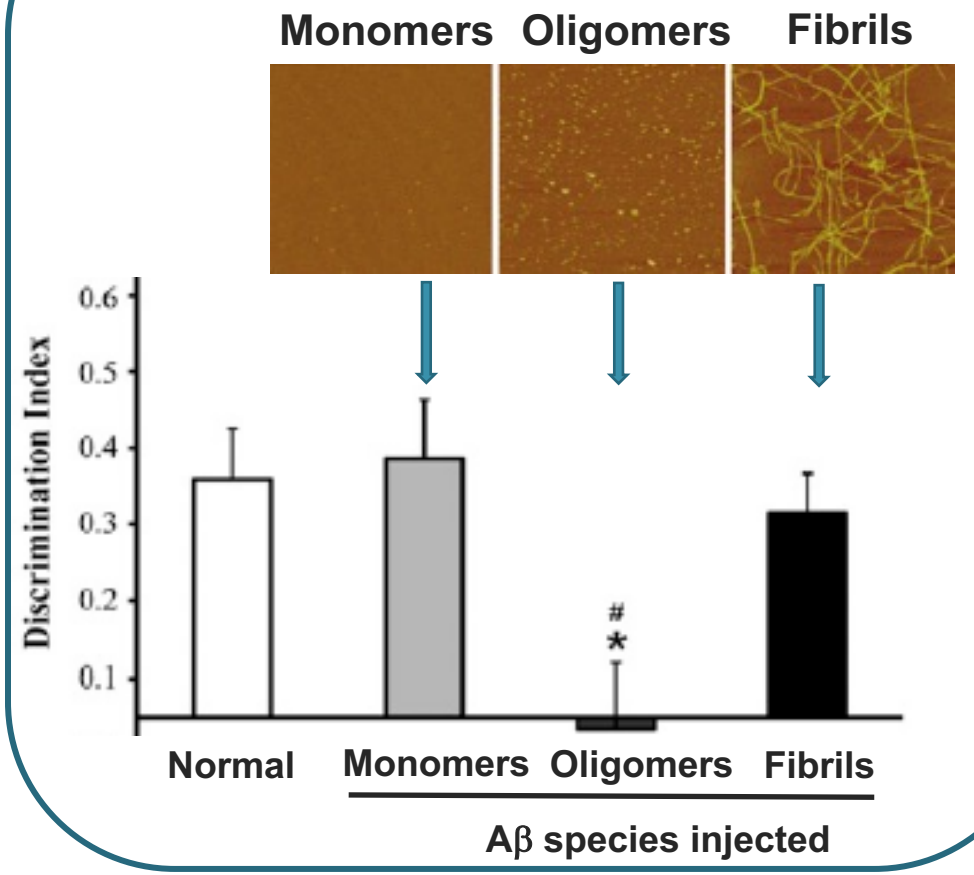
Soluble Aβ oligomers show the highest degree of neurotoxicity[6]

- Toxicity in primary neuron cultures and brain slices[3,5,7-9]
- Induction of cognitive impairment in rodents[3,4,10]

Synaptotoxicity of human Aβ oligomers on hippocampal neurons in vitro[7]



In vivo impairment of recognition memory by Aβ oligomers, not monomers and not fibrils[10]



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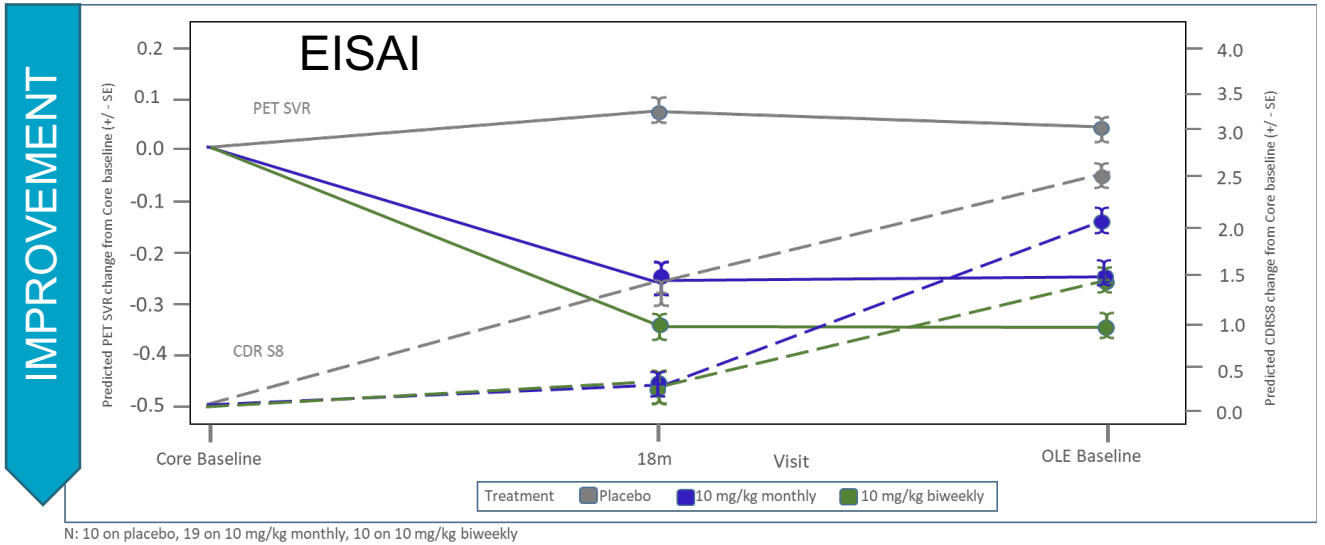
[1]Jacobsen et al, 22006, PNAS; [2]Brier et al, 2016, Science Trans Med; [3]Shankar et al, 2008, Nature Med; [4]Cleary et al, 2005, Nature Neuroscience; [5]Hong et al, 2016, Science; [6]Benilova et al, 2012, Nature Neuroscience - Review; [7]Lacor et al, 2007, J Neuroscience; [8]Jin et al, 2011, PNAS; [9]Lauren et al, 2009, Nature; [10]Balducci et al, 2010, PNAS

Treatment gap data with lecanemab and Aduhelm suggest that *oligomers* (protofibrils) are critical target for disease modifying treatment

EISAI - CTAD, 2019[1]:

"Continued clinical progression with persistent amyloid {*plaque*} reduction during Gap Period suggests:

- A potential role for soluble amyloid aggregate species (e.g. protofibrils) in clinical decline
- Continued treatment may be necessary even after amyloid {*plaque*} is removed"



N: 10 on placebo, 19 on 10 mg/kg monthly, 10 on 10 mg/kg biweekly

Piecewise regression by treatment: Core phase model. Change from Core baseline + slope month from baseline.
Gap model: change from Core 15m + slope month from 15. OLE Baseline at 24 mo for illustrative purposes (average time off drug.
BAN treated subjects). Gap Period: time off drug between end of Core Phase and Baseline OLE.

Biogen presented nearly identical data for Aduhelm; CTAD 2021

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[1]Swanson, CJ et al, CTAD 2019, Session LB10, https://www.eisai.com/news/2019/news201987.html

The PMN310 Solution: Harnessing the power of selectivity

The Problem

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

The PMN310 Solution: Selectivity

- PMN310 selectively binds Aβ oligomers
- Can reach toxic Aβ oligomers, blocking their action and slowing disease progression, without "loss of ammunition"
- Expected to carry a reduced risk of ARIA-E
- Potentially allows for the safe administration of higher doses to achieve a greater clinical benefit

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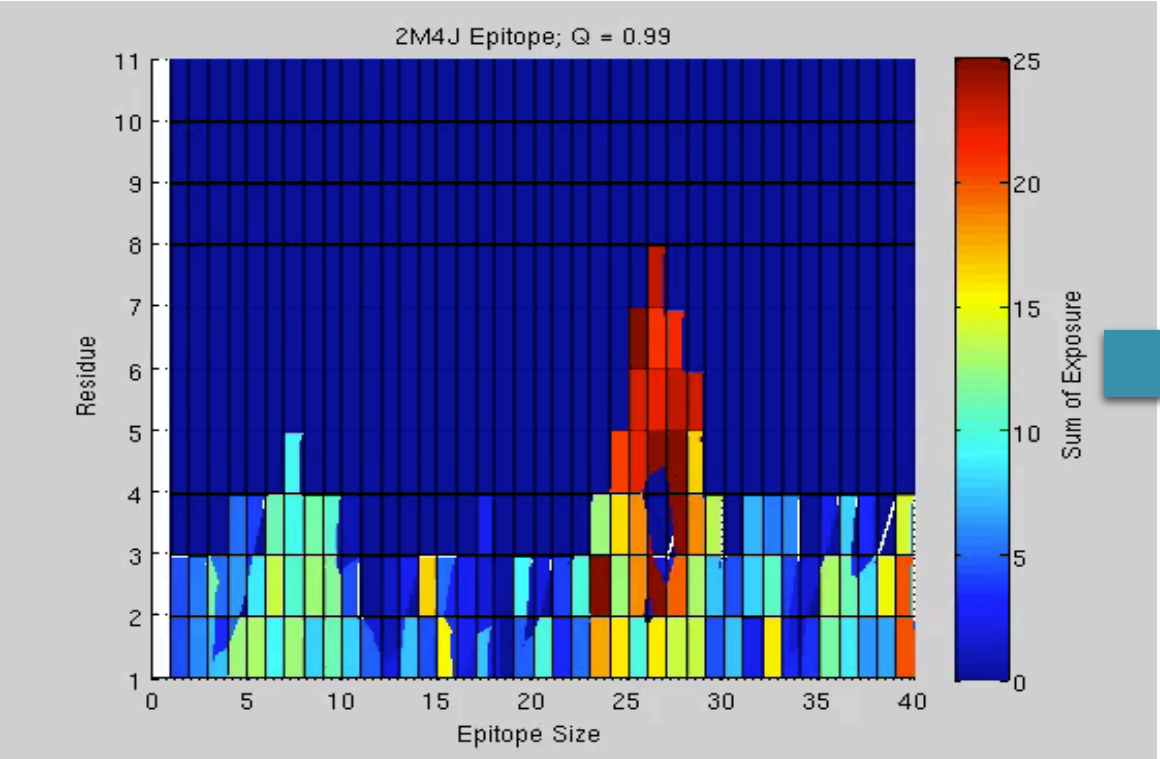
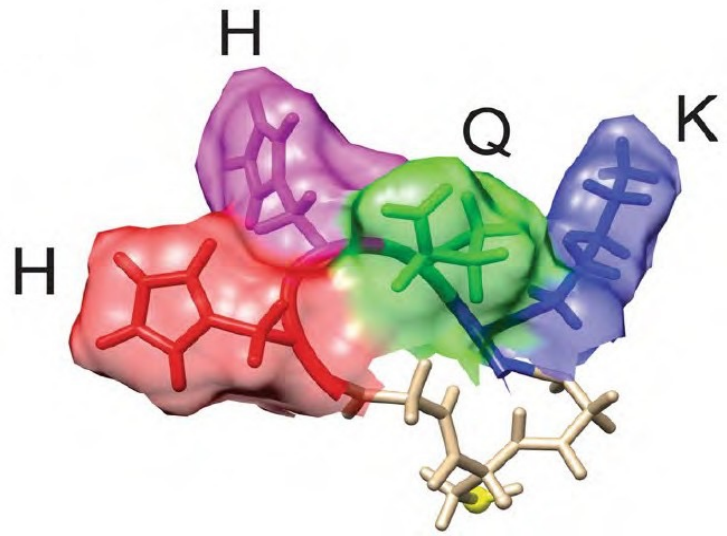
PMN310 targets the epitope predicted by in silico modeling.





DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIG

Computational modeling identifies sequences (epitopes) likely to be exposed in toxic oligomers but not in monomers or fibrils → Regions most prone to exposure thermodynamically

Rationally scaffolded cyclic peptide mimics the conformation of the epitope exposed in the oligomer, distinct from the monomer or fibril → Use for immunization to generate selective antibody

[1]*Gibbs et al, 2019, Scientific Reports*

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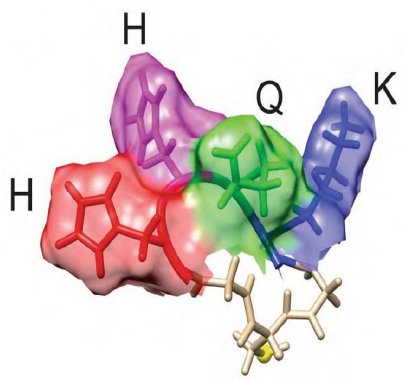
ProMIS platform and rational design capabilities enabled PMN310



Immunization
With misfolded
Protein epitope

Monocolonal antibody candidates

Screen for selectivity and binding to patient samples

Screen for in vitro and in vivo benefit

PMN310

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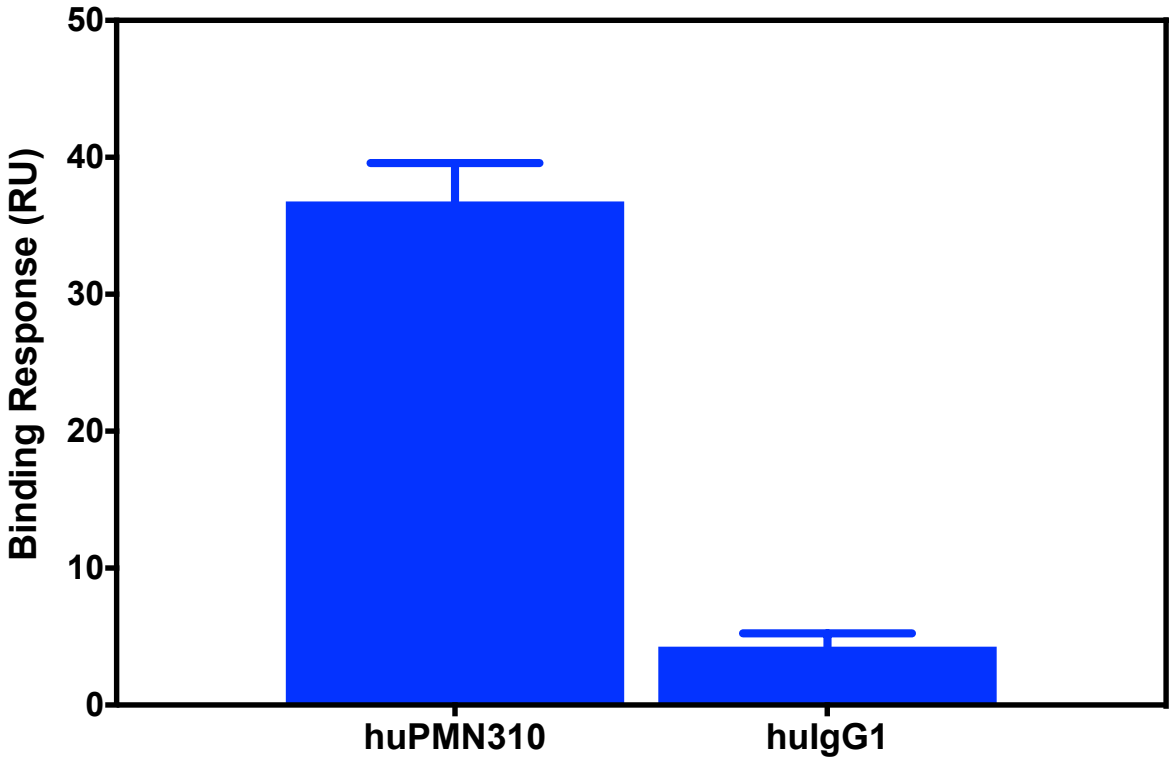
PMN310 showed strong *ex vivo* target engagement to toxic oligomers in Alzheimer's brain extract



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

- AD soluble brain extract fractionated by molecular weight (Yang et al, 2017)
- Low molecular weight fraction (8 kDa – 70 kDa) found to contain the most toxic oligomers*
- ProMIS PMN310 shows strong binding by SPR to LMW brain extract, enriched for toxic oligomers (Gibbs et al, 2019, Scientific Reports)

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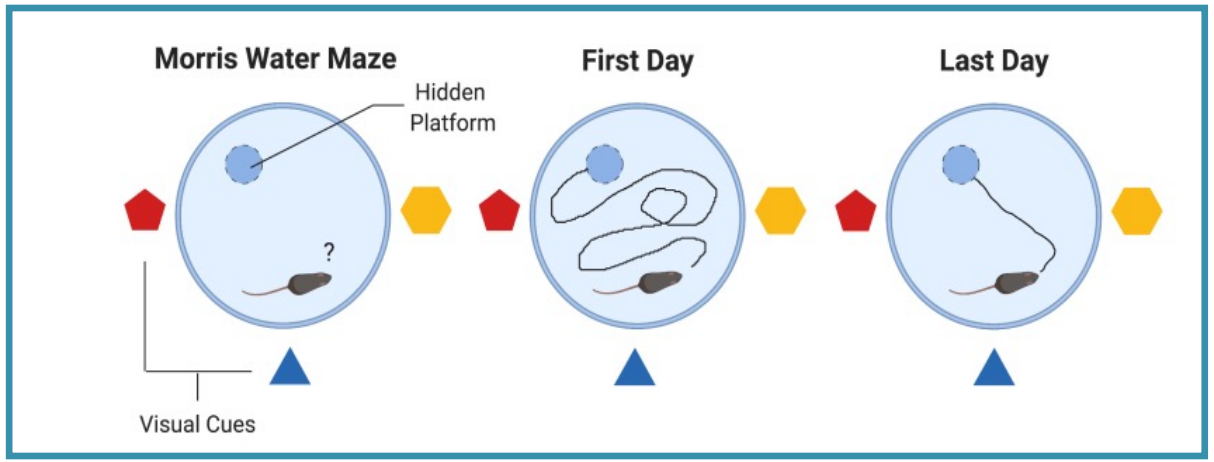
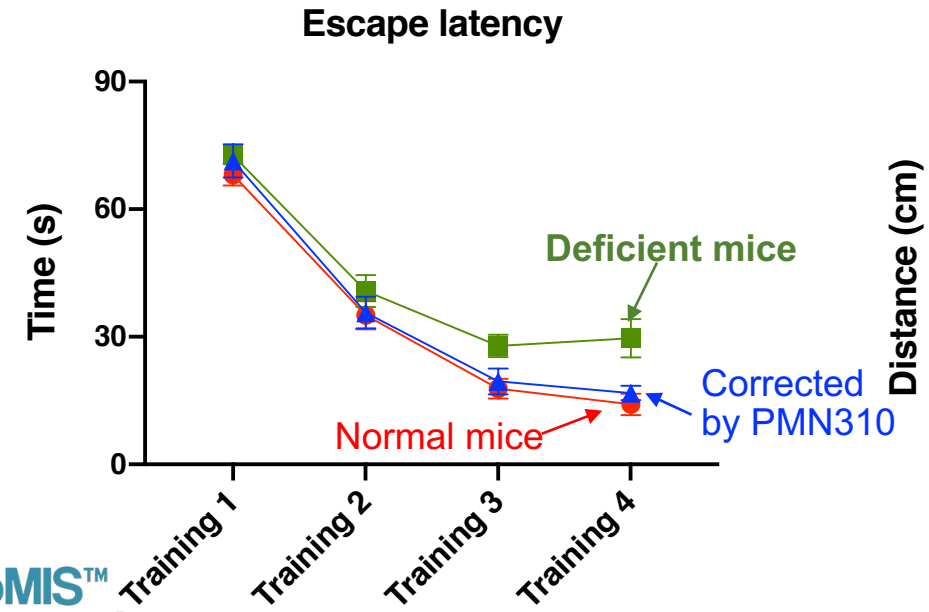
**Toxic as assessed by inhibition of long-term potentiation (LTP), Shankar et al, 2008; induction of cognitive deficit in rats, Cleary et al, 2005 & 2011; decrease in neuronal β-adrenergic receptors, activation of microglia, Yang et al, 2017*

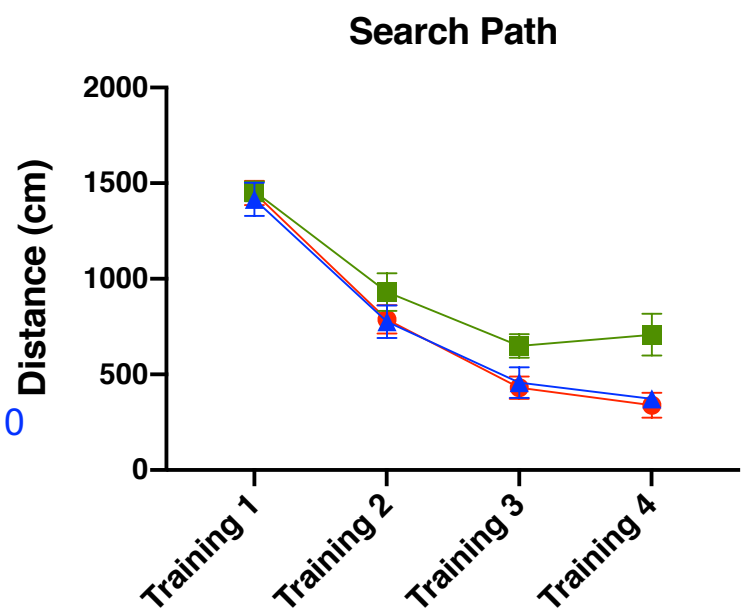
PMN310 dosed systemically (IP*) corrects the cognitive defect of APP/L transgenic mice in the water maze task

Water maze task: Mice learn the location of a hidden platform in a pool of water

- APP/L Tg mice (AD model) have memory and learning deficits
- They take take longer and swim greater distances before finding the platform
- PMN310 corrects this defect -> Treated APP/L mice behave like normal mice







hAPP-Tg, Vehicle

hAPP-Tg, PMN310 mIgG2a antibody (30 mg/kg)

Non-Tg, Vehicle

IP = Intraperitoneal injection

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Several antibodies in the amyloid area have had clinical readouts in recent years – the clinical data support the need for oligomer selectivity

Drug	Latest Trial	Results	High Dose (Monthly)	Notes re: Clinical Trial
Solanezumab (Lilly)	Phase 3 Nov 2016	No clinical benefit Nov 2016	6mg/kg	
Lecanumab (Eisai)	Phase 2 July 2018	Benefit: CDR-SB 26%, ADAS-COG 47%	20mg/kg (10 mg 2x/month)	APOE-4 carriers restricted in high dose arm per EMA
Crenezumab (Roche)	Phase 3 Jan 2019	No clinical benefit Jan 2019	60mg/kg	
Aduhelm (Biogen)	Phase 3 Mar 2019	Benefit – Approved CDR-SB 22%, ADAS-COG 27% (EMERGE study)	10mg/kg (Actual ~7mg/kg)	Initially APOE-4 carriers in high dose arm given low dose of 6mg/kg (due to ARIA-E concern); futility analysis conducted despite mid trial dose increase, program suspended March 2019
Donanemab (Lilly)	Phase 2 Jan 2021	Benefit - iADRS	20mg/kg	Trial “treat to target”, treatment ceased after plaque reduction goals met, 55% of subjects off treatment by trial end

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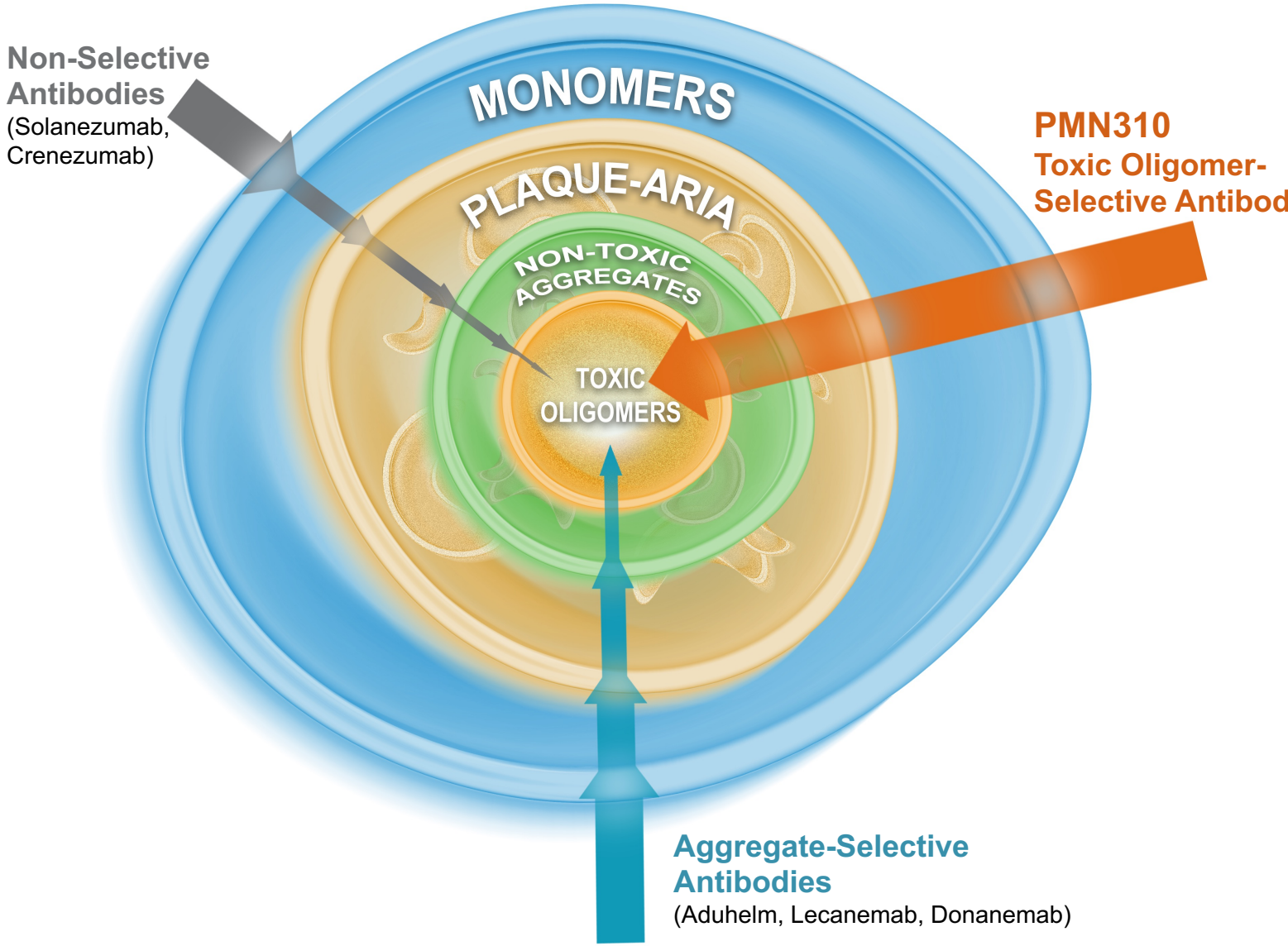
Importance of specific targeting of toxic Aβ oligomers

- Non-selective antibodies bind abundant non-toxic monomers and are diverted away from the toxic oligomer target -> No clinical benefit
- Aggregate-selective antibodies target oligomers more effectively but incur an increased risk of ARIA associated with plaque binding -> Modest clinical benefit
- PMN310 selectively targets toxic oligomers -> Potential for the safe administration of higher doses to achieve a greater clinical benefit



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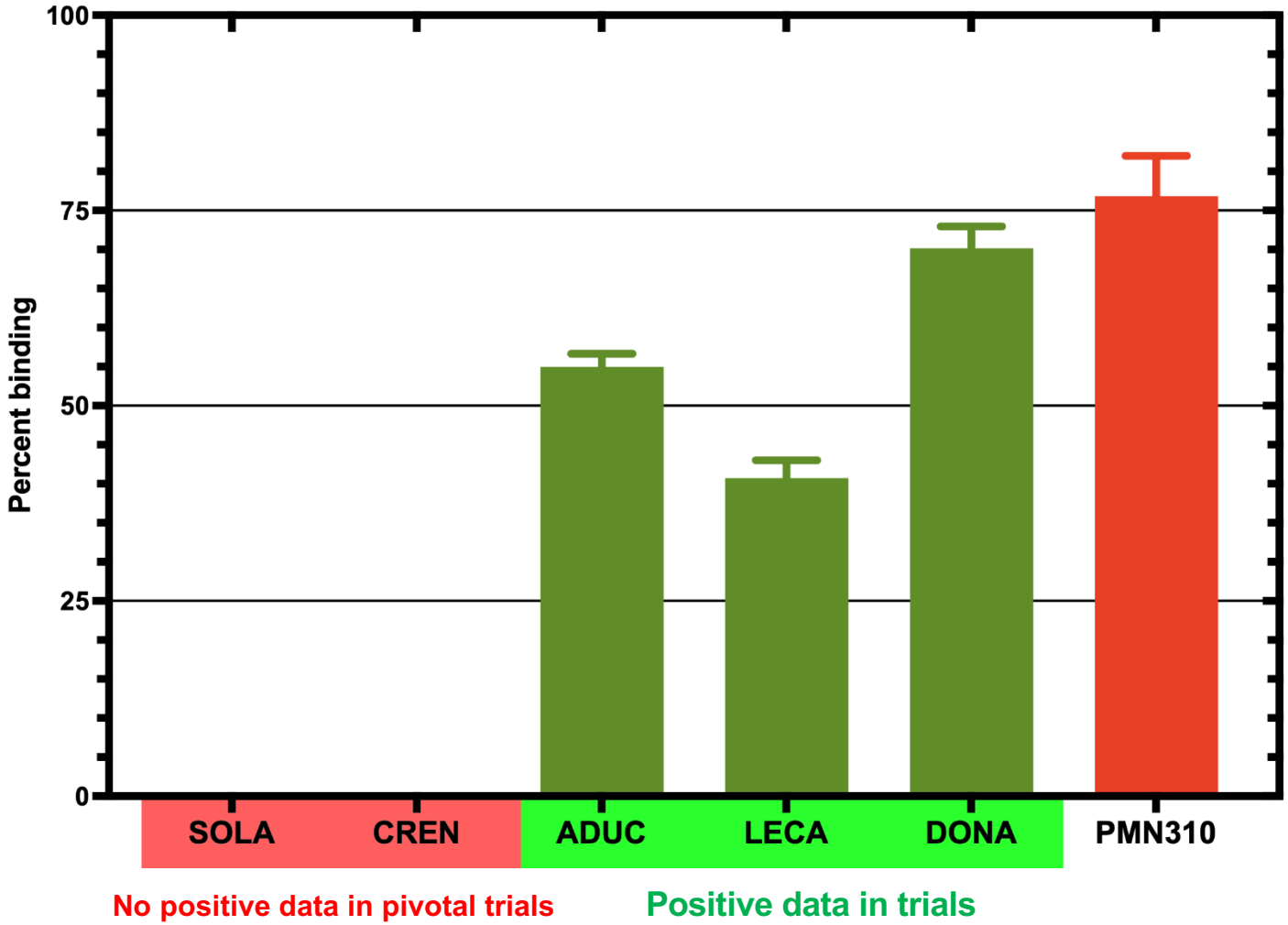
Positive clinical data correlate with avoiding *monomer target distraction* and retaining a binding signal to LMW oligomers



- Percent SPR binding to toxic oligomer-enriched LMW fraction retained after pre-exposure to monomers
- In SPR assays, PMN310 showed little inhibition of LMW fraction binding in the face of monomer competition
- Antibodies that failed in the clinic have toxic oligomer binding negated by monomer exposure
- PMN310 targeting of Aβ oligomers is minimally impacted by monomer competition

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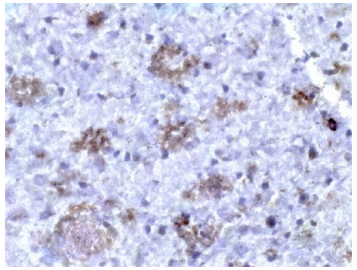
PMN310 expected to allow for higher dosing due to lower risk of ARIA-E

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

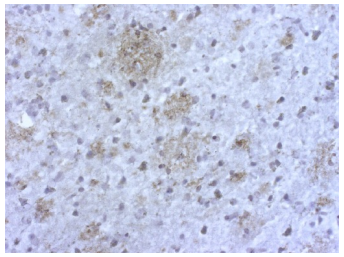
Dose limited to 10mg/kg



Aducanumab

ARIA-E ~35%

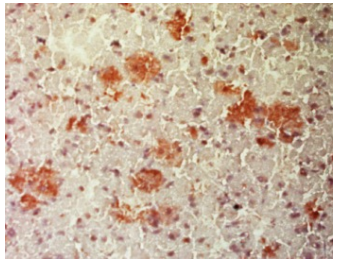
Dose limited to 20mg/kg



Donanemab

ARIA-E ~30%

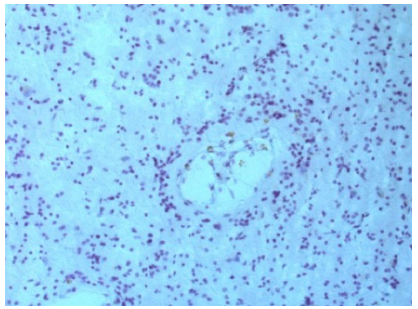
Dose limited to 10mg/kg



Lecanemab

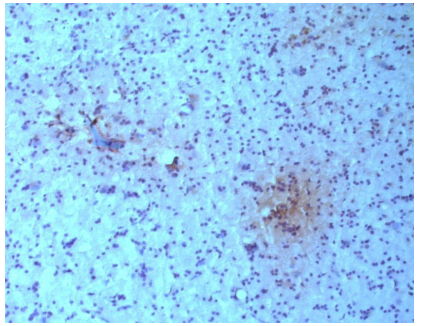
ARIA-E ~15%

PMN310 shows no detectable plaque binding



PMN310

No detectable plaque binding



Solanezumab

No detectable plaque binding,
Low incidence of ARIA-E

ARIA-E = Amyloid Related Imaging Abnormality with Edema = brain swelling

[1]*Sperling RA et al, 2011, Alzheimer's and Dementia, https://doi.org/10.1016/j.jalz.2011.05.2351*

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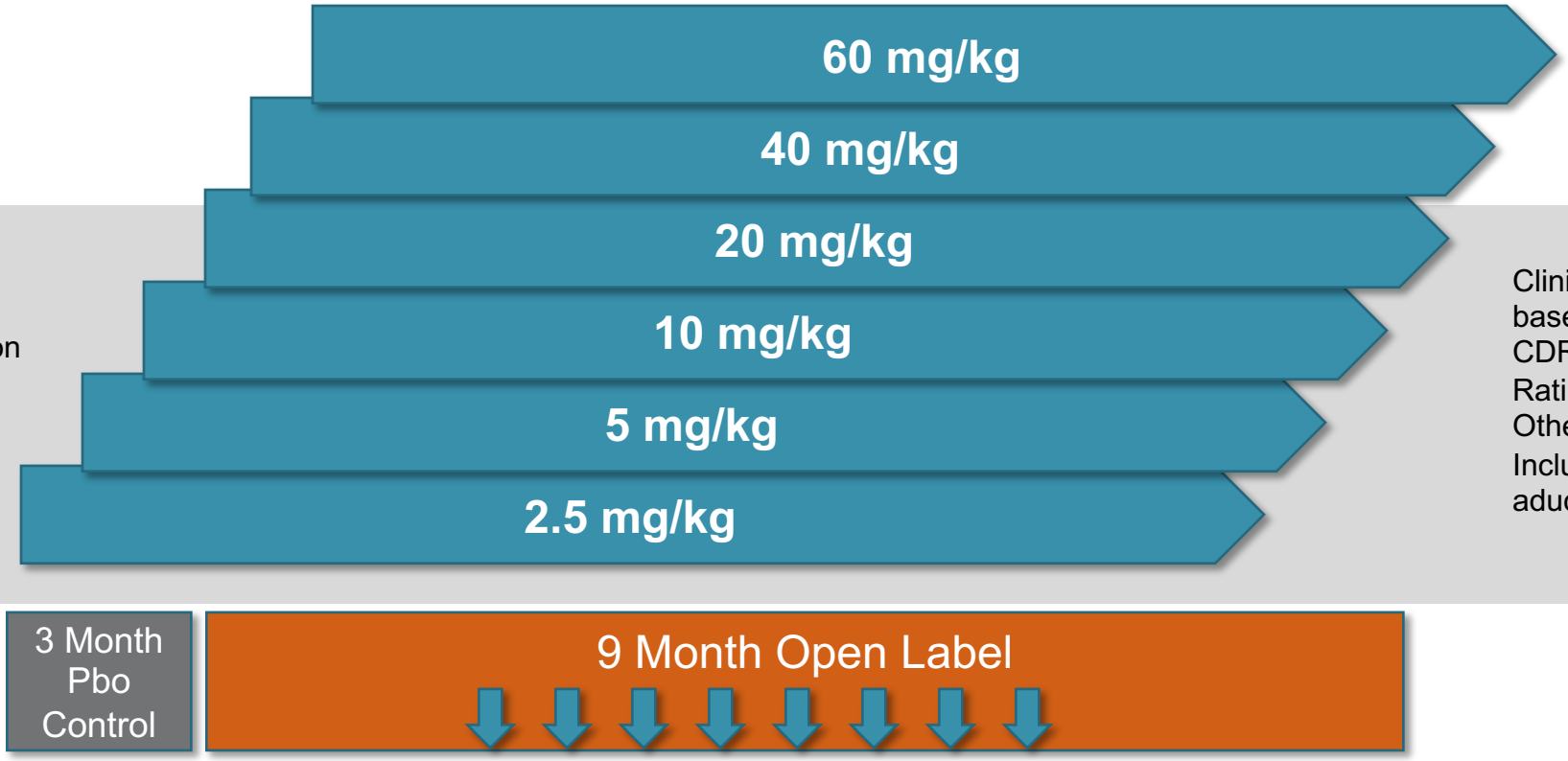
PMN310 Phase 1b MAD* trial design: Goals – assess safety of high doses; assess pharmacodynamic effect with biomarkers

3-month placebo-control, to assess ARIA-E

9-month open-label extension
Biomarkers including:

- NfL p-tau181
- p-tau 217
- p-tau231
- GFAP
- Ab42/40



Clinical endpoints measured at baseline and month 12:
CDR-SB (Clinical Dementia Rating, Sum of Boxes)
Other clinical endpoints
Inclusion criteria similar to aducanumab, lecanemab trials

Monthly biomarker readouts in an open label trial
Assess pharmacodynamic markers of a treatment effect at 3, 6, 9, 12 months

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** Multiple Ascending Dose*

PMN310: Lead program for the potential treatment of Alzheimer's Disease

Selectively binds misfolded, toxic oligomers of amyloid-beta, avoiding binding to monomer or plaque

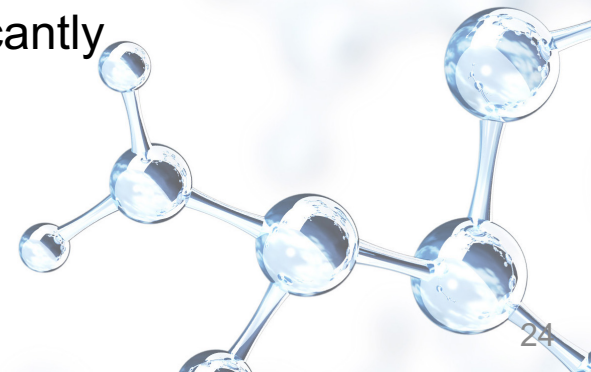
Strong *ex vivo* target engagement in tests with human Alzheimer's Disease brain material

Statistically significant results in both chronic and acute mouse models of amyloid oligomer-generated cognitive deficit

Analysis of competitor antibody programs with recent clinical results supports hypothesis that amyloid oligomer is the desired target for therapy

- Binding to monomer (target distraction) associated with lack of benefit in clinic
- Lack of correlation between plaque removal and sustained cognitive benefit

ProMIS multiple-ascending dose (MAD) trial in sporadic AD patients designed to evaluate safety, including potential for fewer ARIA adverse events, and potential to dose significantly higher than competitor antibodies



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ProMIS platform has generated a robust pipeline of selective antibody product candidates for toxic misfolded proteins

Product Candidate	Target Protein	Disease Indication	Discovery	Pre-Clinical	Phase 1	Phase 2	Phase 3
PMN310	Amyloid-Beta	AD					
PMN267	TDP-43	ALS					
PMN442	Alpha-Synucelin[1]	MSA					
Discovery	RACK1	ALS[2], HD					
Discovery	TAU	Alzheimer's[2], FTLD, PSP, BCD					
Discovery	SOD1	ALS					
Discovery	DISC1+Interactome	Schizophrenla					
Discovery	Amyloid Vaccine	Alzheimer's Prevention					

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[1] The company plans to investigate additional synucleinopathies, including PD and DLB
[2] Initial indication

ProMIS Antibody PMN442:
Lead candidate against misfolded alpha-synuclein

- Biologically relevant target - ProMIS platform-predicted epitope plays a direct role in alpha-synuclein pathogenicity
- Selectivity for toxic misfolded alpha-synuclein, blocks neurotoxicity in dopaminergic neurons and propagation of aggregation in vitro
- Undergoing humanization, *in vitro* and *in vivo* testing
- Lead target indication MSA (multiple system atrophy, rare disease, elevated biomarkers)
- Parkinson's disease and dementia with Lewy bodies additional potential indications

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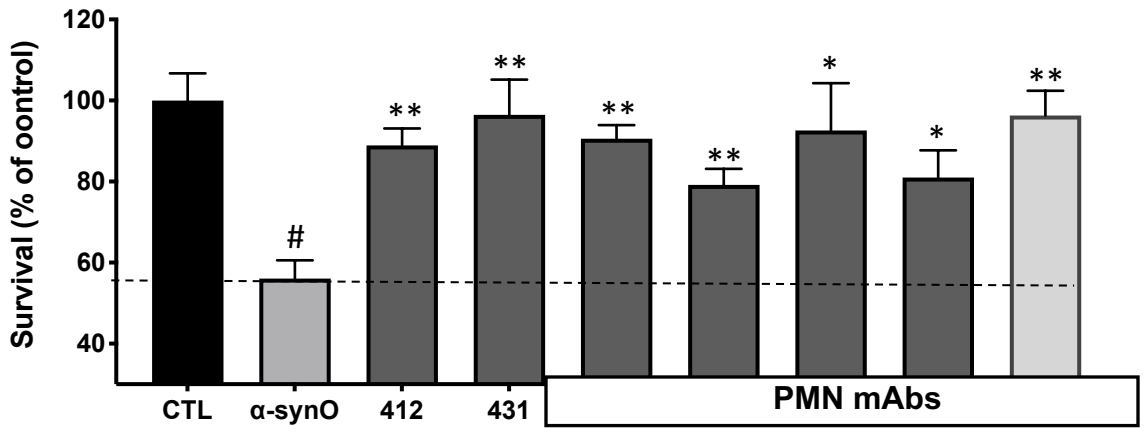
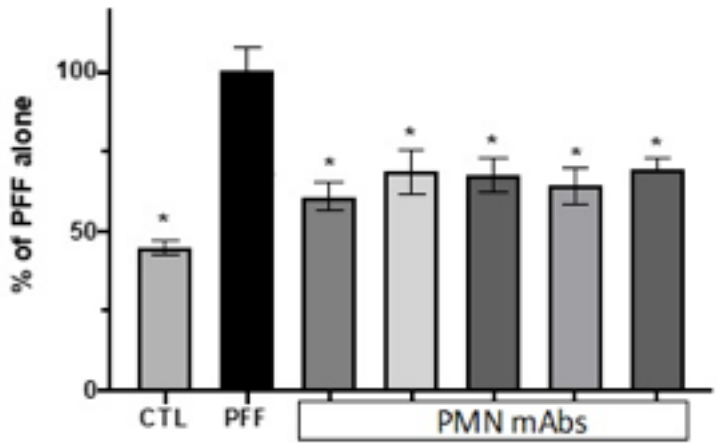
In vitro protective activity of ProMIS mAbs against a-syn pathogenicity



Protection against neurotoxicity

mAbs inhibited a-syn oligomer toxicity for neurons. Cultures of primary rat dopaminergic neurons were exposed to toxic a-syn oligomers with or without mAbs. Survival is expressed as the percentage of viable neurons compared to a control culture with vehicle only (CTL).



Inhibition of seeding activity

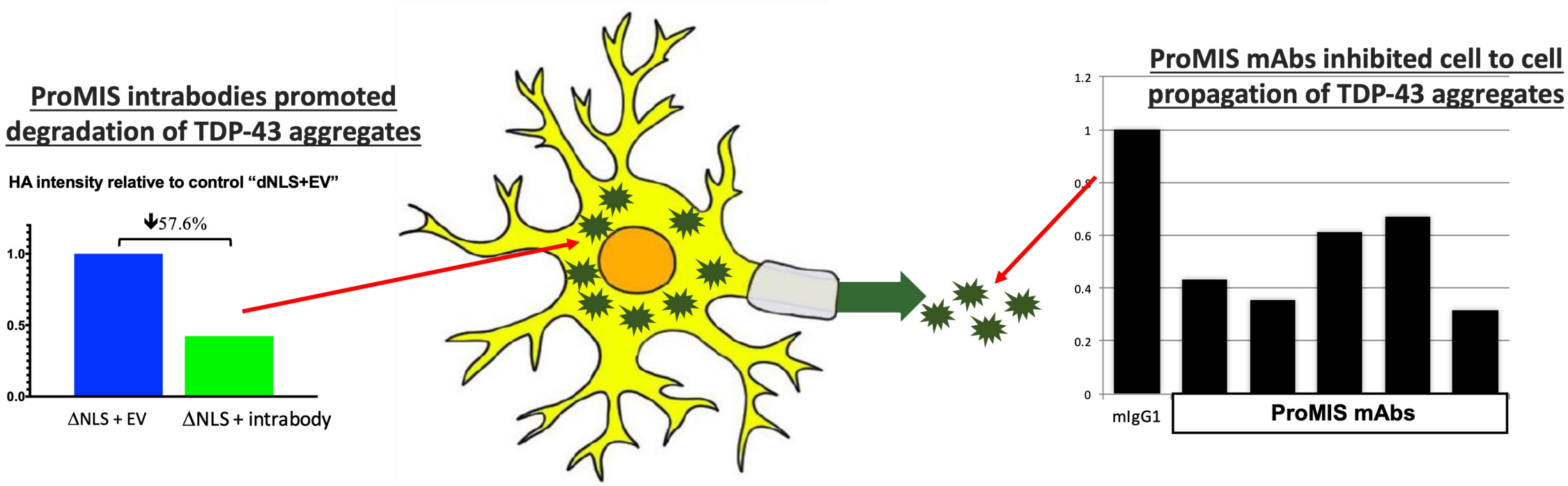
mAbs inhibited the recruitment of endogenous rat a-syn into phosphorylated aggregates. Cultures of primary rat hippocampal neurons were exposed to soluble human a-syn preformed fibrils (PFF) with or without mAbs. CTL = neurons incubated with vehicle alone. Results are expressed as a percentage of the phosphorylated rat a-syn staining area with PFF alone

ProMIS™ Neurosciences

ProMIS Antibody PMN267: Targeting Misfolded TDP-43

- Lead candidate PMN267 demonstrated high affinity and selectivity for toxic TDP-43, sparing normal physiologic TDP-43
- PMN267 showed binding to patient biosamples vs controls, *ex vivo* target engagement
- In pilot studies, an intrabody version of PMN267 targeting intracellular misfolded TDP-43 showed selective binding to misfolded TDP-43 aggregates, no interaction with normal TDP-43 nor detrimental impact on cell viability, and clearance of pathogenic aggregates from inside cells
- PMN267 is undergoing humanization, ongoing *in vitro* and *in vivo* testing
- The lead target indication is ALS
- The evidence for a TDP-43 toxic “interactome” with other ProMIS targets – RACK1, SOD1– suggests a potential synergistic portfolio for ALS disease-modifying treatment

Inhibition of cell to cell propagation of misfolded TDP-43 with ProMIS mAb and clearance of intracellular aggregates with intrabody



Transfection of HEK293 cells with a ProMIS intrabody results in degradation of HA-tagged mutant TDP-43 (DNLS) aggregates compared to an empty vector (EV) control.

Supernatant from HEK293 cells transfected with misfolding mutant TDP-43 was incubated with test antibodies and added to naïve recipient cells to assess transmission of misfolding TDP-43 (HA-tagged). Compared to a mouse IgG1 negative control (mIgG1), several mAbs inhibited transmission to recipient cells

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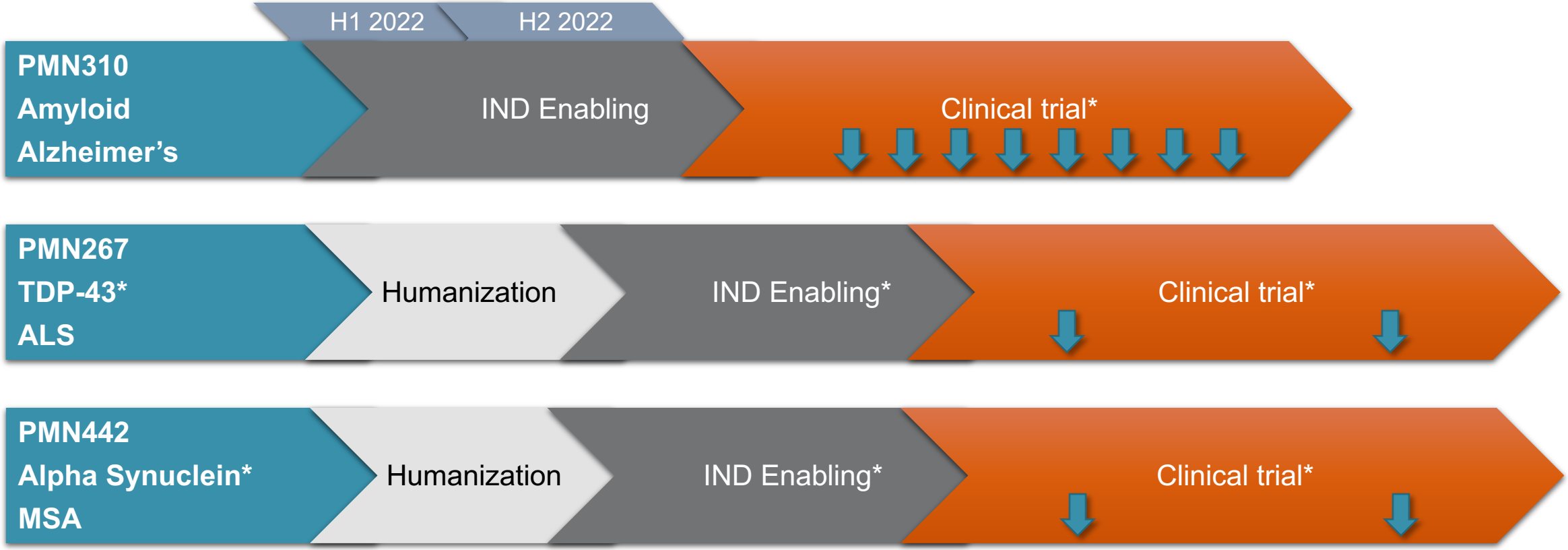
Poised for several INDs and clinical readouts in next 2-3 years



Eisai Lecanemab AD readout
CTAD Nov 29, 2022

= Potential Monthly biomarker readouts, biomarker-based
*Specific timing based on capital availability.
Start of clinical trials subject to IND acceptance and discussion with FDA

ProMIS™ Neurosciences

Leadership Team

Management Team

Gail Farfel, Ph.D.
Chief Executive Officer

Neil Cashman, M.D.
Chief Scientific Officer

Johanne Kaplan, Ph.D.
Chief Development Officer

Larry Altstiel, M.D., Ph.D.
Chief Medical Officer

Gavin Malenfant
Chief Operating Officer

David Wishart, Ph.D.
Chief Physics Officer

Dan Geffken
Chief Financial Officer

Board of Directors

Eugene Williams
Chairman and Co-founder

Neil Cashman, M.D.
Chief Scientific Officer and Co-founder

Richard Gregory
Independent Director

Patrick Kirwin
Independent Director

Josh Mandel-Brehm
Independent Director

Maggie Shafmaster
Lead Independent Director

Neil K. Warma
Independent Director

William Wyman
Independent Director

ProMIS™ Neurosciences

Developing the next generation of neurodegenerative treatments

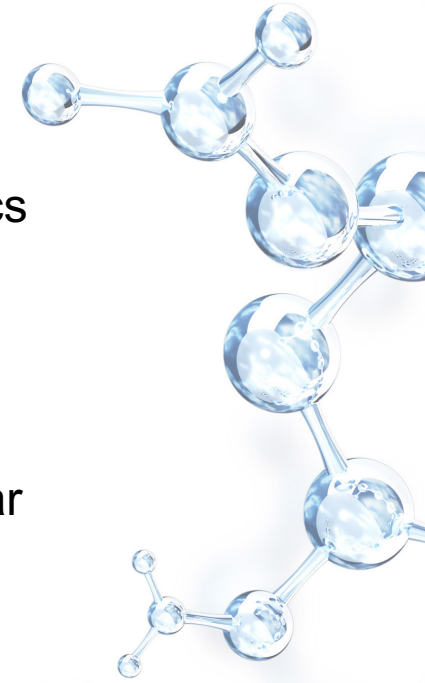
Current approach to neuro treatments leaves **significant unmet need for highly selective, precision treatments**

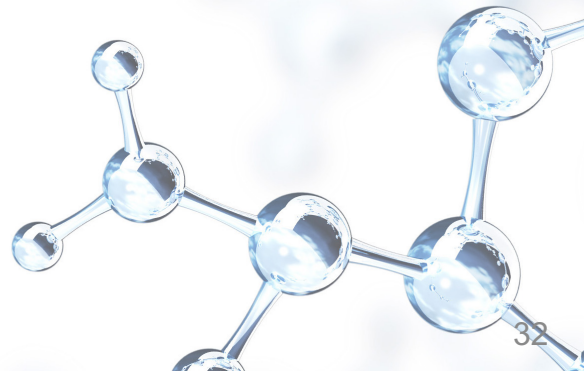
Differentiated computational platform at the cross-section of science: biology and physics

Pipeline of highly selective antibodies for toxic misfolded proteins implicated in a wide range of neurodegenerative disorders

Lead program, PMN310 selectively targeting toxic, misfolded amyloid on track for IND by year end

Leveraging of serum-based biomarkers designed to provide rapid insight into potential clinical benefits for all programs





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