ProMIS Neurosciences: “Best in Class” therapy for misfolded protein diseases, based on a proprietary discovery platform

Toronto Stock Exchange (TSX) ticker: PMN
OTCQB ticker: ARFXF

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Forward looking statement: safe harbor

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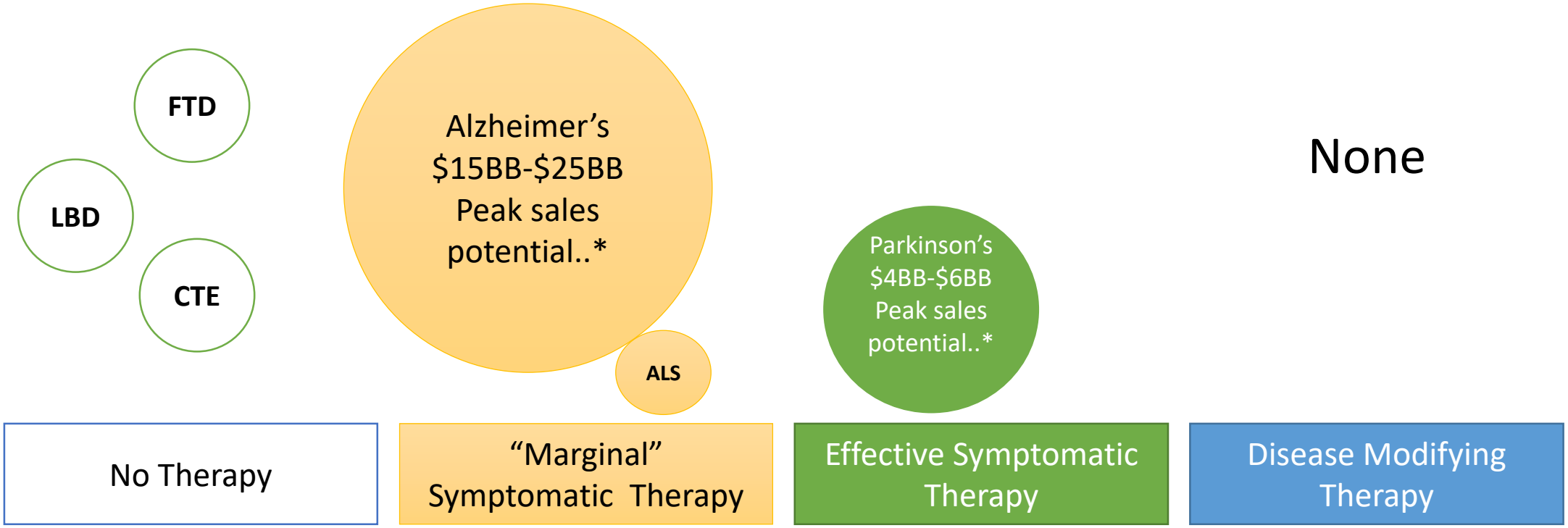
ProMIS Overview: selectively targeting toxic mis-folded proteins in Alzheimer's and other neurodegenerative diseases

- Launched in 2014 following 1st ever **positive** effect on cognitive decline in AD shown by Biogen's aducanumab phase 1b; further confirmation with phase 3 aducanumab results

- **Lead program PMN310**: ProMIS unique platform used to achieve improvement over Biogen's aducanumab
  - PMN310 selective for toxic oligomer of amyloid, no plaque or monomer binding
  - Likely to avoid aducanumab dose-limiting side effect, PMN310 can dose higher

- Unique capability and track record creating antibodies highly selective for mis-folded proteins leading to a portfolio of mAb therapeutics for AD, ALS, PD
  - Active partnering discussions could lead to deals in near/medium term

Neurodegenerative diseases: in need of disease modifying therapy attacking the *root cause*



FTD = Frontotemporal dementia
LBD = Lewy Body dementia
CTE = Chronic traumatic encephalopathy

- Analysis by Centerline: assumes market average penetration, diagnosis, 40% mkt share

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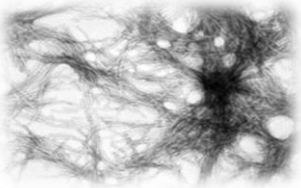
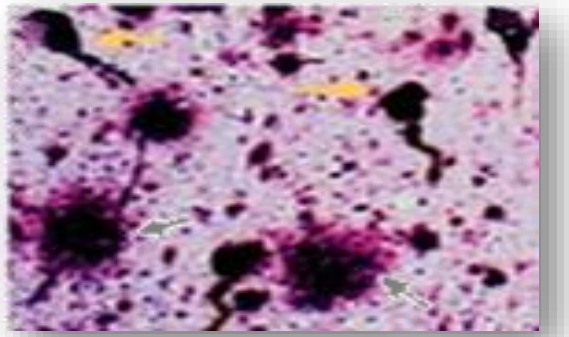
Alzheimer's, Parkinson's and ALS are protein mis-folding diseases, where the toxic mis-folded proteins propagate in a prion-like manner

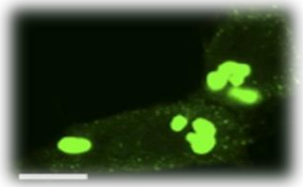
Huntington's disease
(huntingtin)



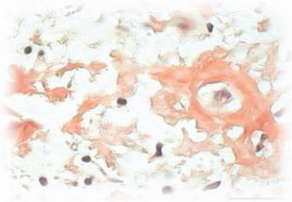
Alzheimer's disease
(amyloid-beta and tau)



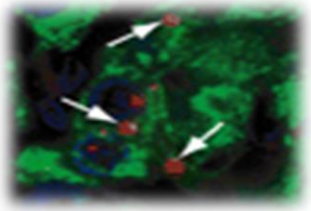
Schizophrenia
(DISC1)

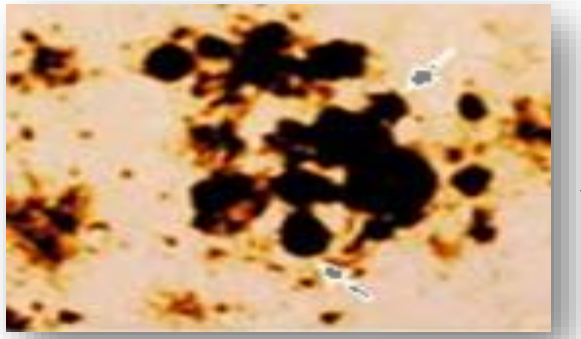


Senile amyloidosis
(transthyretin)

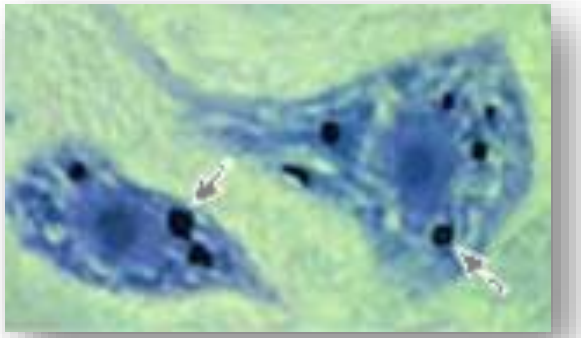


Type 2 diabetes
(amylin)

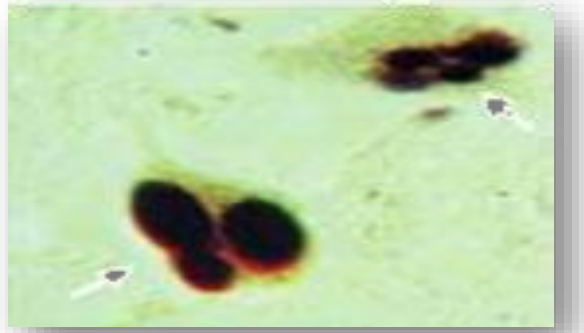




Prion diseases
(prion protein)

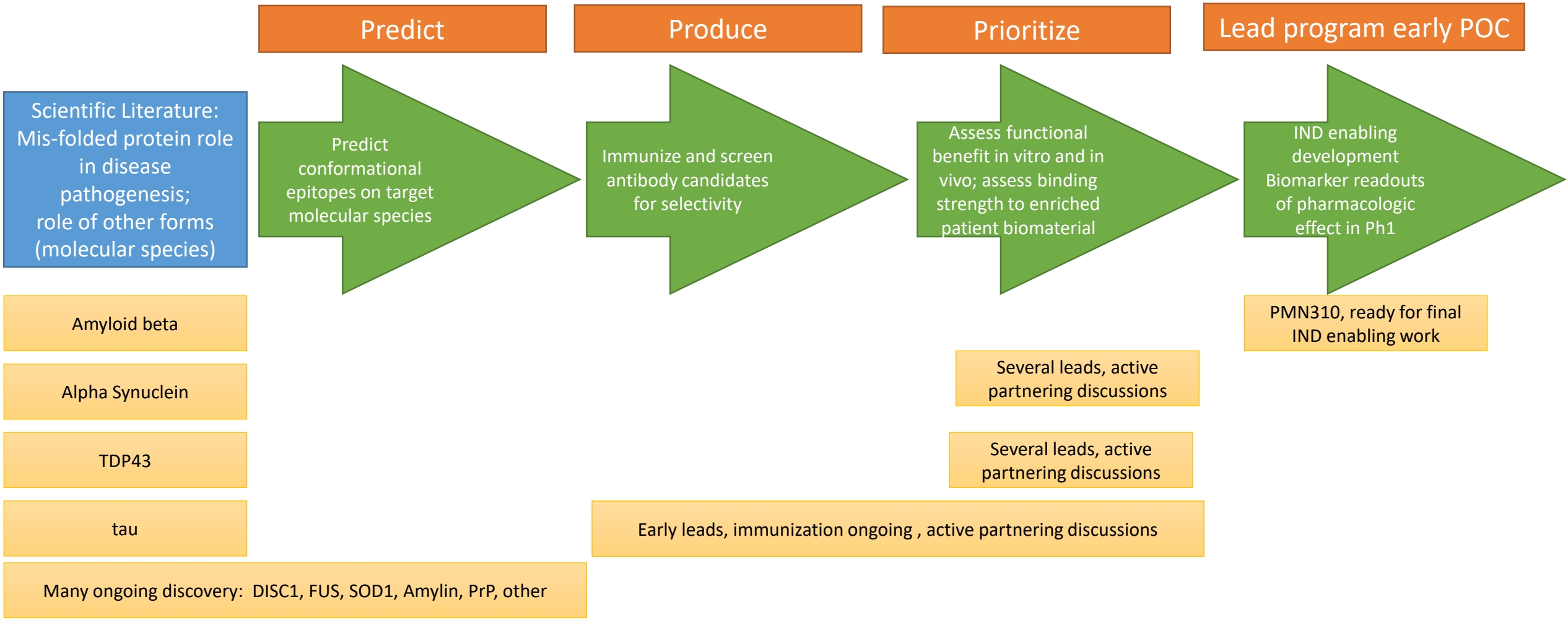


ALS
(TDP43, SOD1, FUS)



Parkinson-like diseases
(alpha-synuclein)

ProMIS: current portfolio of mAbs selectively targeting toxic mis-folded proteins



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Anti-amyloid therapy in Alzheimer's disease

Updating the amyloid hypothesis in light of aducanumab pivotal trial data: amyloid matters and PRoMIS is on the right track

- There is no question that amyloid plays a role in AD pathology
- Critical question - can neutralizing amyloid be clinically beneficial in symptomatic patients? Is it too late in the disease? Are other targets more important?
- Aducanumab pivotal data indicate neutralizing amyloid provides clinical benefit in symptomatic patients
- Biogen ran two pivotal trials, the data were less clear than we would have liked due to two management decisions:
  - a) starting the pivotal with 2/3 of the patients receiving a suboptimal high dose (6mg instead of 10mg); and then
  - b) after correcting the first error mid-trial through a protocol amendment (V4), failing to account for that change in a pre-planned futility analysis and stopping the trial in March 2019.
- At CTAD, Biogen presented an analysis of only the V4 subset of patients. Those data are probably most representative of what will happen in the real world if/when aducanumab is approved. **It will be used at 10mg/kg**. In the V4 subset, both pivotal trials showed a meaningful slowing of clinical progression by 30% and 27% respectively, with a ~30% rate of the dose-limiting ARIA-E side effect

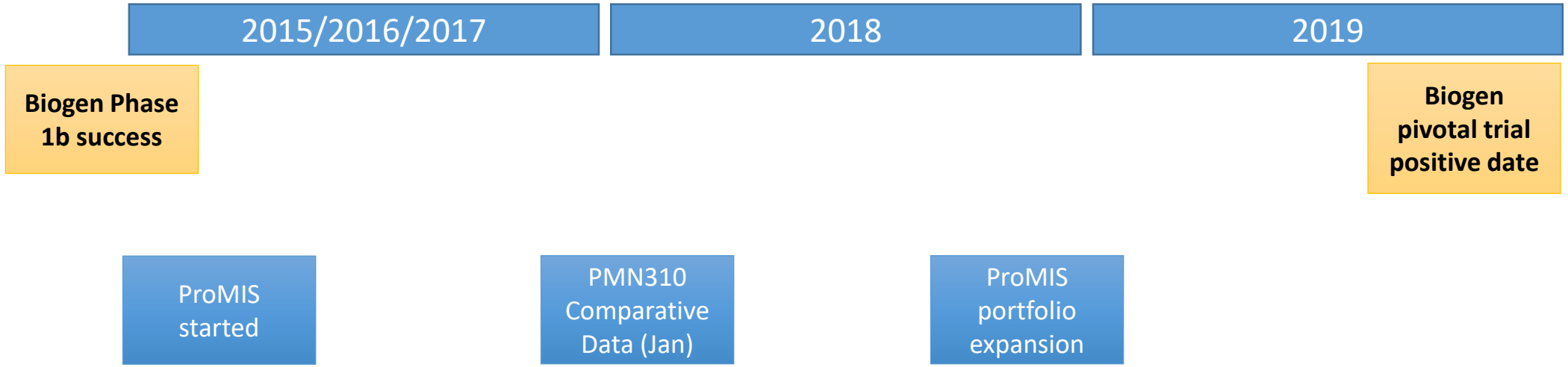
Updating the amyloid hypothesis in light of aducanumab pivotal trial data: PMN 310 well-designed to be "best in class"

- Aducanumab differs from all other failed programs - it does not bind the simplest form of amyloid - monomer. It only binds aggregated forms, oligomer and plaque (like EISAI's BAN2401, which also had a positive Phase 2 study with a dose dependent slowing of progression).

- That raises the question - which of the two (oligomer or plaque) is the disease culprit? The data are overwhelming that **the culprit is the oligomer**. Thousands of studies have been published evaluating what forms of amyloid are toxic to neurons - oligomers are toxic, plaque is not.
  - Biogen in their aducanumab Nature publication in Sep 2016 suggested that clinical benefit might come from neutralizing oligomers.
  - In the aducanumab pivotal program, plaque reduction was not correlated with clinical benefit - the full dataset from one pivotal ENGAGE, showed no clinical benefit despite the same level of plaque reduction as the EMERGE pivotal that did show benefit.
- All studies of aducanumab and BAN2401 have shown a **strong dose response curve**, only the highest doses showed clinical benefit, suggesting that delivery of a higher dose would increase efficacy.
  - But both products have reached their maximum tolerated dose, due to ARIA-E side effect associated with plaque binding.
- Based on all clinical and scientific data to date a product that avoids plaque binding while strongly binding only AβOs would likely have greater clinical benefit vs. aducanumab V4 data, with little/no side effect

- **PMN310 is that potentially best in class product**

ProMIS history: evaluating positive aducanumab data to create best in class amyloid-targeting therapy



Evaluated positive PRIME dataset through scientific lens of “mis-folded protein hypothesis”

Designed ’best in class’ PMN310, with selective binding of AβOs

Proprietary discovery engine used to create mAbs selective for toxic forms of tau, TDP-43, alpha-synuclein

Corrected aducanumab pivotal data are positive, but with room for improvement as predicted by the “mis-folded protein” hypothesis

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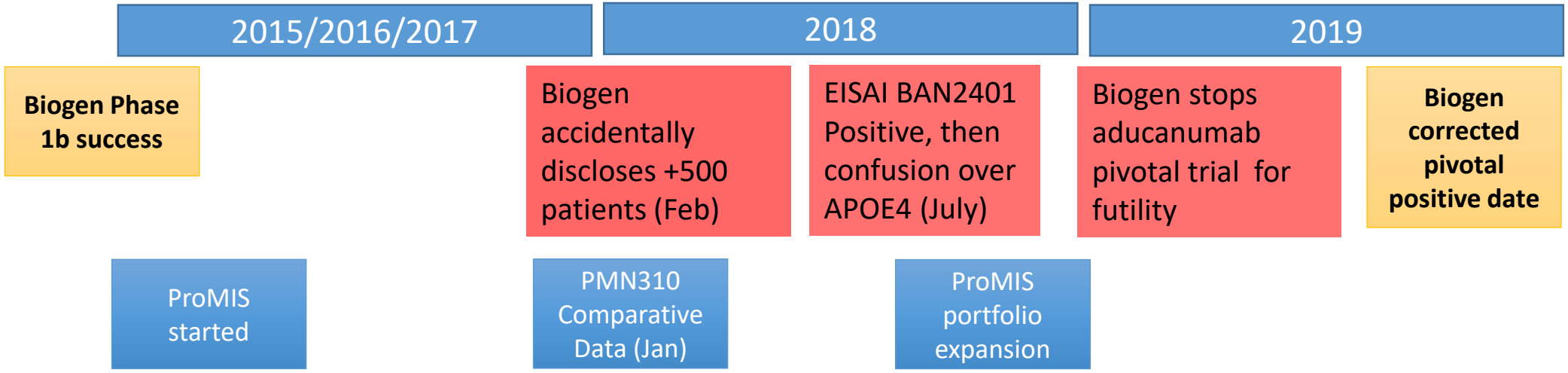
Despite positive aducanumab results recent history fueled negative sentiments; however, 2020 marks a new era in AD therapeutic progress



- 2018 and 2019 saw numerous failures of amyloid targeted programs, many as predicted by the mis-folded protein view of disease
- Miscommunication and mistakes by Biogen and EISAI, with products that appear to provide clinical benefit, created significant negative sentiment
- 2020 marks the beginning of an era of progress in AD

Aducanumab provides clinical benefit of 20% - 30% *only at the highest dose, 10mg/kg* - strong dose response curve

PRIME Phase 1B -52 wks

CDR -SB

***Treatment effect: -22%**

V4 pivotal high dose -72 wks

EMERGE	ENGAGE
High dose (n=288) 10mg/kg	**High dose (n=282) 10mg/kg**
Difference v. placebo P<0.01	Difference v. placebo P<0.01
CDR-SB Treatment effect -30%	**CDR-SB Treatment effect -27%**

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There are three forms of amyloid, choosing the correct target is critical….

Monomer – Important for brain health

Toxic oligomers – thousands of scientific studies showing neurotoxicity

Plaque – usually present, but no role in disease

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Early amyloid targeted programs, typically designed 10-15 years ago, were targeted at amyloid monomer, or were non-selective..*None has ever resulted in a positive Ph2 or Ph3 trial*

Monomer – Important for brain health

Toxic oligomers – thousands of scientific studies showing neurotoxicity

Plaque – usually present, but no role in disease

Over 20 Phase 2 and 3 clinical trials targeting monomer
ZERO POSITIVE

~10 Phase 2 and 3 clinical trials non-selectively targeting all forms of amyloid
ZERO POSITIVE

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Biogen's aducanumab and EISAI BAN2401 are the first partially selective amyloid programs, targeted aggregated amyloid, *both have had only successful trial results*

Monomer – Important for brain health

Toxic oligomers – thousands of scientific studies showing neurotoxicity

Plaque – usually present, but no role in disease

Over 20 Phase 2 and 3 clinical trials targeting monomer
ZERO POSITIVE

~10 Phase 2 and 3 clinical trials non-selectively targeting all forms of amyloid
ZERO POSITIVE

Two drugs from Biogen and EISAI partially selective -
THREE OUT OF THREE POSITIVE
Two Phase 2 trials, one Phase 3 program
- *But – side effect ARIA-E due to plaque binding*

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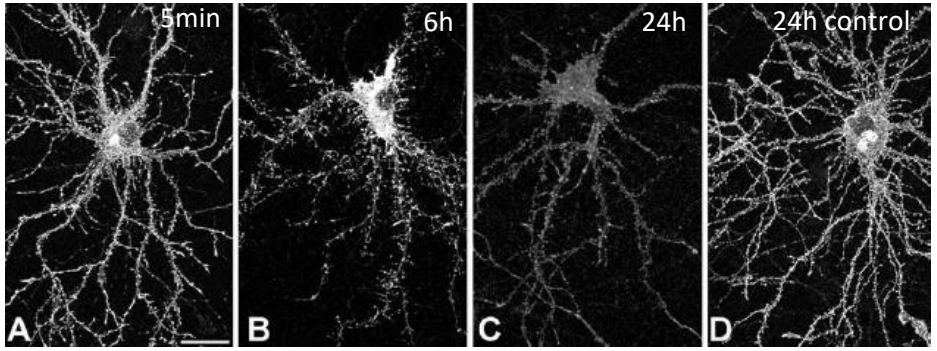
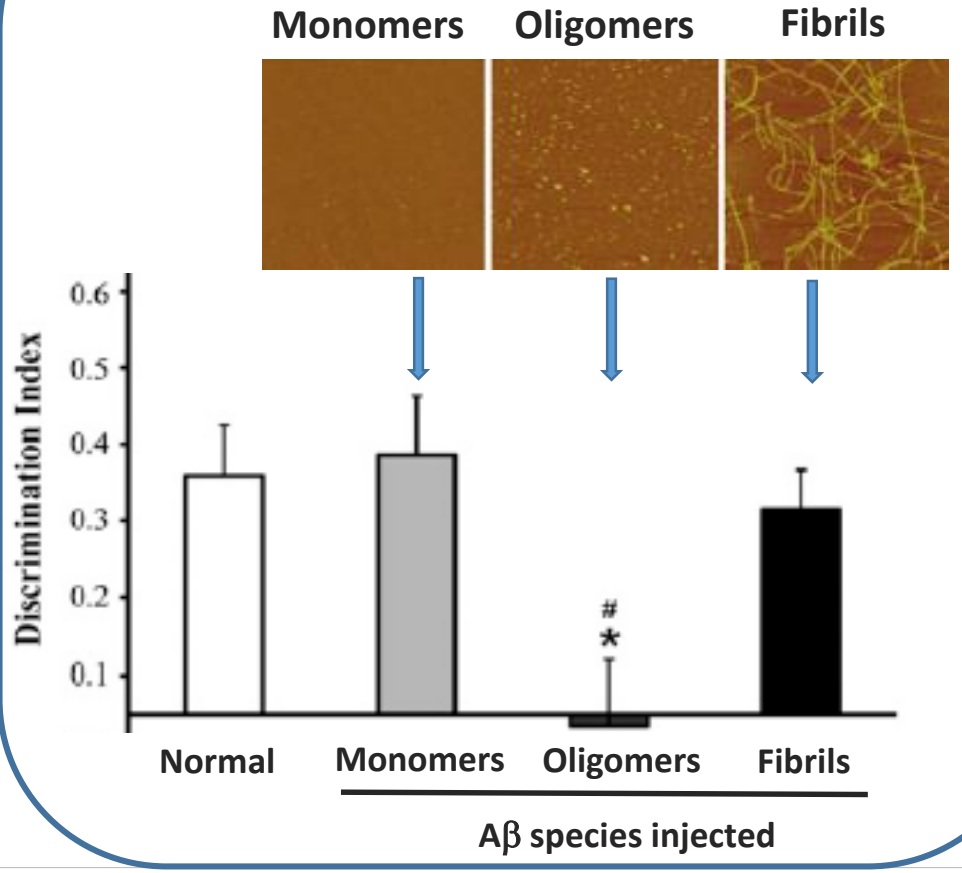
Alzheimer's disease: soluble toxic Aβ oligomers – not plaque or monomers – are the most neuropathogenic Aβ species

- 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

The logic supporting selective targeting of mis-folded, toxic AβOs

Q1: Is amyloid beta a valid target for disease modifying therapy in AD?

-Results of aducanumab PRIME & V4 pivotal, and BAN 2401 phase 2 show efficacy on cognitive decline.

Q2: Which form of amyloid beta is the correct target?

- Clinical trials targeting Aβ monomer have all failed
- Plaque is not the pathogenic species of Aβ
- Misfolded AβOs are the toxic species and a root cause of AD

Q3: Targeting toxic AβO: dose matters

- Aducanumab shows dose response, with 10mg/kg the effective dose
- Dose-limiting side effect prohibits higher dosing of aducanumab (owing to plaque binding)
- PMN310 selective binding of toxic AβOs should allow higher dosing and greater therapeutic potential

ProMIS PMN310, oligomer selective mAb

Binding the right form of amyloid beta is critical: the toxic oligomer is the target

Bapineuzumab
- Phase 2 failure
- Phase 3 failure
- ARIA-E side effect

Solanezumab
- Phase 2 failure
- Phase 3 failure

Aducanumab
- Phase 2 & 3 success
- ARIA-E side effect

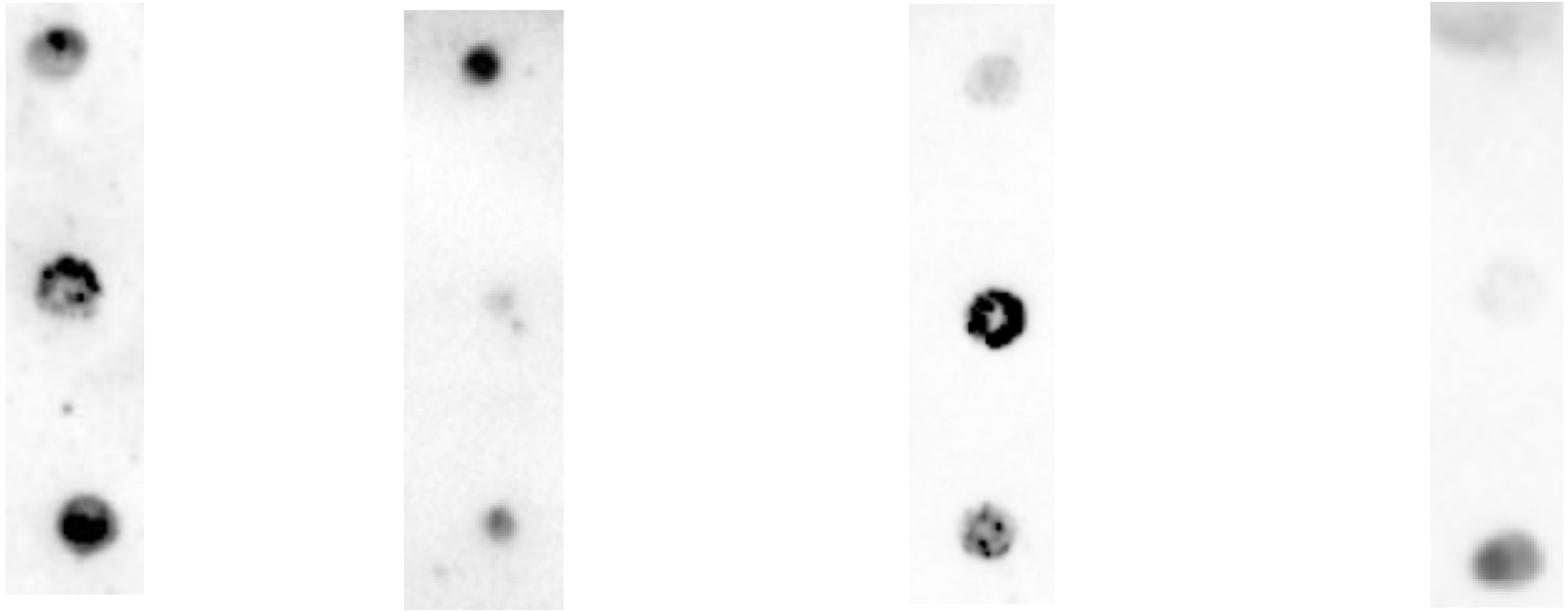
PMN310
- Selective binding to oligomers

-> Expected improvement in efficacy & safety

MONOMERS
- binding wastes therapeutic ammunition

FIBRILS (Plaque)
- binding wastes therapeutic ammunition
- contributes to ARIA-E side effect

OLIGOMERS*
- the right target



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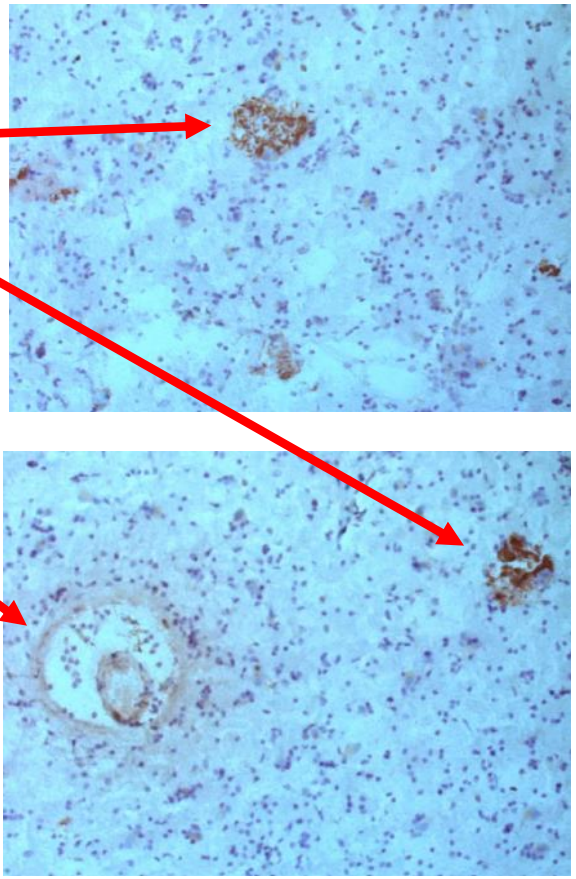
* Synthetic oligomers

ARIA-E associated with both aducanumab & bapineuzumab; PMN310 lack of binding to Aβ plaque strongly suggests a potential safety advantage

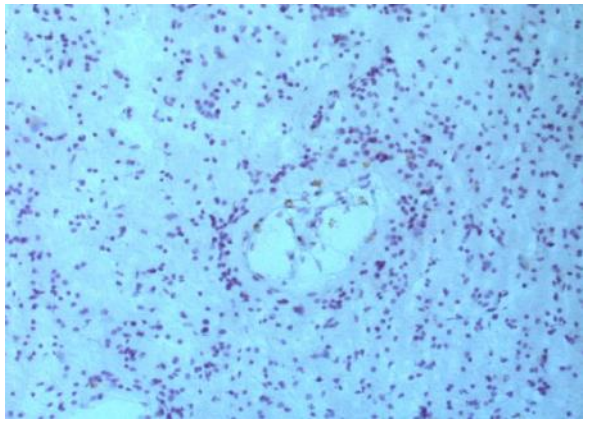
Aducanumab



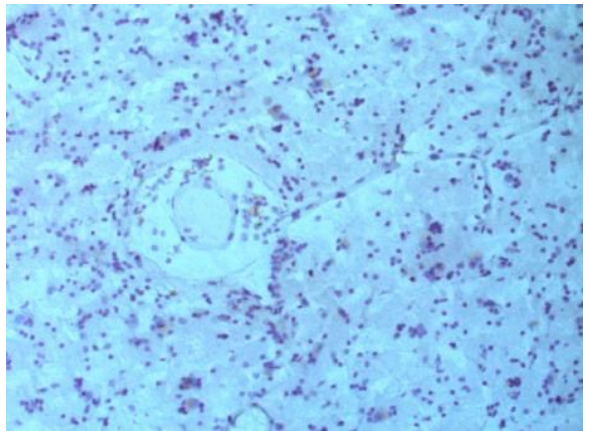
Plaque binding

Vascular deposit binding

PMN310



No binding to plaque or vascular deposits



PMN310 IgG4 isotype also correlated with lack of ARIA-E

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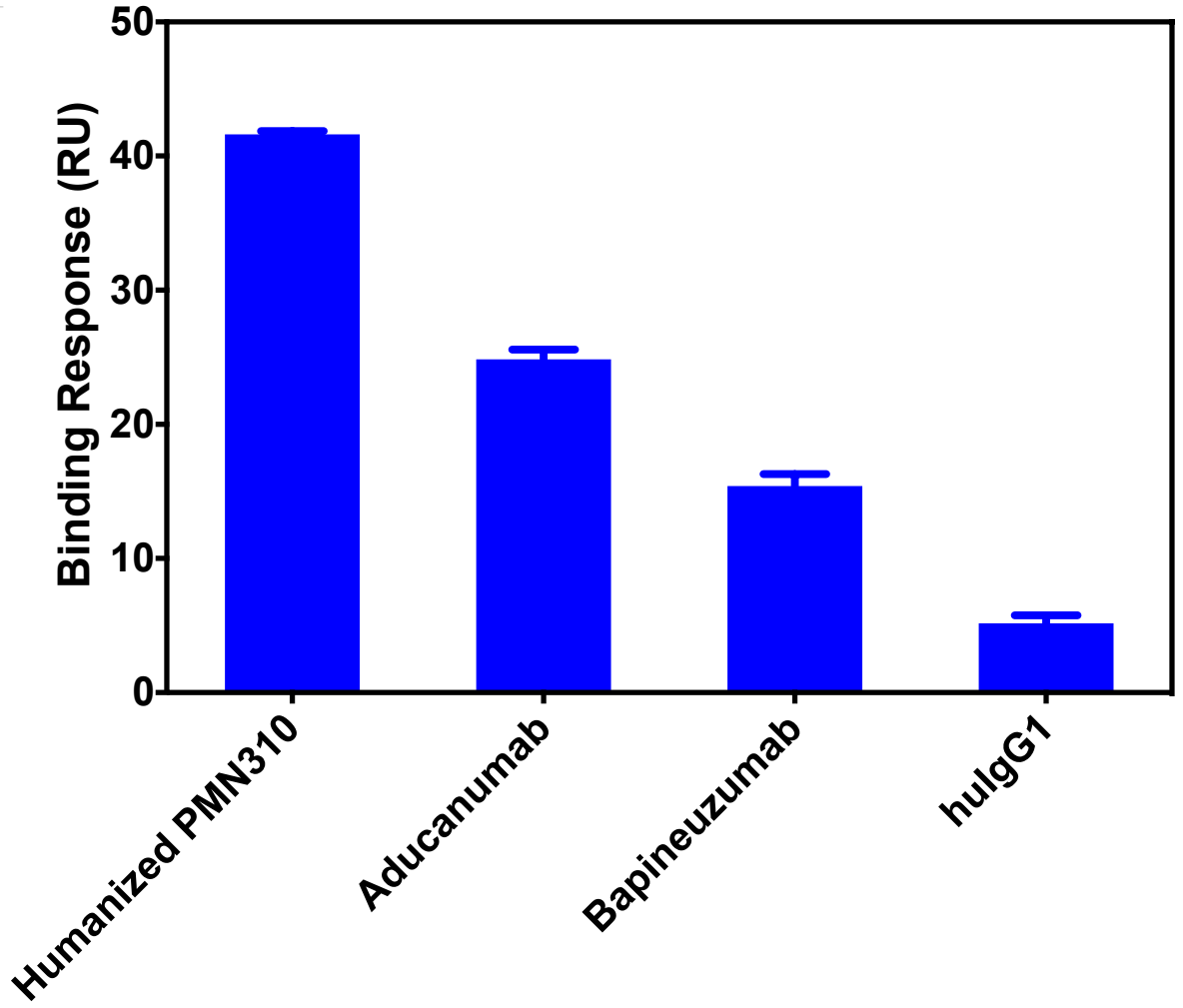
huPMN310 shows superior binding to toxic oligomers from human AD brains vs other antibodies directed against amyloid-beta



- Binding of antibodies to the toxic oligomer-enriched LMW fraction of soluble human AD brain extract was evaluated by surface plasmon resonance (SPR)
- Results representative of over 10 SPR runs with extracts from 11 different AD brains
- huIgG1 = Background control

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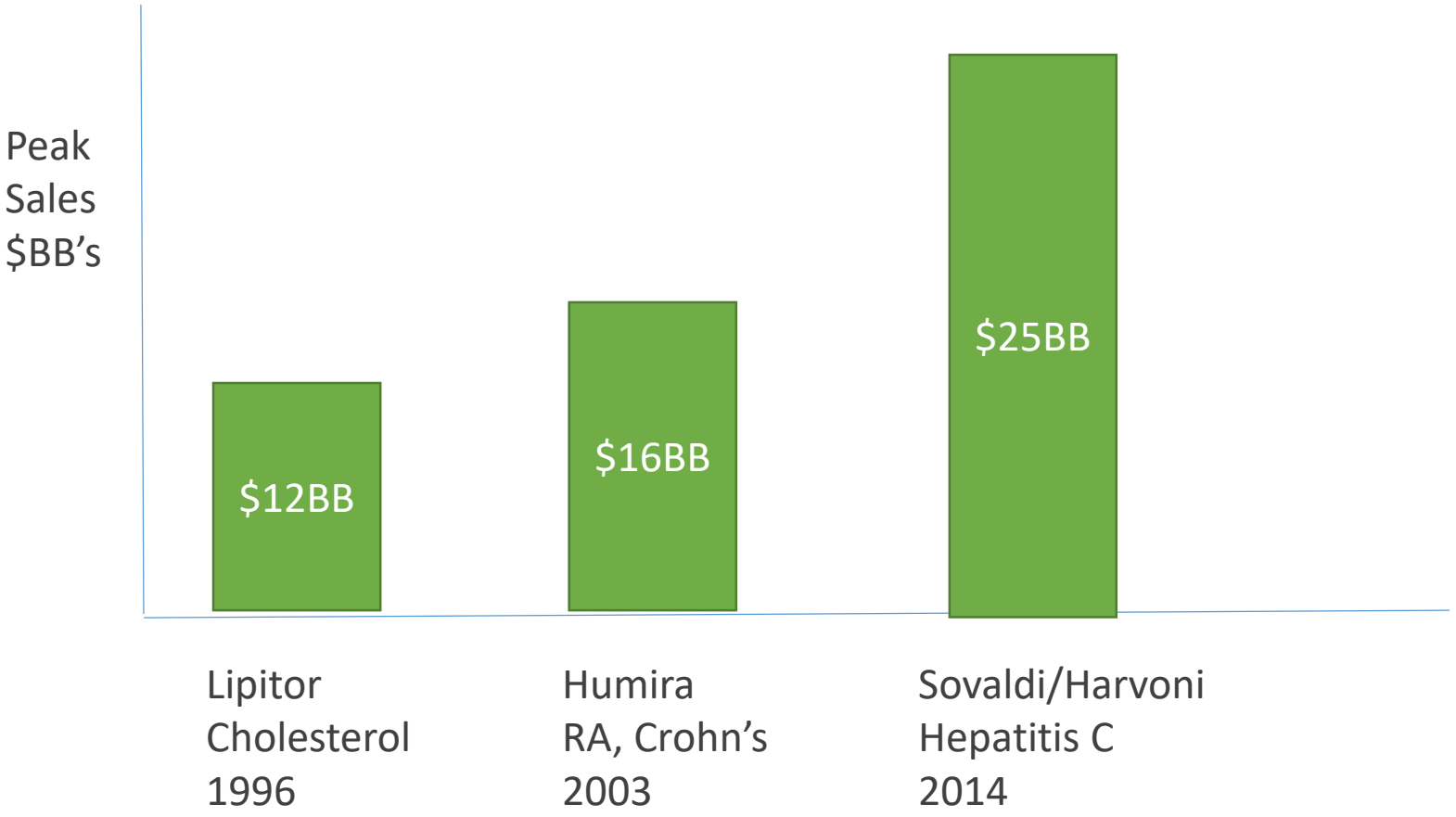
Source for comparative reagents: Creative Biolabs

The three largest products in industry history were not first in class, but "best in class" – the inventors identified improvements to existing drugs



ProMIS following the "best in class" playbook:

- Took advantage of "proof of biology" developed by earlier products: the scientific rationale for aducanumab's success, when all prior programs failed
- Used ProMIS proprietary science platform to design an improved product, which may yield superior clinical results

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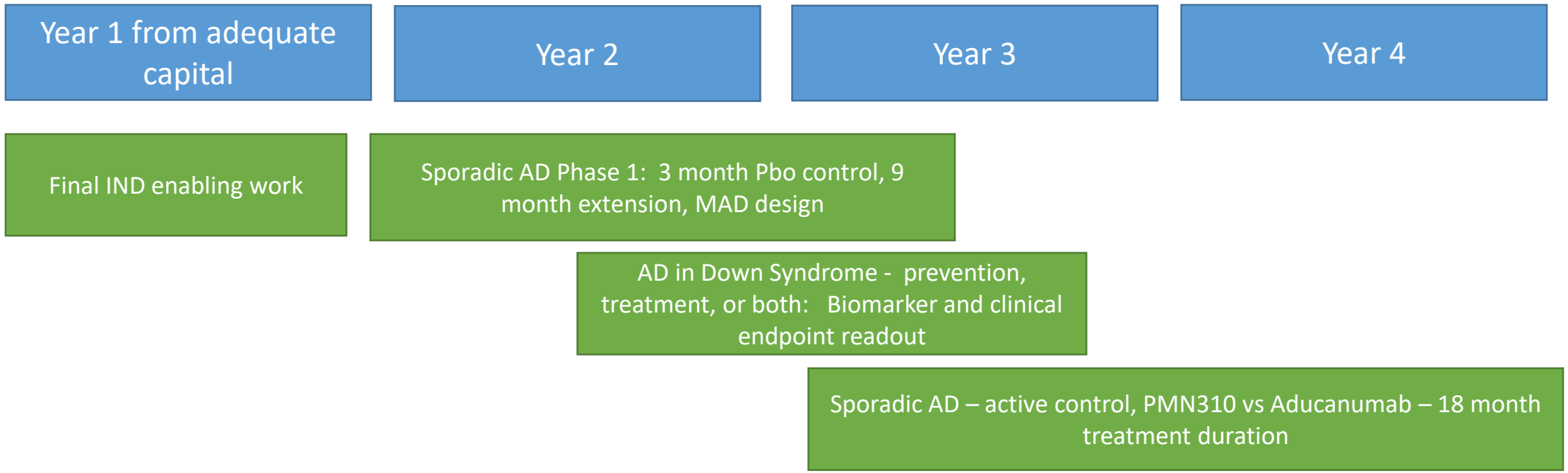
PMN310 development plan – significant data readouts over coming 2-4 years



Potential approval pathway: AD in Down Syndrome, pre-symptomatic, or post symptomatic

- Potential for accelerated approval per FDA guidance , Feb 2018
- Rapid progress, well organized community creates potential for rapid program

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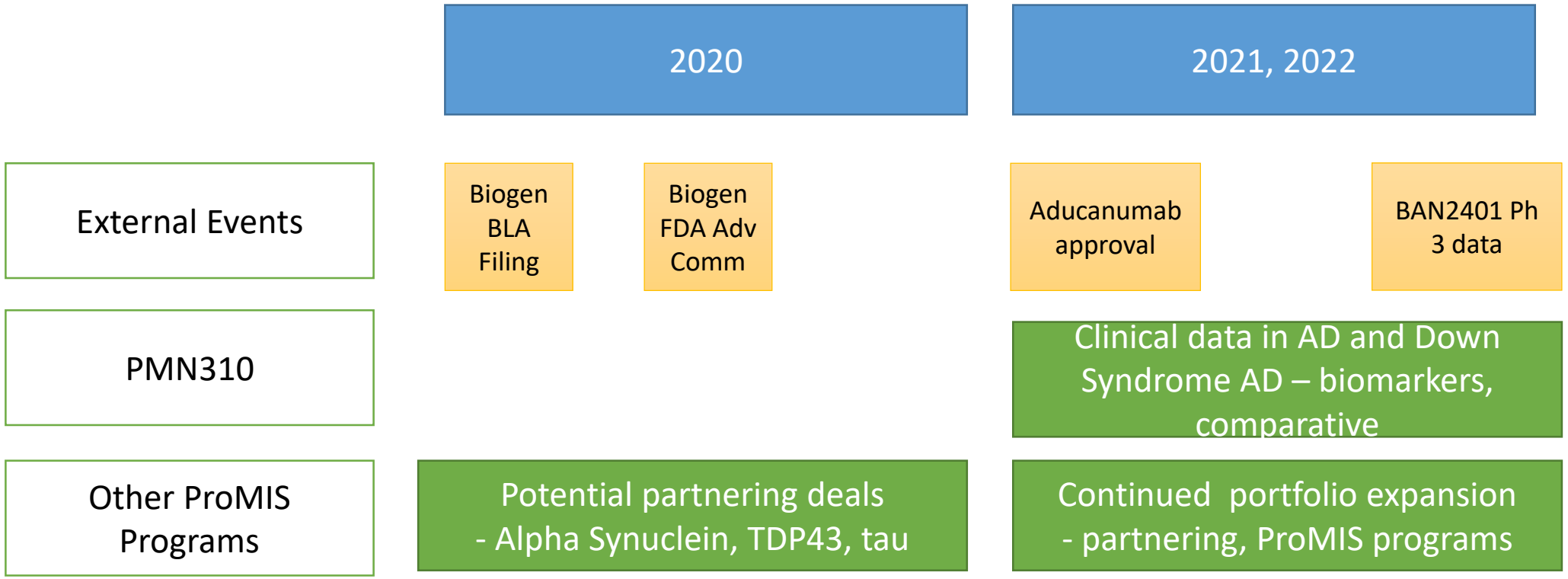
Outlook & Summary

ProMIS going forward : potential for numerous catalysts and value creation



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Summary: ProMIS is on the right track selectively targeting toxic mis-folded proteins in Alzheimer's and other neurodegenerative diseases

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  - PMN310 selective for toxic oligomer of amyloid, no plaque or monomer binding
  - Likely to avoid aducanumab dose-limiting side effect, PMN310 can dose higher
- ProMIS will capitalize on emerging fluid-based biomarkers for rapid and cost efficient early clinical POC
- Unique capability and track record creating antibodies highly selective for mis-folded proteins leading to a portfolio of mAb therapeutics for AD, ALS, PD
  - Active partnering discussions could lead to deals in near/medium term

Thank You

Please feel free to contact us with any additional questions.

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