



Early Clinical Development Strategy: Demonstrating Proof-of-Concept With Innovative Biomarkers and Focused Patient Populations

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Early Clinical Development Strategy at ProMIS

Pursue rapid, cost-effective development of our assets that creates an early inflection point in program value

- ✓ Utilize innovative, informative fluid-based biomarkers to rapidly show a disease-modifying treatment effect
- ✓ Focus on disease populations in each program that have the highest odds of showing a biomarker response in an early, relatively small clinical study

What is a Biomarker?

A characteristic that is objectively measured and evaluated as an indicator of:

1. Normal biologic processes,
2. Pathogenic processes, or
3. Pharmacologic responses to a therapeutic intervention

NIH Biomarkers Definition Working Group 2001

Commonly known biomarkers		
Disease	Biomarker	Clinical Endpoint
Hypertension	Blood pressure	Stroke, vascular disease
Dyslipidemia	Cholesterol, LDL	Coronary artery disease
Diabetes	Glucose, HbA1c	Retinopathy, Nephropathy, Neuropathy, heart disease
Glaucoma	Intraocular Pressure	Loss of vision
Prostate Cancer	PSA	Prognosis

Biomarkers must undergo a rigorous validation process after identification:

- ✓ Establish relevance to the targeted population
- ✓ Identify clinical utility
- ✓ Widespread adoption

Biomarkers can enhance and accelerate drug development

Drug Development Continuum



Clinical Biomarkers can:

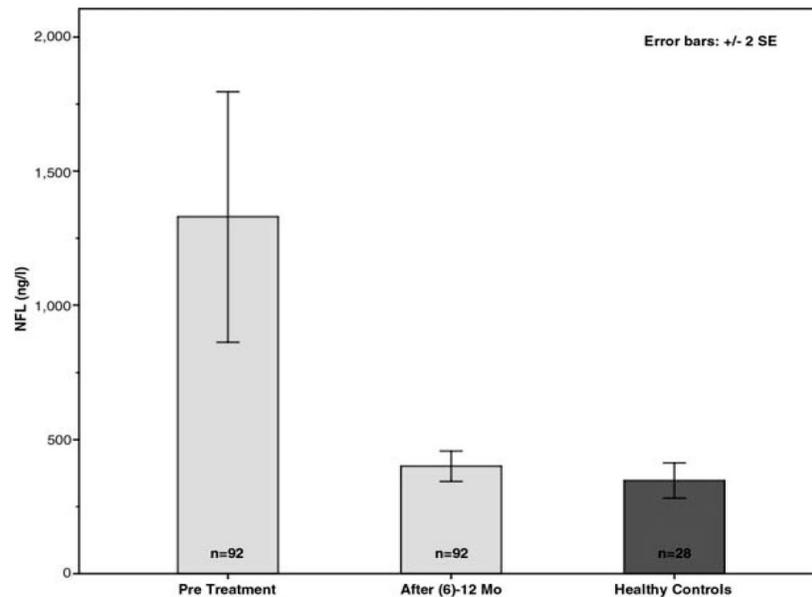
- ✓ Monitor the safety of a therapy
- ✓ Predict patients who might respond better
- ✓ Potentially enable time and cost savings in trials
- ✓ Determine if a treatment is having the desired effect on the body

Pharmacodynamic Biomarker

- Show a drug hits its target with an biochemical impact
- Demonstrates proof of the drug's mechanism of action
- Can help determine dose and dose schedule

Two examples of a pharmacodynamic marker (NfL) in neurology

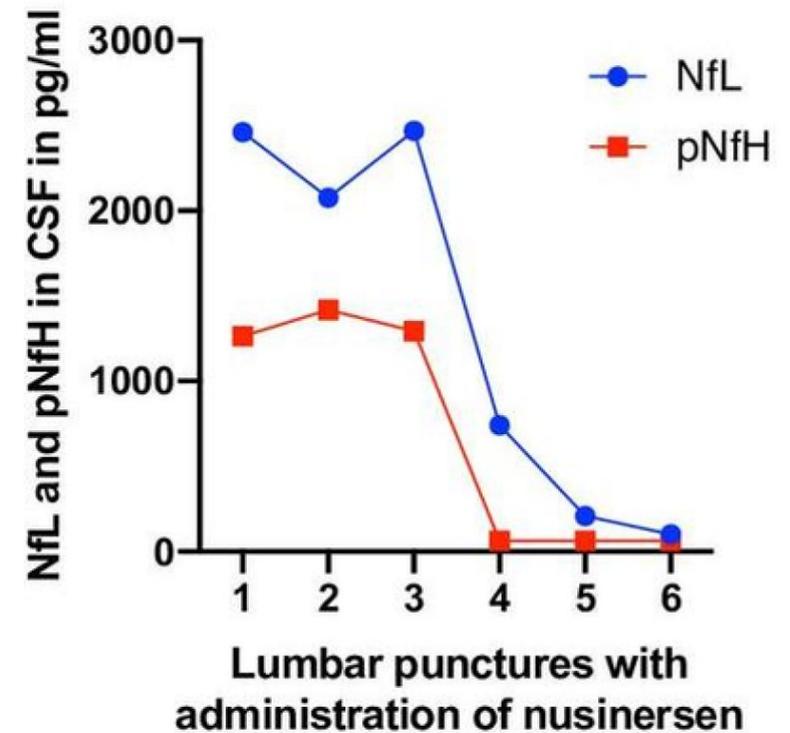
Tysabri in multiple sclerosis



Neurofilament light in cerebrospinal fluid following monthly administration of natalizumab (300 mg) in 92 patients with multiple sclerosis

Gunnarsson, et al Annals of Neuro 2011

Spinraza in spinal muscular atrophy

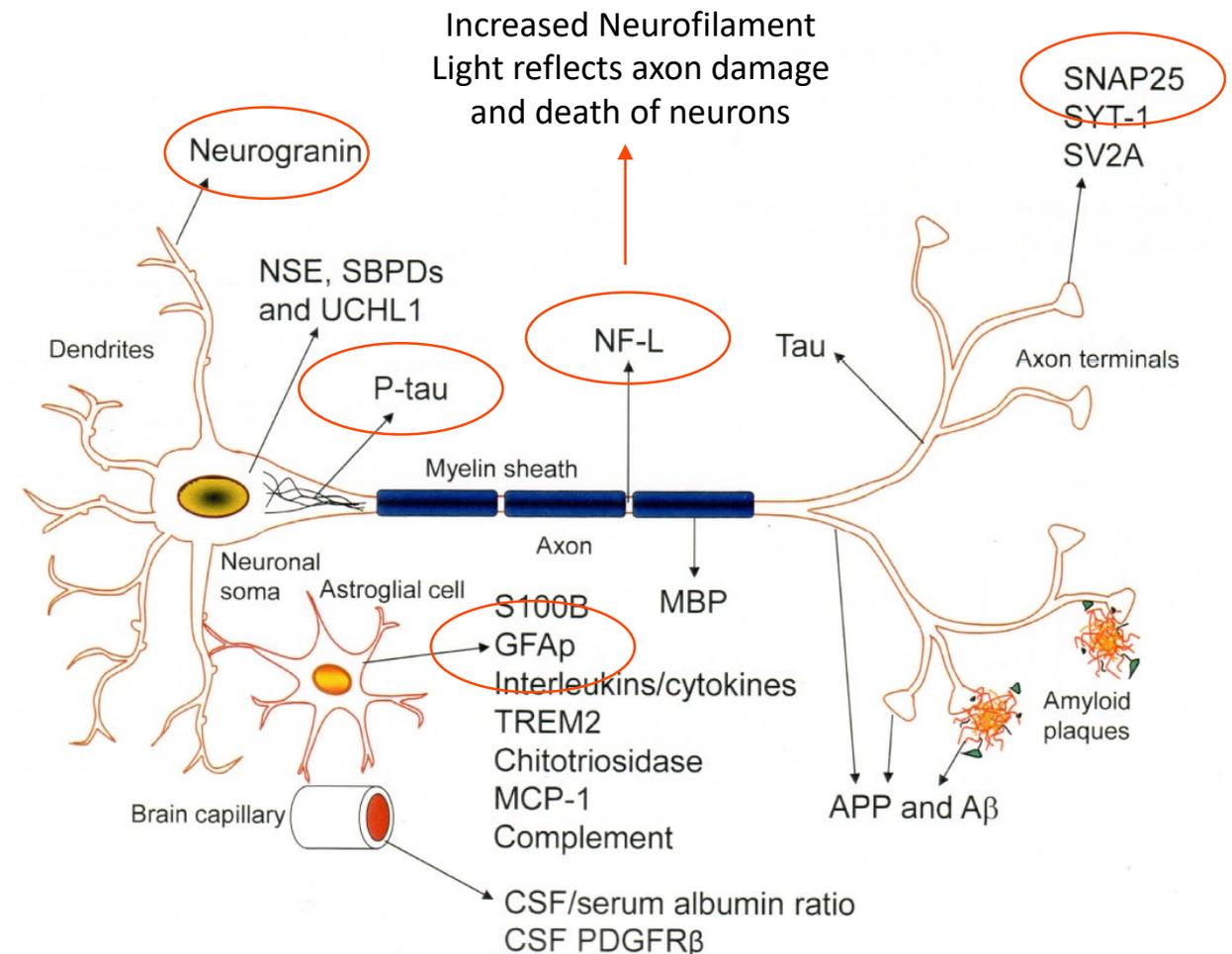


Winter B. et al, J Neurol Neurosurg Psychiatry 2019

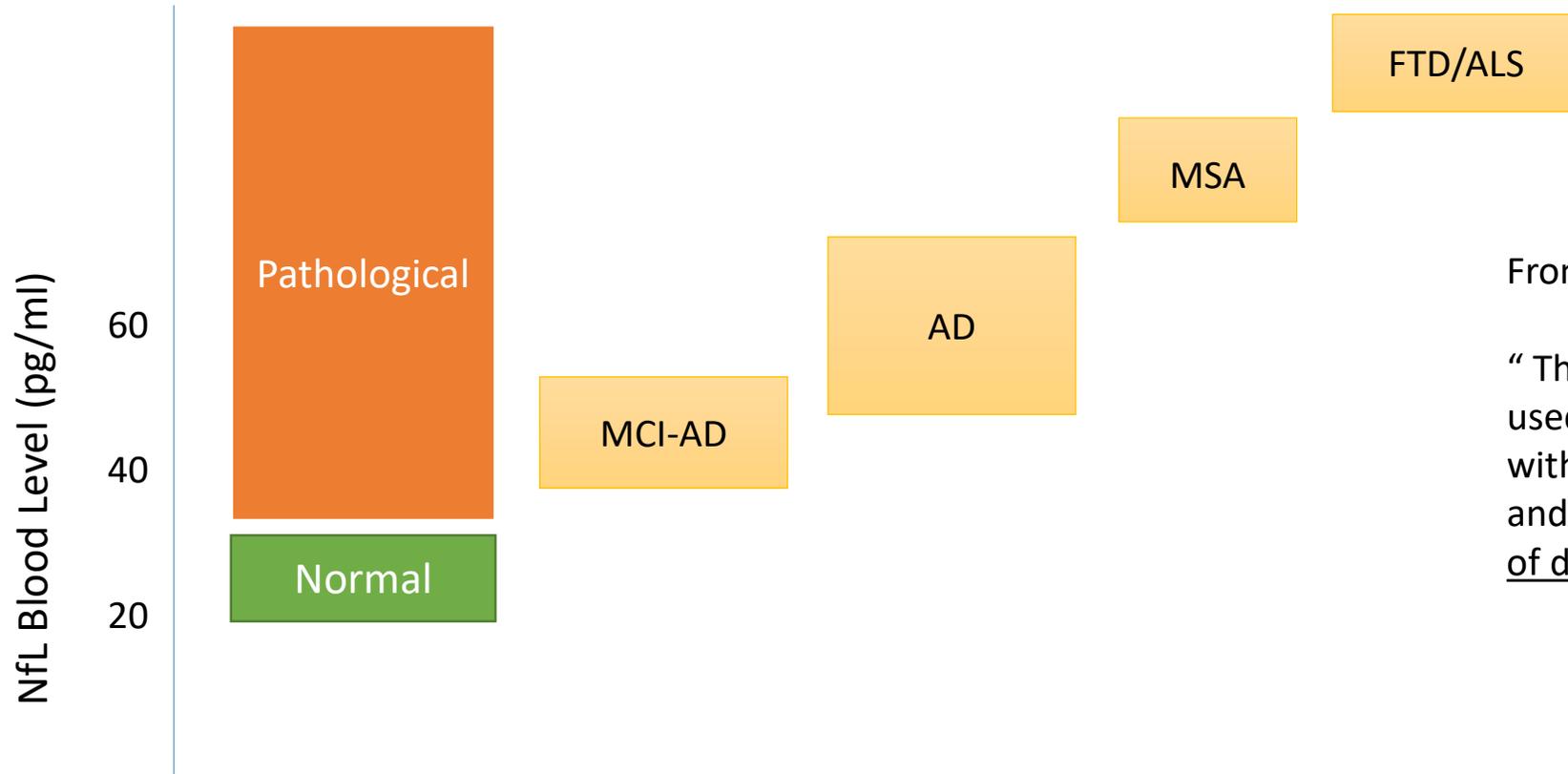
There's a revolution in available fluid-based biomarkers that reflect neurologic disease pathophysiology

The research community is at the cusp of a new era by having highly sensitive blood-based biomarkers that will enable:

- (1) the earlier screening for disease, and
- (2) the efficient monitoring of disease intervention early in the drug development process



Neurofilament light (NfL) is a measure of the rate of neuronal death.....



From JAMA Neurology, April 22 2019

“ The findings suggest that plasma NfL can be used as a noninvasive biomarker associated with neurodegeneration in patients ... and may be useful to monitor effects in trials of disease-modifying drugs”

Mattsson, et al, JAMA Neurology

Sources: from AAIC 2018 ABBVIE, Wash U, U Sorbonne;
Rohrer et al, 2016 AAN; Mattson et al, JAMA Neurology 2017



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 - **Three examples: different neurodegenerative disorders, each associated with misfolded, aggregated proteins that cause synaptic loss and neuronal death**

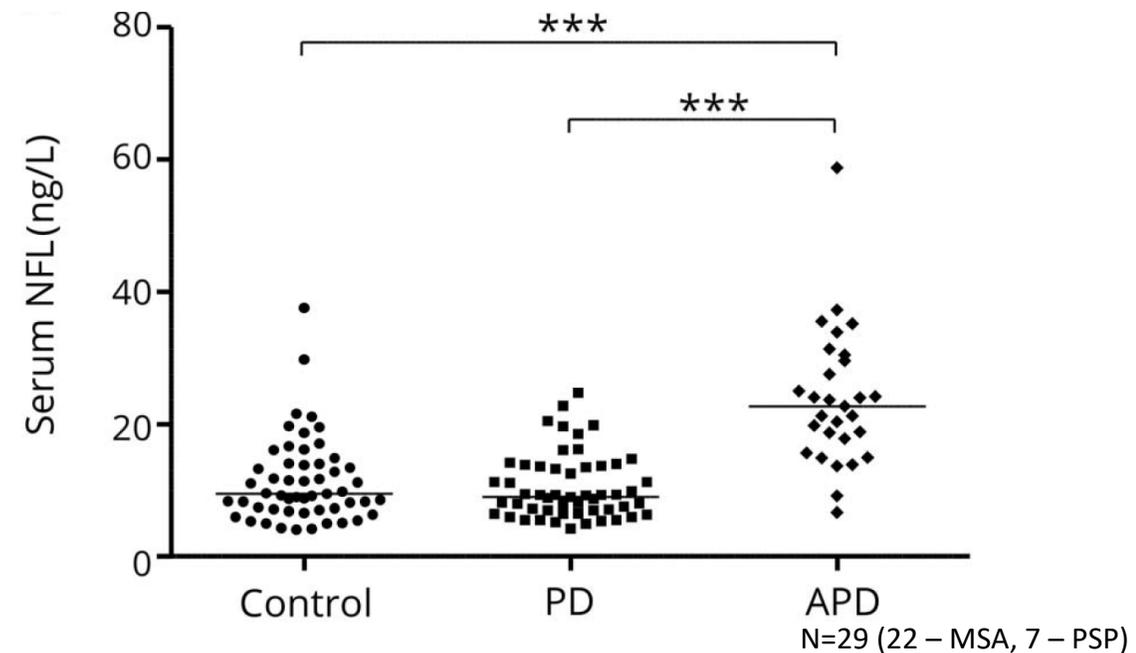
Example #1: Multiple System Atrophy (MSA)

Multiple System Atrophy

- Aggressive, rare neurodegenerative disease driven by toxic-misfolded, aggregated forms of α -synuclein
- Attacks oligodendroglia and neurons
- One of several synucleinopathies (others include PD and LBD)
- Symptoms: autonomic dysfunction, parkinsonism and cerebellar ataxia
- NfL markedly elevated

ProMIS has multiple antibodies with highly selective binding to the toxic form of α -synuclein and strong binding to brain tissue from patients who died of MSA

Serum NfL highly discriminates atypical parkinsonism disorders (including MSA) from Parkinson disease or healthy controls



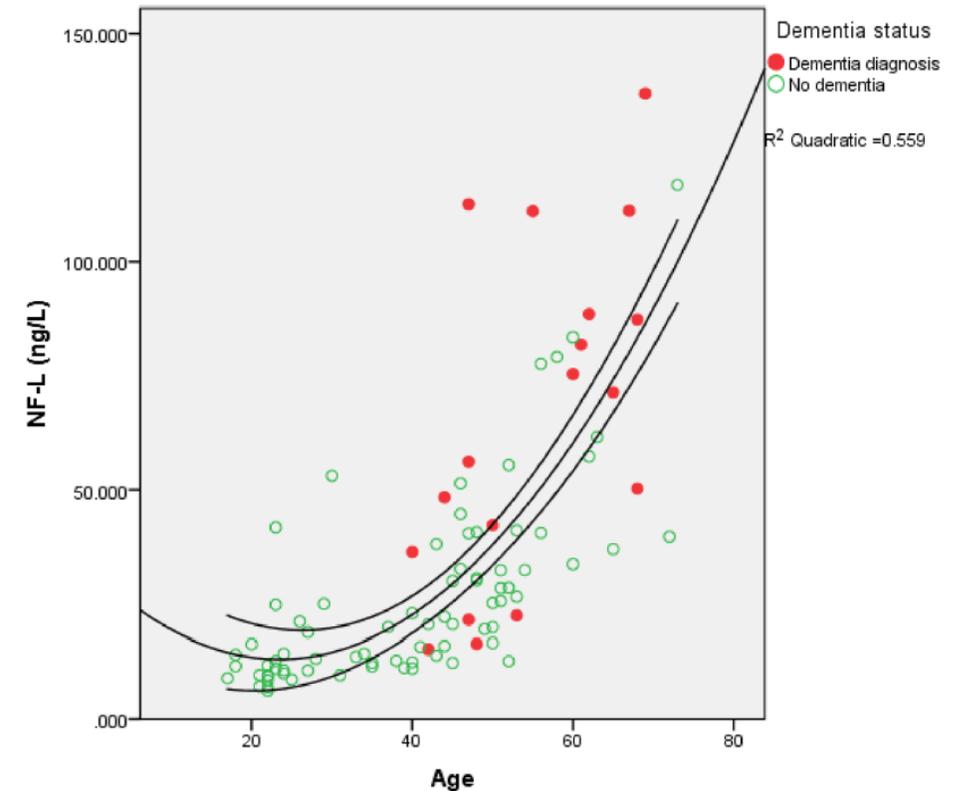
Marques, TM, et al. NEUROLOGY 92(13) March 2019

Example #2: AD in Down Syndrome

- Caused by a third copy of chromosome 21 (extra copy of the amyloid precursor protein)
- Associated with physical growth delays, moderate intellectual disability and characteristic facial features
- Almost all people with Down syndrome by age 40 have amyloid brain deposits; the majority will show AD symptoms in their 50's and 60's and ultimately develop dementia
- Highly motivated DS community for clinical research; established clinical network of research sites (US and EU).
- NfL is elevated in DS and increases rapidly after age 40
- Presymptomatic DS patients with elevated NfL identified and available for interventional studies

PMN310, the ProMIS lead candidate, has highly selective binding to the toxic form of β -amyloid and strong binding to brain tissue from patients who died of AD

Neurofilament light (NfL) concentration by age and dementia status of individuals with Down syndrome



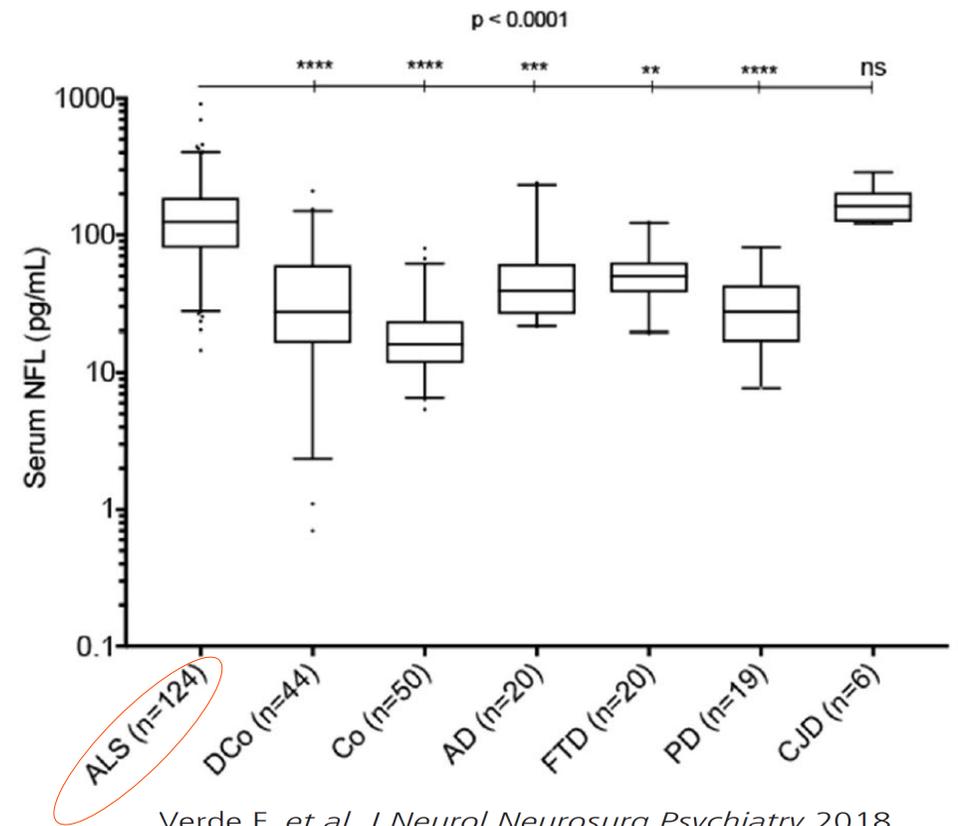
Strydom et al. *Alzheimer's Research & Therapy* (2018) 10:39

Example #3: Amyotrophic Lateral Sclerosis

- Aggressive disease that causes the death of neurons controlling voluntary muscles
- Characterized by stiff muscles, muscle twitching, muscle weakness and atrophy, difficulty with speaking or swallowing
- Majority of sporadic ALS patients (up to 97%) have brains containing TDP-43 protein deposits at autopsy, suggesting its pivotal role in ALS; the current thinking is that TDP-43 pathologic oligomerization and aggregation leads to these deposits
- Highly motivated patients for clinical research
- Well established clinical trial networks in the US and EU

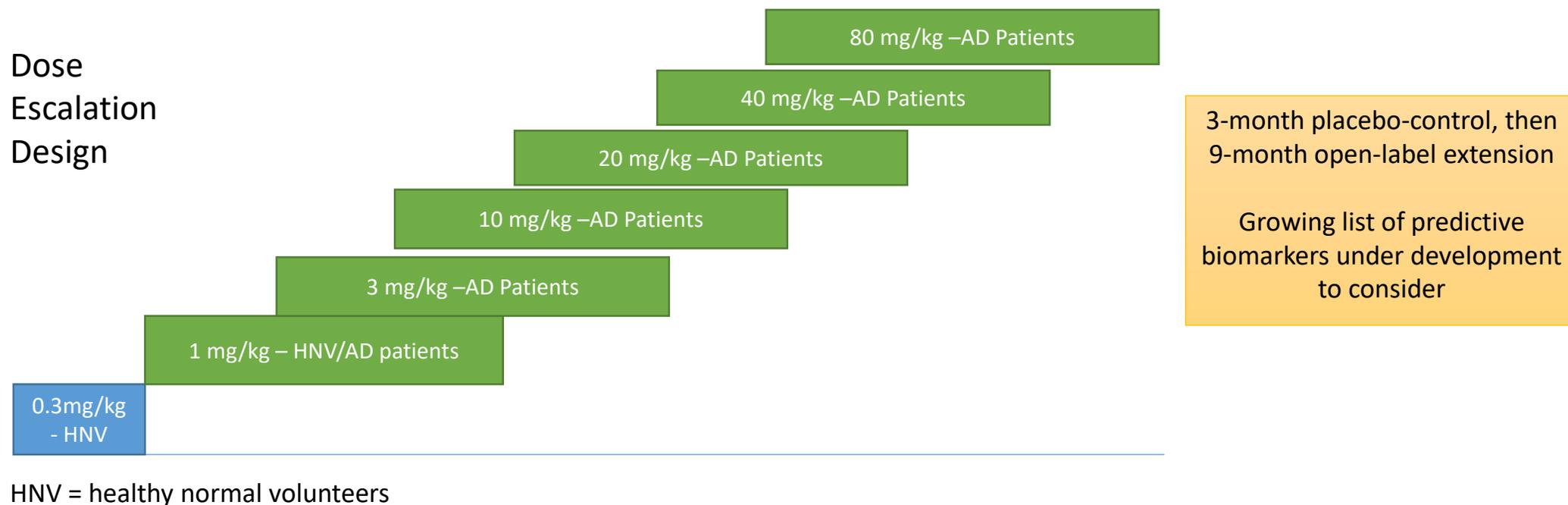
ProMIS has multiple antibodies in preclinical development with highly selective binding to the toxic form of TDP-43 and strong binding to brain tissue from patients who died of ALS. ProMIS is in active partnering discussions with large pharma.

Neurofilament light chain in serum for the diagnosis of amyotrophic lateral sclerosis (ALS)



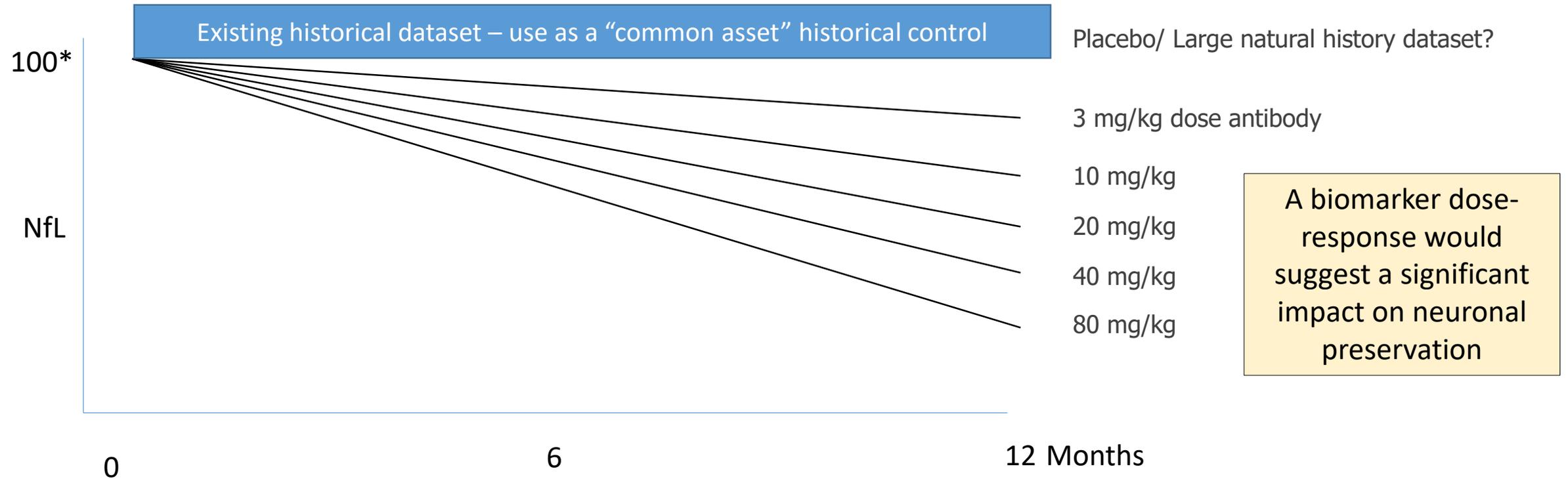
Verde F, et al. *J Neurol Neurosurg Psychiatry* 2018

Phase 1 trial design concept: in higher dose arms, biomarkers can give a signal suggesting therapeutic benefit early in clinical development



Dose levels are representative examples, drawn from other neurodegenerative monoclonal antibody programs
Possibility to use HNVs in lower dose arms, or as sentinel subjects in each cohort

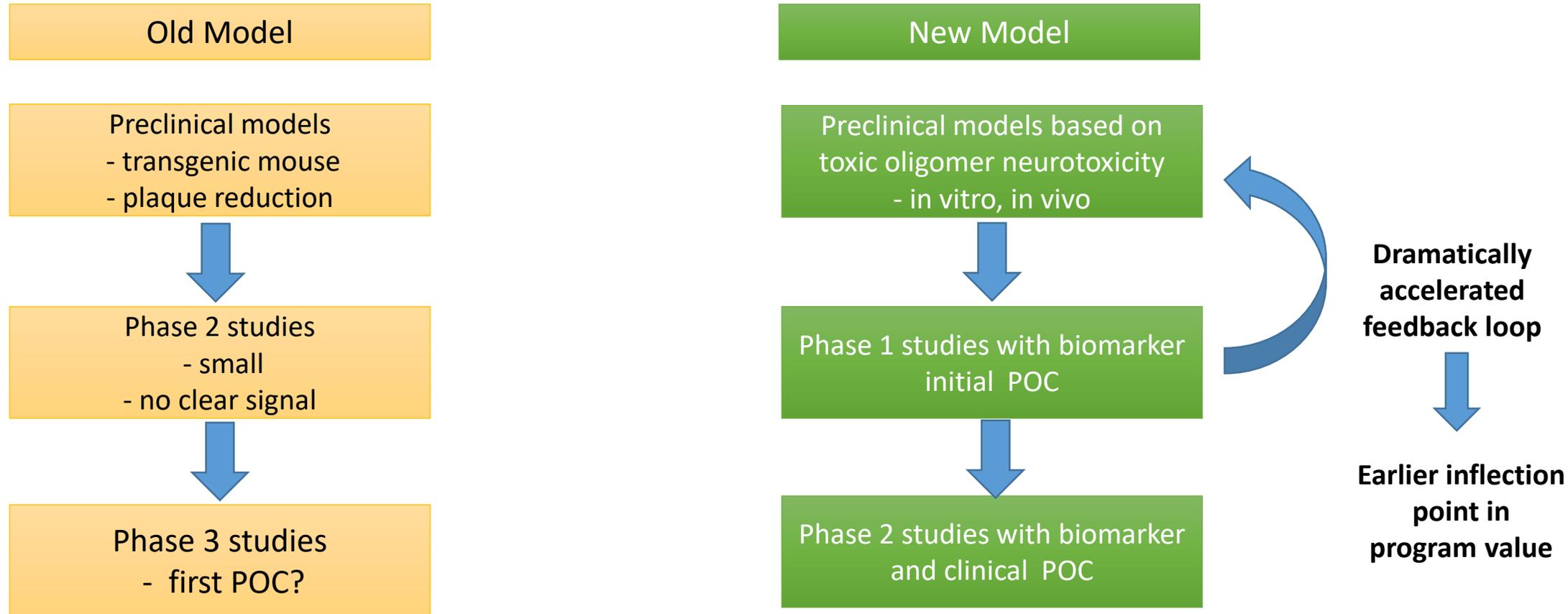
Hypothetical example – Phase 1 biomarker readout



A biomarker dose-response would suggest a significant impact on neuronal preservation

* 100 = patient baseline value

A new development paradigm for neurodegenerative diseases will dramatically improve cost, risk....and success





Clinical Development Strategy at ProMIS: summary of key points

Pursue rapid, cost-effective development of our assets that creates an early inflection point in program value

- ✓ Utilize innovative, informative fluid-based biomarkers to rapidly show a disease-modifying treatment effect
 - **NfL, GFAP, p-181Tau (plasma)**
 - **Neurogranin, SNAP25, YKL-40 etc (CSF)**
- ✓ Focus on disease populations in each program that have the highest odds of showing a biomarker response in an early, relatively small clinical study
 - **Anti-alpha-synuclein** **Multiple System Atrophy**
 - **Anti-amyloid beta** **AD in Down Syndrome**
 - **Anti-TDP-43** **Amyotrophic Lateral Sclerosis**

The impressive, recent development of fluid-based biomarkers represents a revolutionary advance in the development of drugs for neurodegenerative disorders and one that will quickly accelerate the assessment of disease-modifying therapies in early phase clinical development