

Development of a novel, phosphospecific α -synuclein antibody as a therapeutic for MSA

Team

Sreeganga Chandra, PhD

Professor of Neurology and
Neuroscience

Yale School of Medicine

PI/Co-Inventor

Leah Harmon, MPhil

Graduate Student Researcher
Co-Inventor

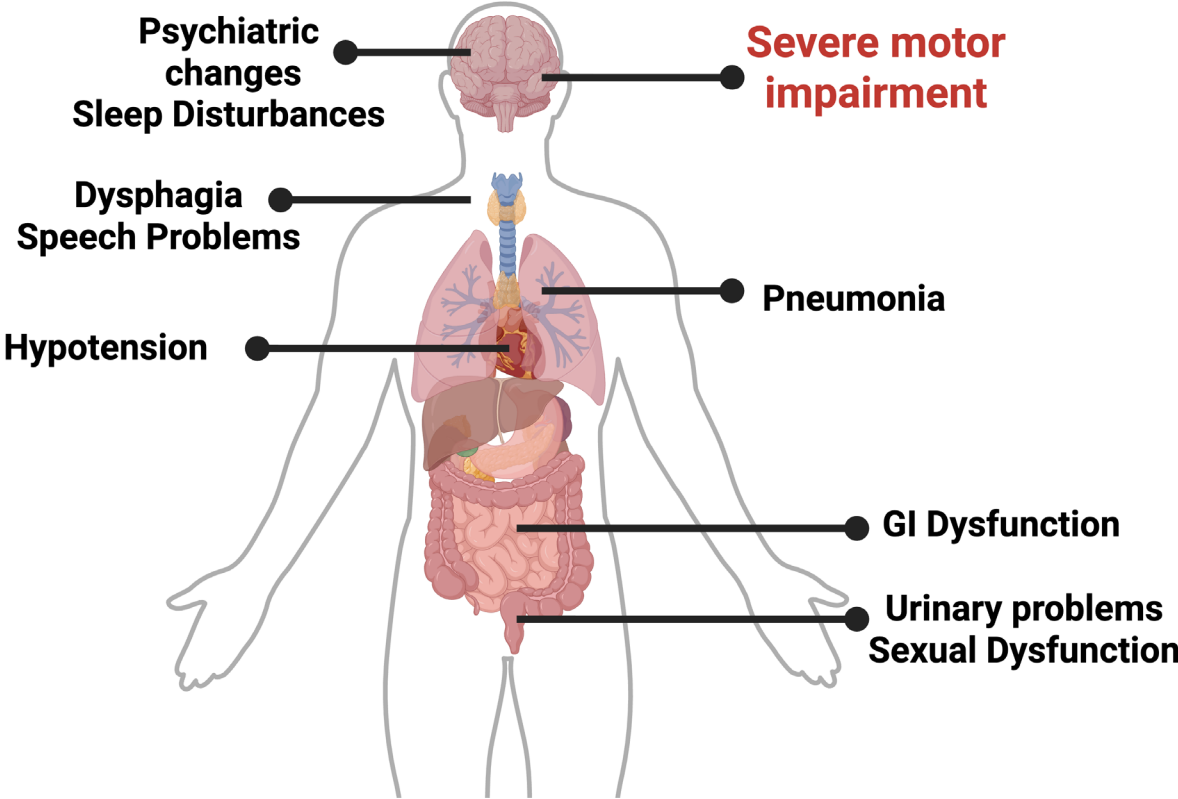
Brian Gibbs, PhD

Blavatnik Fellow 2025-2026

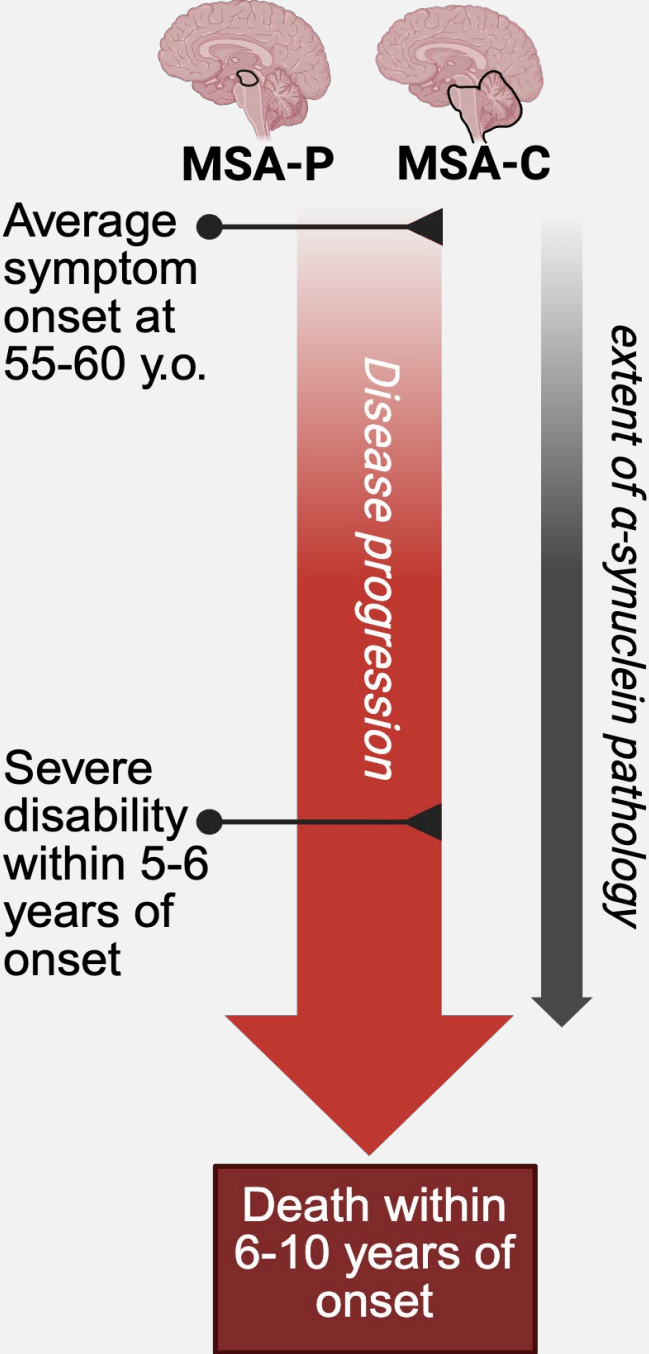
IP Pending, U.S.
Provisional Application
No. 63/794,944

PTThera**Mab**

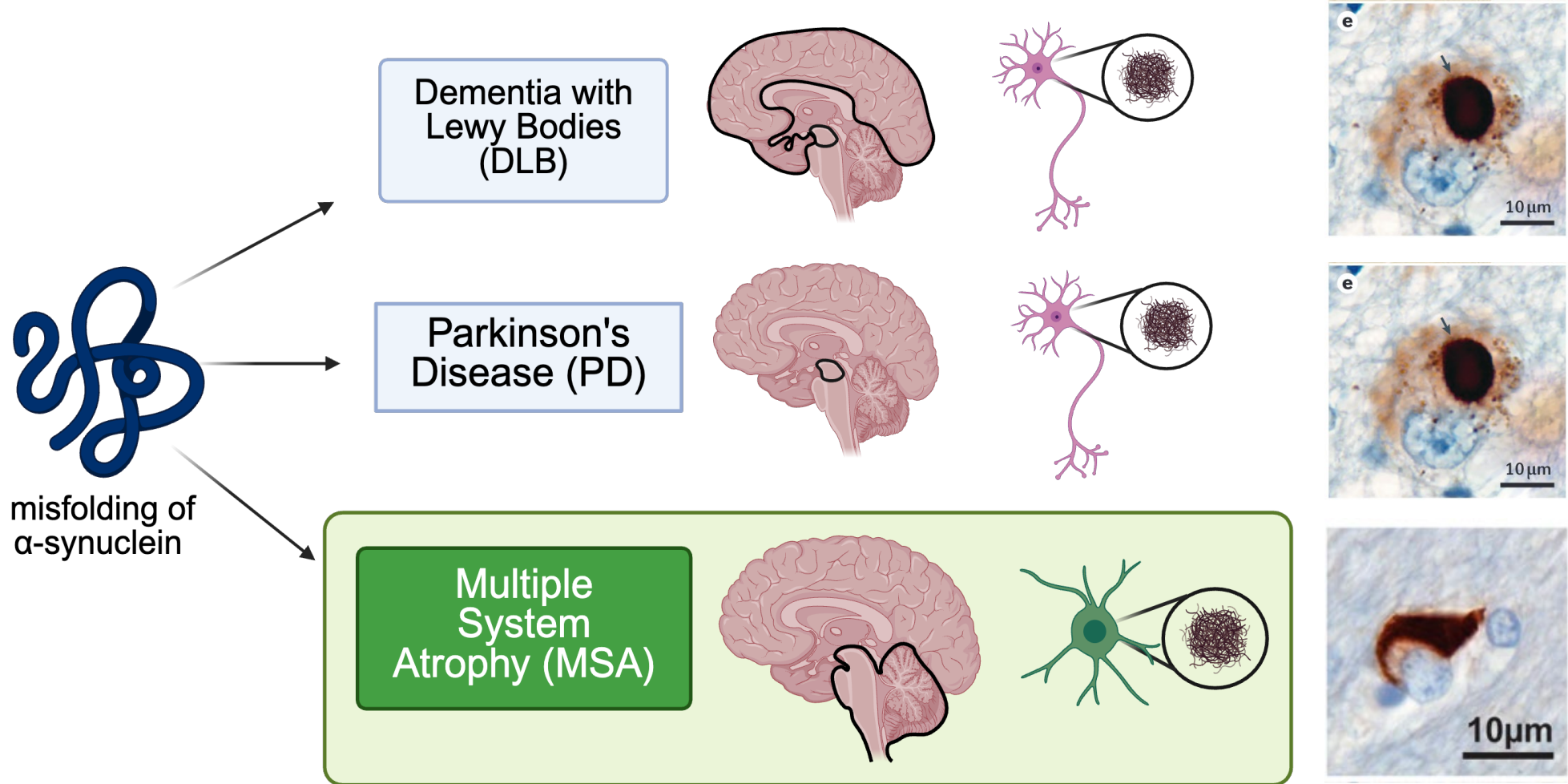
MSA IS AN AGGRESSIVE NEURODEGENERATIVE DISEASE LEADING TO DISABILITY AND DEATH



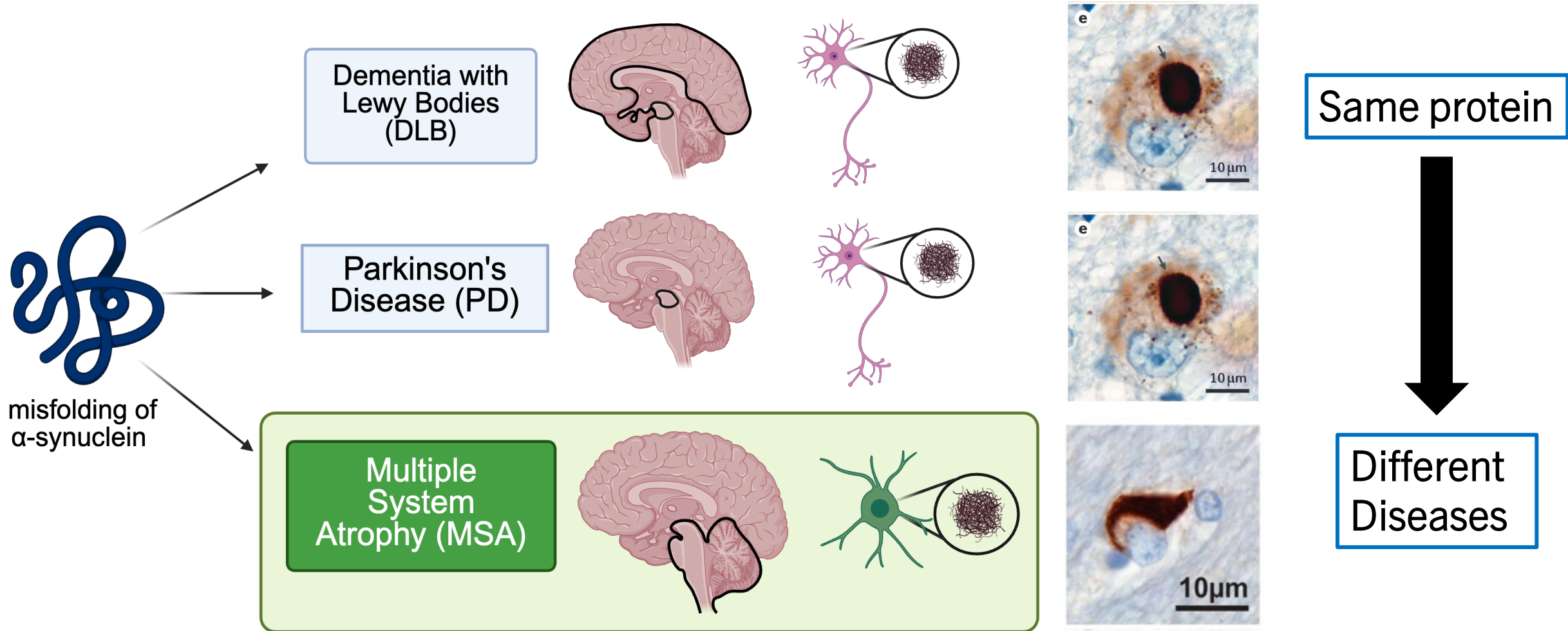
Multiple System Atrophy (MSA) causes degeneration of motor areas in the brain and autonomic dysfunction



MSA IS CHARACTERIZED AS A SYNNUCLEINOPATHY



MSA IS CHARACTERIZED AS A SYNUCLEINOPATHY



Disease specific structural variants must exist

THERE IS CURRENTLY NO DISEASE-SPECIFIC THERAPEUTIC FOR MSA

Previous lack of understanding of how misfolding of the same protein leads to different diseases



Lack of disease-specific therapeutics for MSA

THERE IS CURRENTLY NO DISEASE-SPECIFIC THERAPEUTIC FOR MSA


Previous lack of understanding of how misfolding of the same protein leads to different diseases




Lack of disease-specific therapeutics for MSA

Levodopa/Carbidopa Therapy:

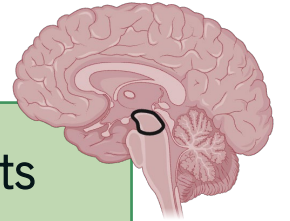
- Standard of care for PD/MSA for 50 years

 Dopamine
(compensates for
DA neuron loss)

 Motor symptoms (NOT
disease-modifying)

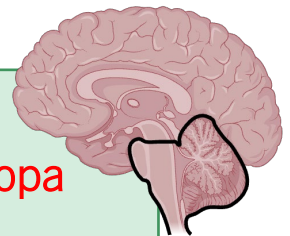
MSA-P Patients: ~70% of US patients

- **Poor response to levodopa is hallmark of MSA**



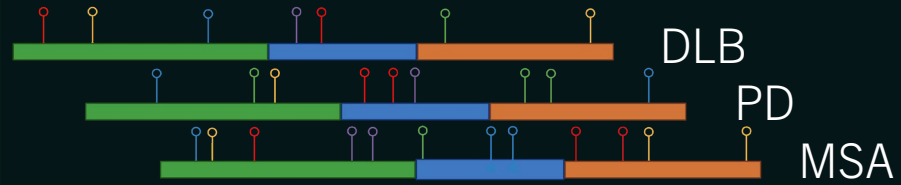
MSA-C Patients: ~30% of US patients

- **Absent to minimal response to levodopa**



Our approach

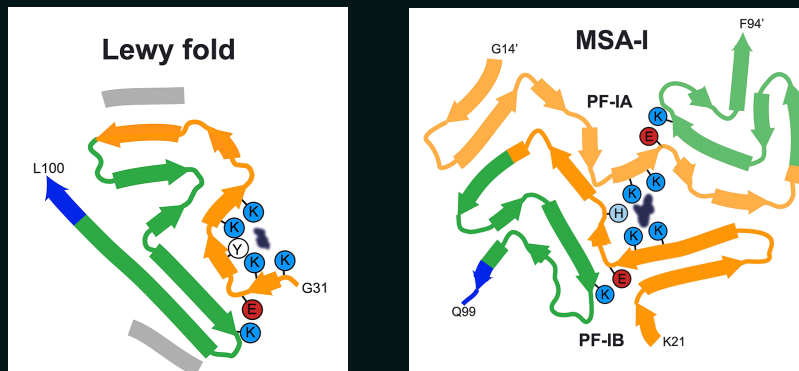
Different post-translational modifications (PTMs)



*Disease specific PTMs =
disease-specific drug targets*



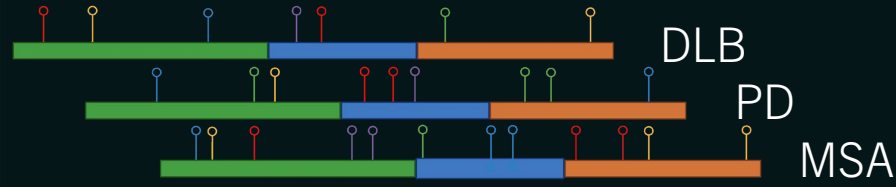
Different fibril structure



Different pathology

Our approach

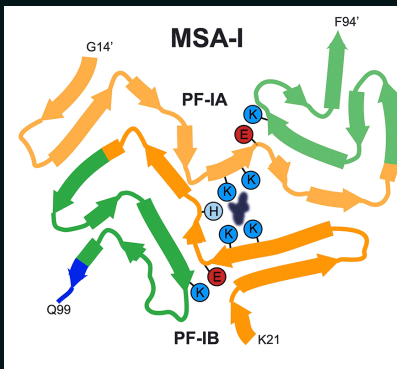
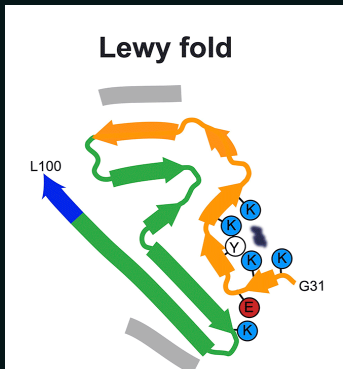
Different post-translational modifications (PTMs)



Disease specific PTMs = disease-specific drug targets



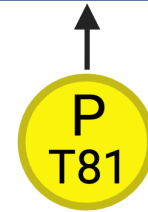
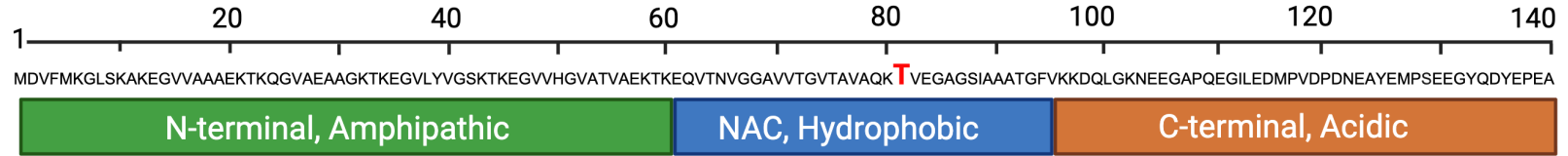
Different fibril structure



Different pathology

PHOSPHORYLATED T81 α -SYNUCLEIN (PT81) IS SPECIFIC TO MSA

human α -synuclein

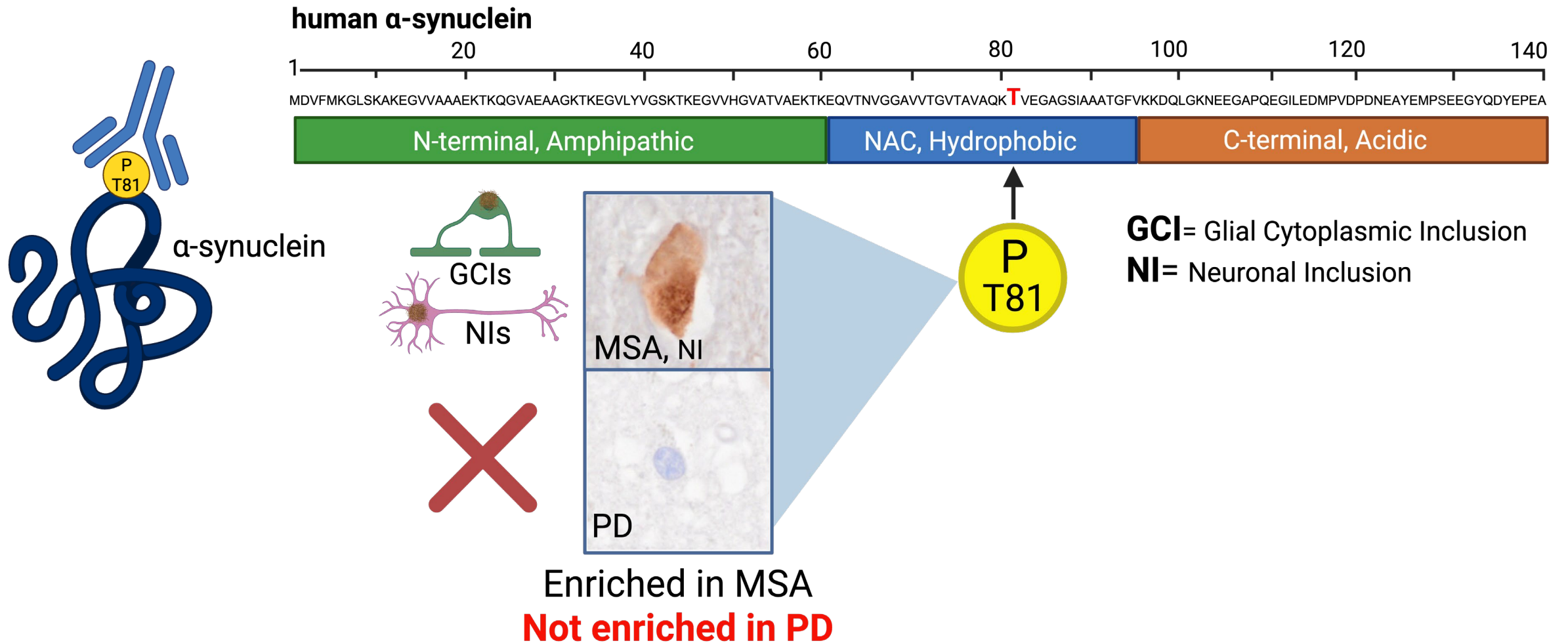


Other PTMs on α -synuclein occur across synucleinopathies, making them non-specific

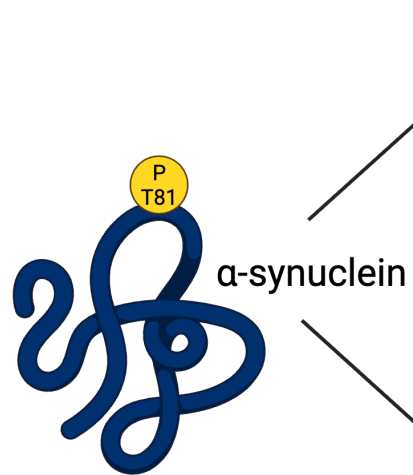


pT81 is enriched in MSA patient brains, but not in other synucleinopathies, making it a disease-specific target

OUR NOVEL PHOSPHOSPECIFIC PT81 ANTIBODY IS SPECIFIC TO MSA TISSUE

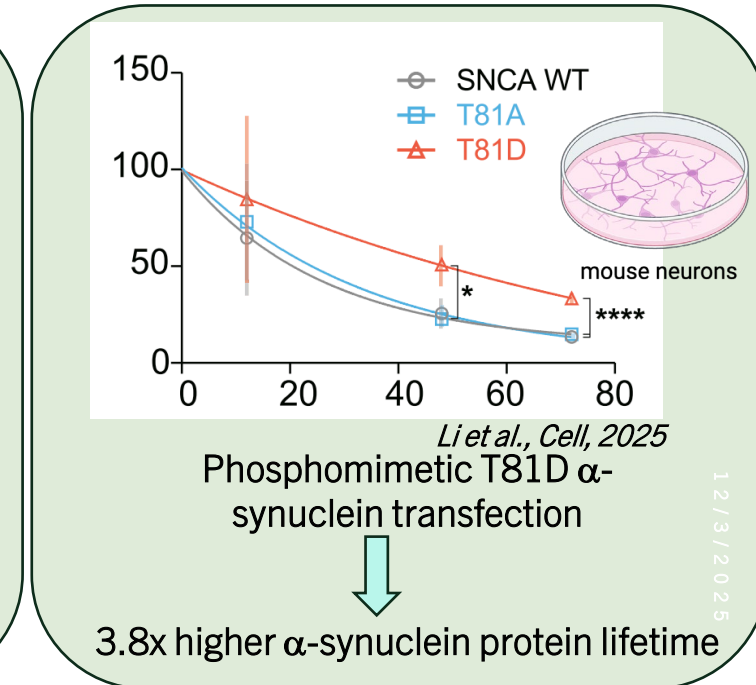
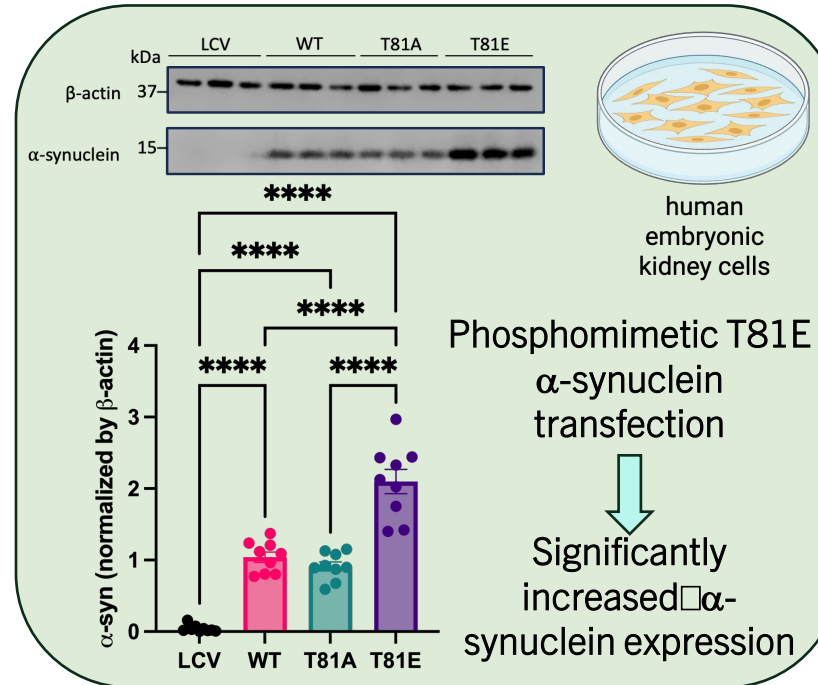


T81 PHOSPHORYLATION INCREASES PROTEIN STABILITY AND OVERALL α -SYNUCLEIN LEVELS



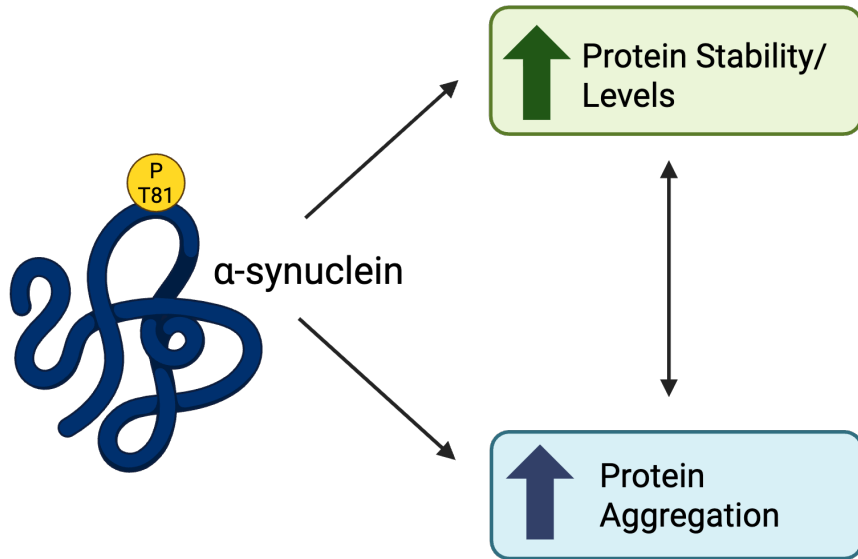
↑ Protein Stability/
Levels

↑ Protein
Aggregation

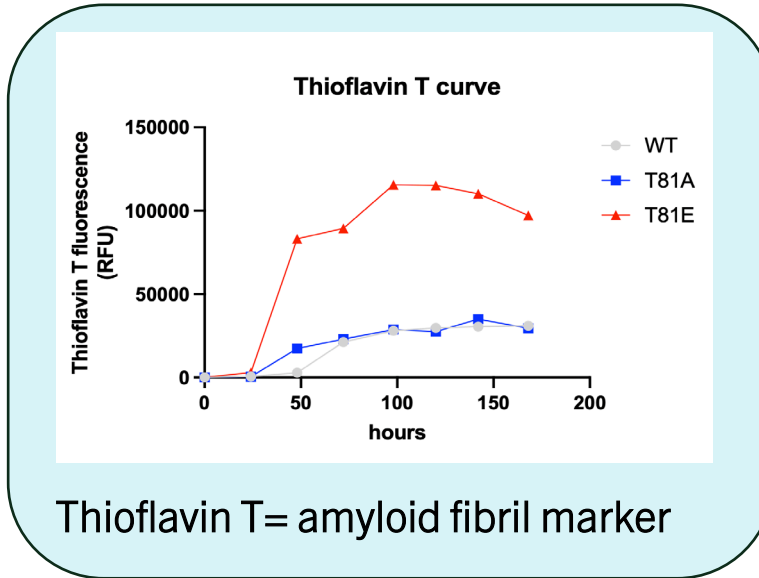


Blocking the T81 phosphorylation site with our antibody could prevent α -synuclein accumulation and aggregation and therefore **alter disease course**.

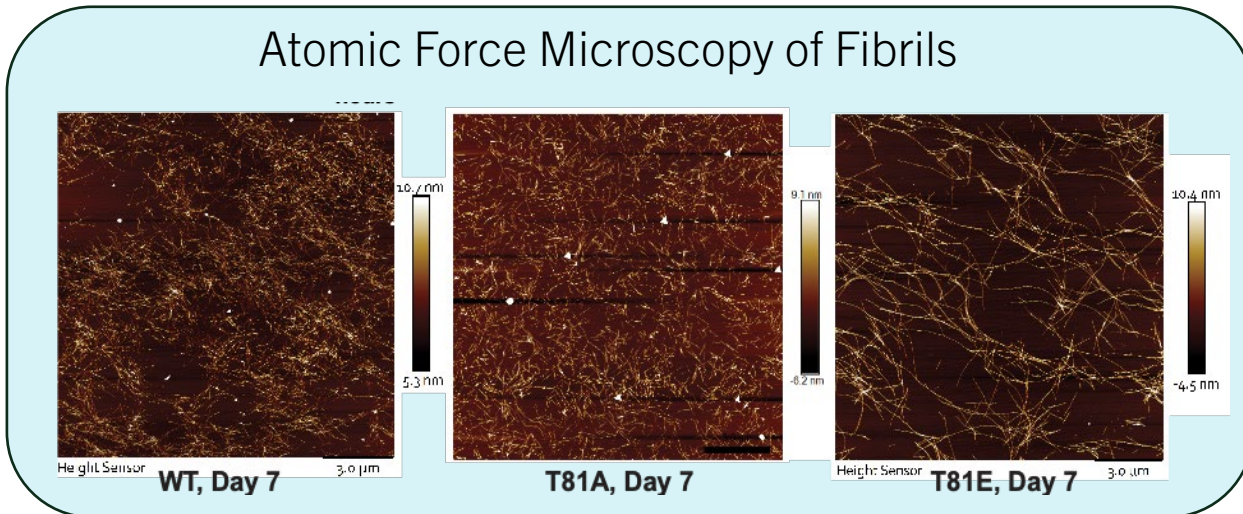
T81 PHOSPHORYLATION INCREASES α -SYNUCLEIN AGGREGATION



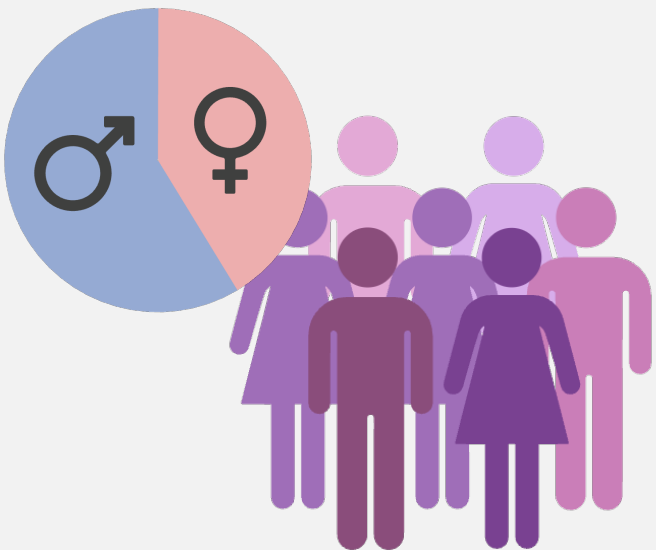
Blocking the T81 phosphorylation site with our antibody could prevent α -synuclein accumulation and aggregation and therefore **alter disease course**.



Phosphomimetic T81E α -synuclein shows increased fibrillization and longer fibrils



A FIRST-IN-CLASS, DISEASE-MODIFYING MSA THERAPY HAS PRIME POTENTIAL FOR ORPHAN DESIGNATION



3 in 100,000 People aged > 50 with MSA in the US

25,000-75,000 patients in US

10,000 new diagnoses in the US each year

Orphan drug designation is likely due to:

- Disease rarity
- Lack of current therapeutic alternatives
- Recent orphan designation for MSA trial drug emrusolim



Proposed use in BOTH subtypes (~50,000 patients)








Orphan Drug Pricing + Diagnostics



\$1B per year

NO EXISTING THERAPY TARGETS MSA-SPECIFIC α -SYNUCLEIN PATHOLOGY

The PTheraMab Approach: Apply current advances in Mab therapeutics to be the first to target an MSA-Specific protein species

	 ATH434	 amlenetug (Mab)	 AK-341 (Mab)	 emrusolim	 pT81 Mab
Target	excess iron	α -syn monomer/aggregate	α -syn monomer/aggregate	general protein aggregates	pT81 α -syn monomer/aggregate
Synucleinopathy Specific?	No	Yes	Yes	No	Yes
MSA Specific?	No	No	No	No	Yes
Phase	Phase 2	Phase 3 underway	Phase 2	Phase 3	Preclinical

FDA Fastrack ►► *FDA Fastrack* ►►

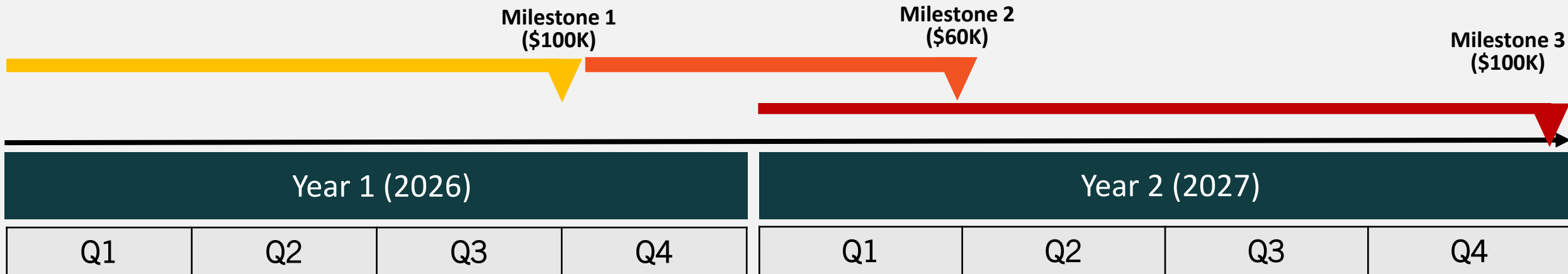
FDA Fastrack ►►
Orphan Designation

IP STRATEGY

US Provisional Application : “ALPHA-SYNUCLEIN PHOSPHO-T81 ANTIBODIES, AND COMPOSITIONS AND METHODS FOR MAKING AND USING THE SAME”

- Yale-owned composition of matter
- Claims over peptides used for immunization, monoclonal antibody and derivative constructs
- No competing IP on pT81 targeting identified
- **Freedom to operate**

BLAVATNIK DEVELOPMENT AWARD MILESTONES




Future: Seed stage of **PTheraMab**

Completed:

- Polyclonal ab generation, validation
- Demonstration of specificity in human patient tissue
- Understanding of target's impact on pathology

In Progress:

T81E α -synuclein knockin mouse 

- ▶ Milestone 1 (\$100K): Monoclonal antibody production
- ▶ Milestone 2 (\$60K): In vitro testing of monoclonal antibody against phosphorylation/fibrillization
- ▶ Milestone 3 (\$140K): In vivo testing in MSA mouse models and patient iPSC-derived brain organoids for efficacy and tolerance

OUR LONG-TERM GOAL...

PTTheraMab

A platform for converting disease-specific PTMs into disease-modifying therapeutics across neurodegenerative disorders