Evaluating the Preclinical Efficacy of a mGluR5 Silent Allosteric Modulator, ALX-001, in Parkinson's Disease Models and Initiation of a First-in-Patient Phase 1b Study

Clinical Trial Registry: NCT 06309147

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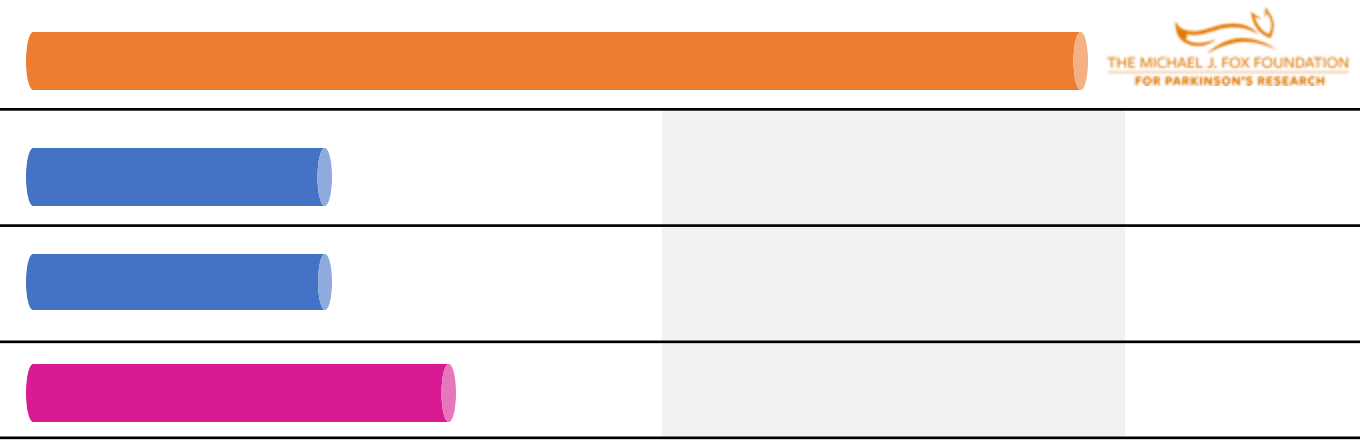
ALX-001: Clinical Stage Program with Opportunity Across Neurodegenerative Diseases

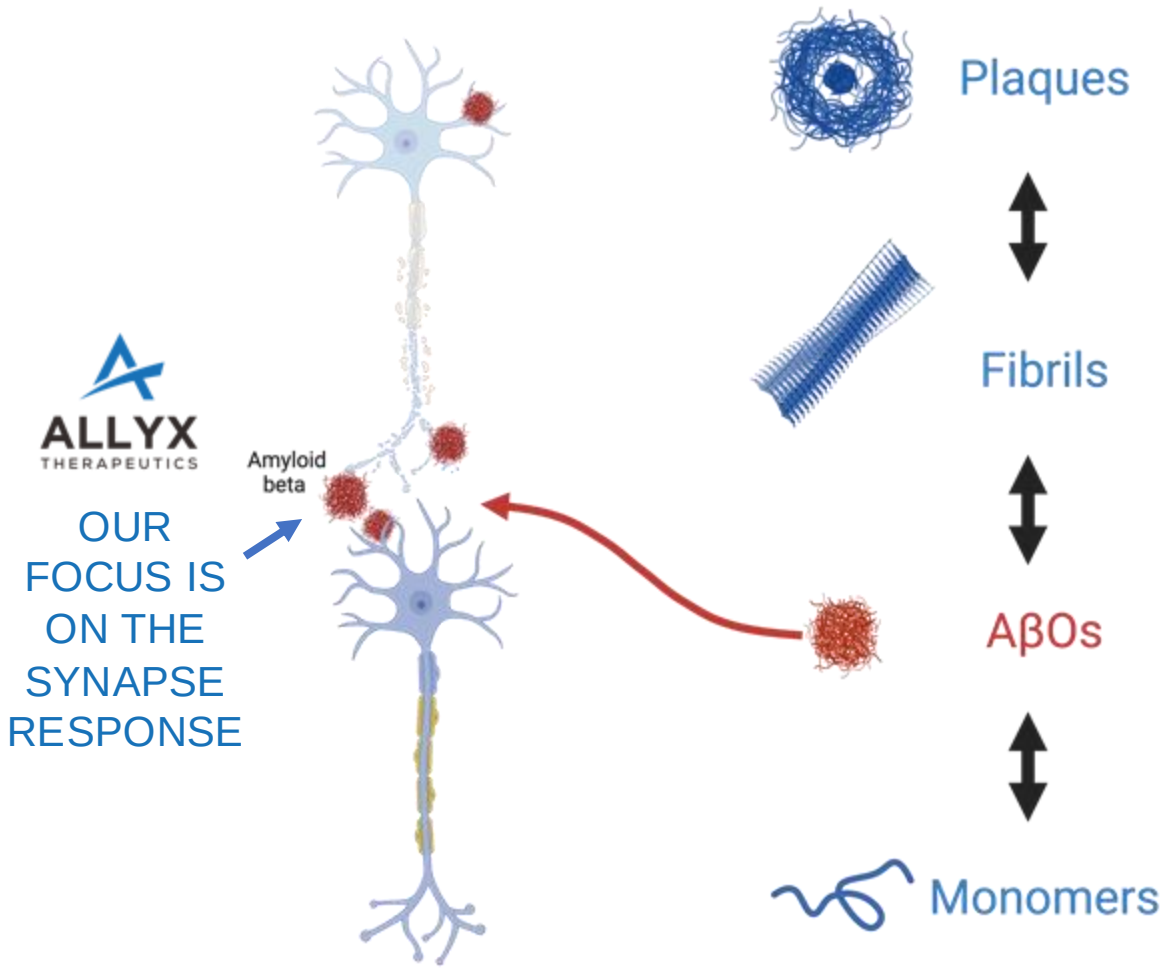
Asset	Target MOA	Indication	Discovery	Pre-Clinical	IND	Phase 1a	Phase 1b	Phase 2	Phase 3
ALX-001	*mGluR5 SAM*	Alzheimer's Disease							
		Parkinson's Disease							
		Traumatic Brain Injury							
		Frontotemporal Dementia							
		Creutzfeldt-Jakob Disease							

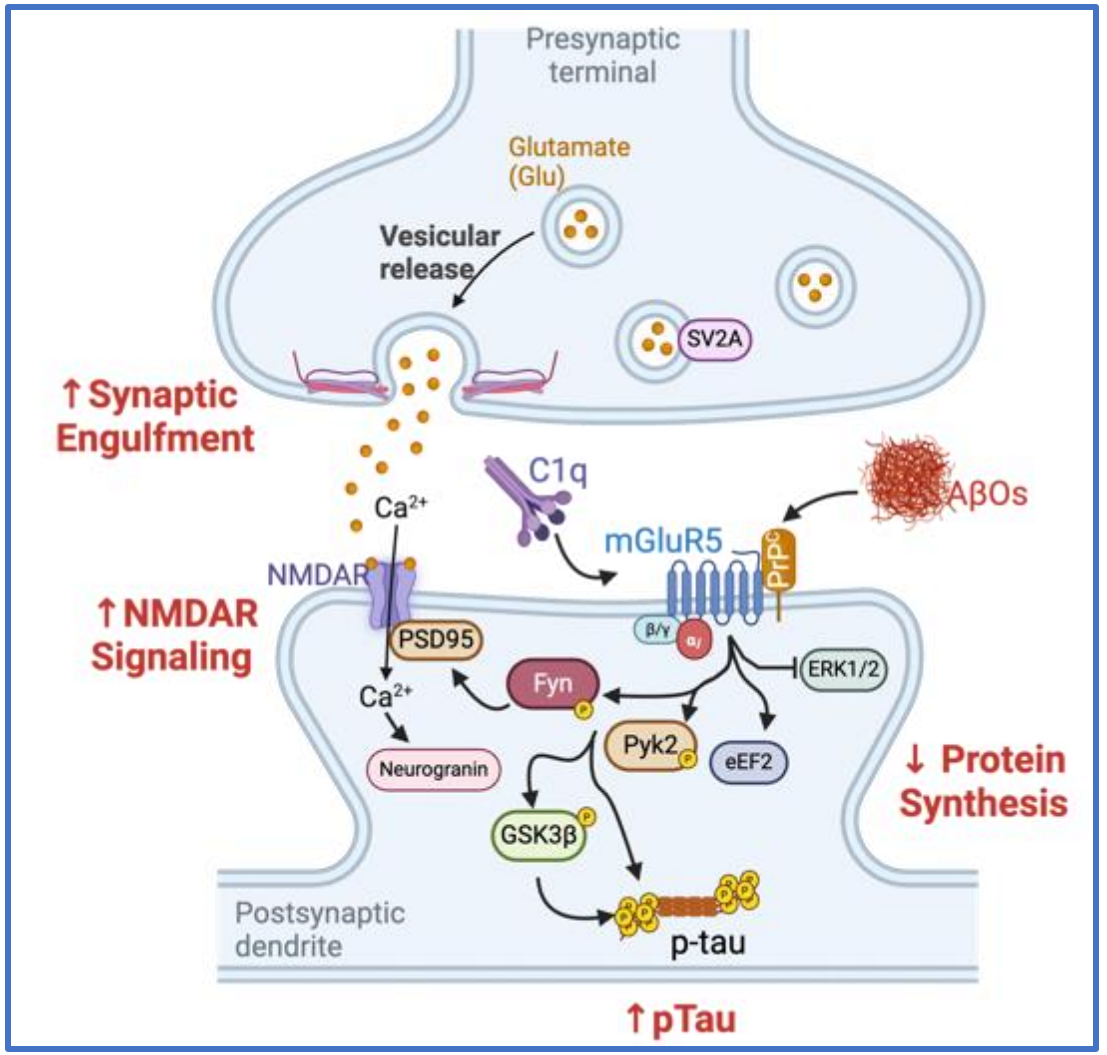


THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Special Thanks to Michael J. Fox Foundation for $4.97 M Grant Support to Leverage Existing Phase 1 Safety Package to Accelerate Parkinson's Disease Program.

Allyx Has Been Focused on Targeting the Process By Which Amyloid Triggers Synaptic Loss in Alzheimer's Disease

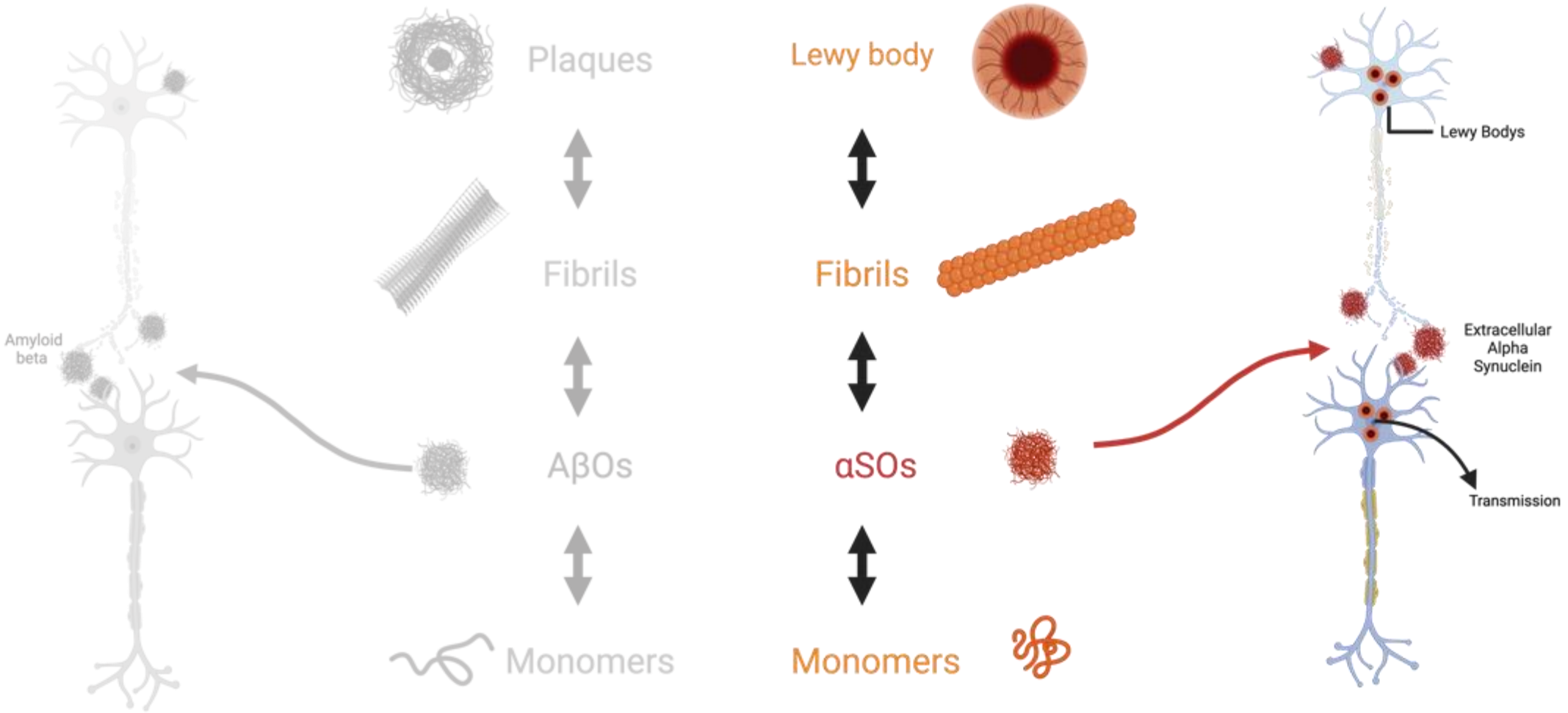




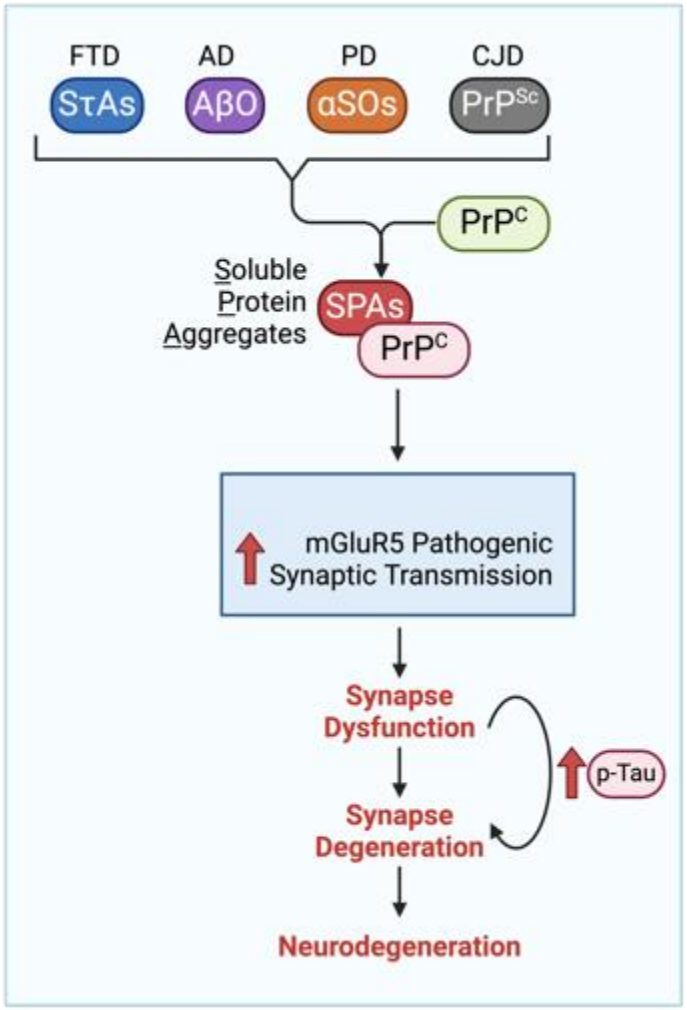
Spurrier et al, Science Translational Medicine *2022* 14(647): p. eabi8593.

mGluR5 = metabotropic glutamate receptor 5
PrP^C = cellular prion protein

Parallels Between Molecular Pathology and Synaptic Damage Across Alzheimer's Disease and Parkinson's Disease



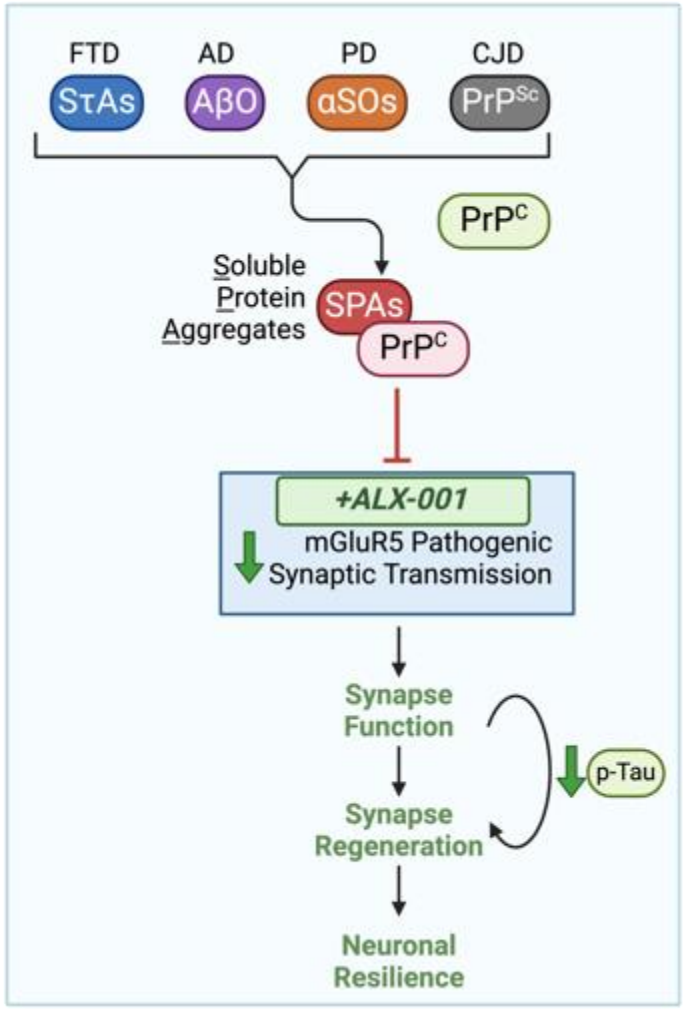
The mGluR5/PrP^{C} Receptor Complex Mediates Synaptic Dysfunction and Loss Across Multiple Neurodegenerative Diseases



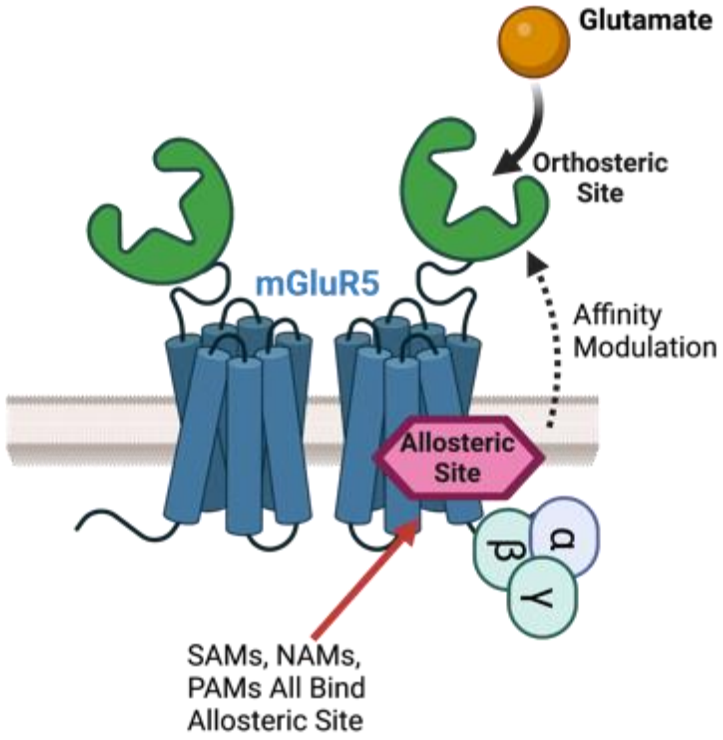
Evidence	AD (Aβo)	PD (αSO)	CTE/FTD (StA)	CJD (PrP^{Sc})
Oligomer Binding PrP^{C} (EC_{50})	39 nM	34 nM	9.55 nM	
Inhibited by Anti-PrP^{C} mAb (IC_{50})	9.5 nM	5.2 nM	2.0 nM	304 pM

Corbett, G. et al *Acta Neuropathologica (2019)* https://doi.org/10.1007/s00401-019-02114-9

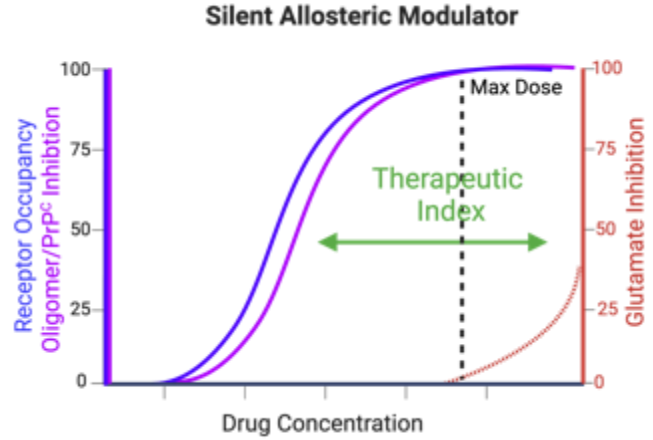
ALX-001 is a Novel, First-in-Class and Disease Selective Silent Allosteric Modulator of mGluR5 to Treat Neurodegeneration



ALX-001 Binds to Allosteric Site

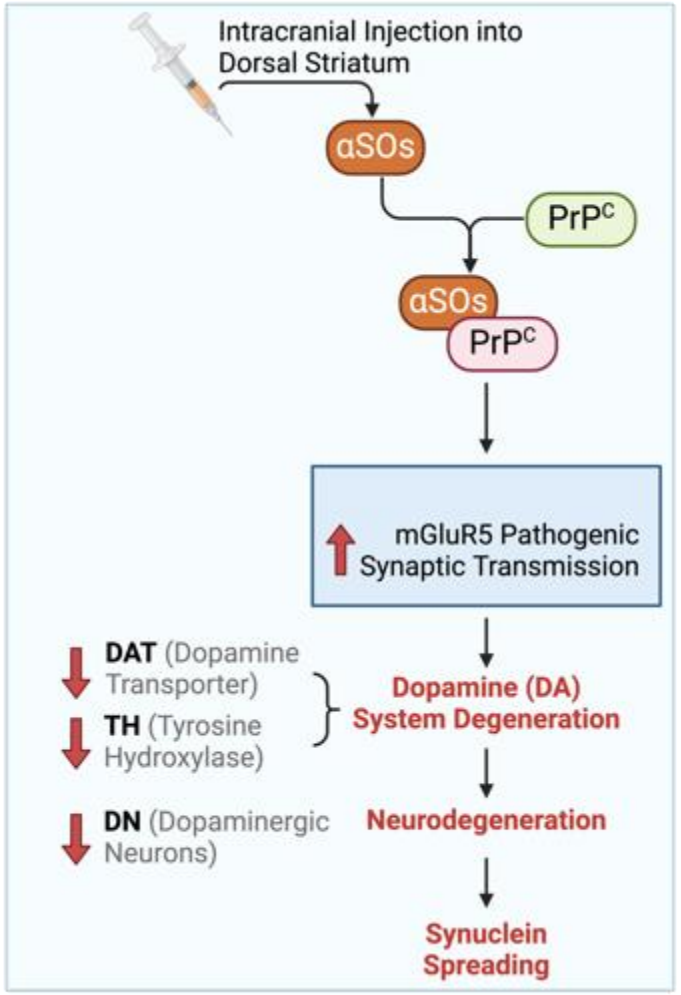


Selectively Blocks Pathogenic Signaling and Preserves Canonical Signaling



	Silent *(SAM)*	Negative *(NAM)*	Positive *(PAM)*
Binding Affinity	+	+	+
SPA/PrP^C Inhibition	+	+	-
Glutamate Inhibition	-	+	-
Glutamate Activation	-	-	+

Preformed Fibril (PFF) Model Evaluates α-Synuclein Aggregate Toxicity With Characteristic Dopamine (DA) System Degeneration



Hypothesis

Extracellular αSOs trigger synaptic damage and neurodegeneration in a PrP^C/mGluR5 dependent manner.

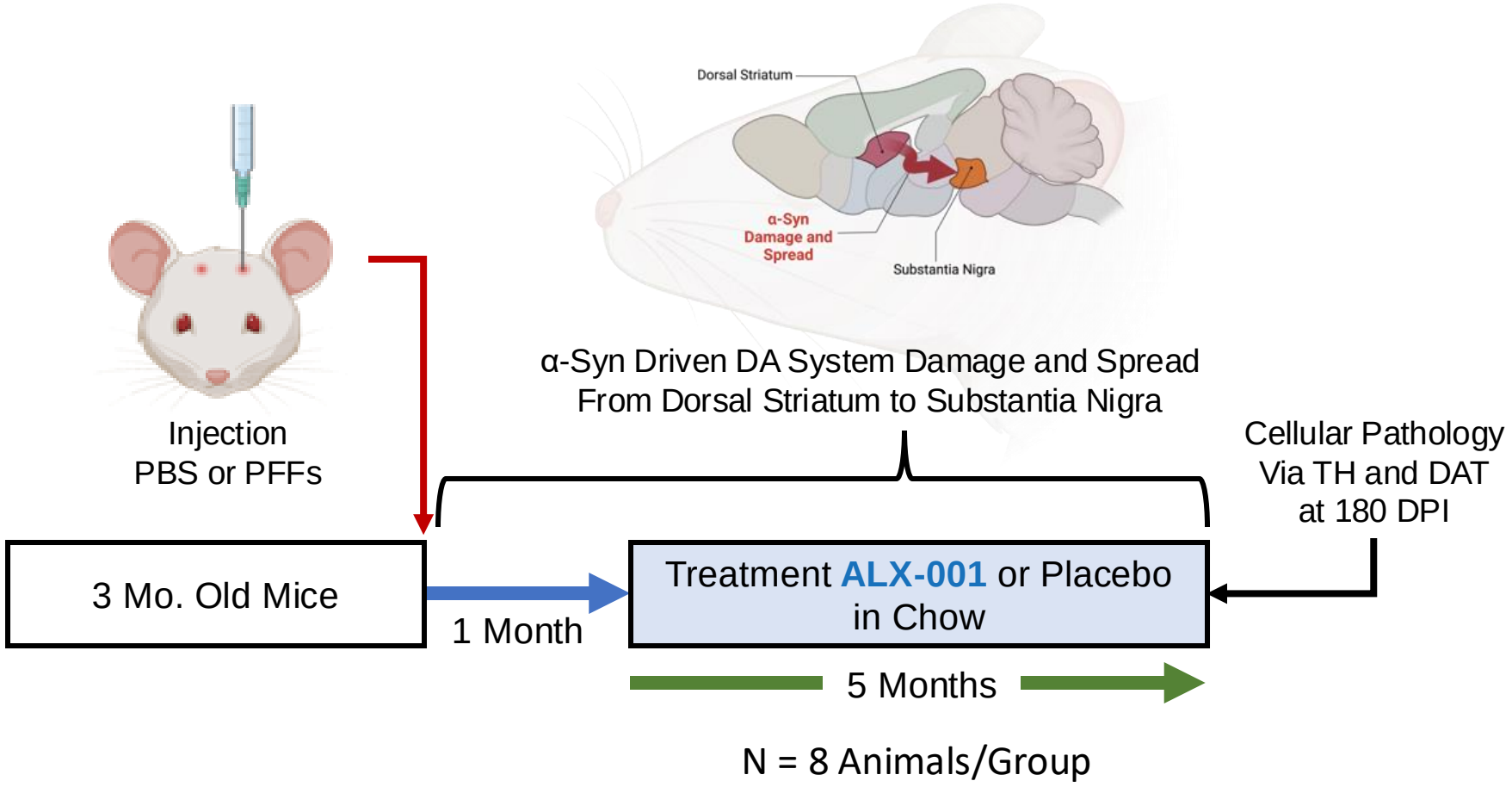
ALX-001 treatment will be neuroprotective by blocking mGluR5 activation by αSO/PrP^C.

Pre-Clinical Strategy

Leverage a model that recapitulates extracellular αSO toxicity, pathology spreading, and neurodegeneration.

C57Bl6/J mice inoculated with 5 µg αSyn preformed fibrils (PFFs) from Luk lab at UPenn injected into dorsal striatum of the right hemisphere (RH, ipsilateral) while left hemisphere (LF, contralateral) serves as an internal control.

Preformed Fibril (PFF) Model Evaluates α-Synuclein Aggregate Toxicity With Characteristic Dopamine (DA) System Degeneration



PsychoGenics
Transforming CNS Discovery

Study Conducted at PsychoGenics, Inc.

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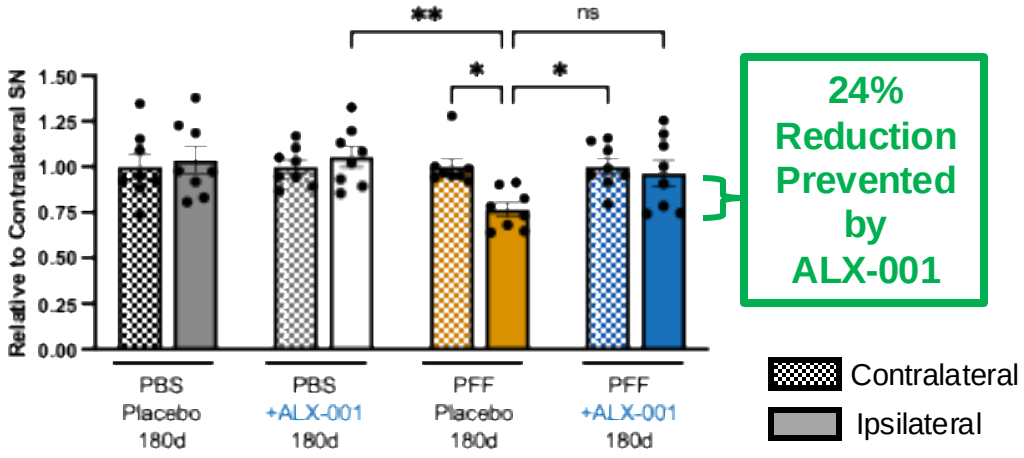
C57Bl6/J mice inoculated with 5 µg αSyn preformed fibrils (PFFs) from Luk lab at UPenn injected into dorsal striatum of the right hemisphere (RH, ipsilateral) while left hemisphere (LF, contralateral) serves as an internal control.

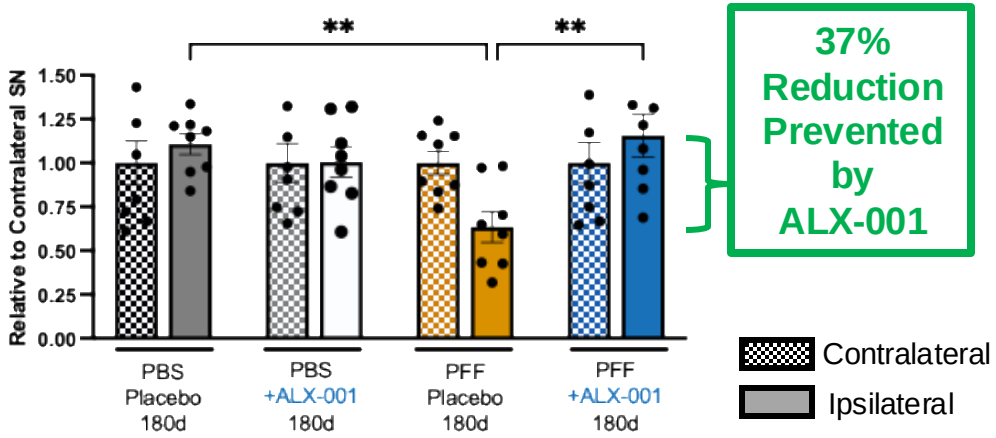
Treatment Effects of ALX-001 on Substantia Nigra (SN) Pathology

Tyrosine Hydroxylase (TH)
Via Immunoreactive Area Percent



24% Reduction Prevented by ALX-001

Tyrosine Hydroxylase (TH) Cell Density
Via Immunoreactive Area Percent



37% Reduction Prevented by ALX-001

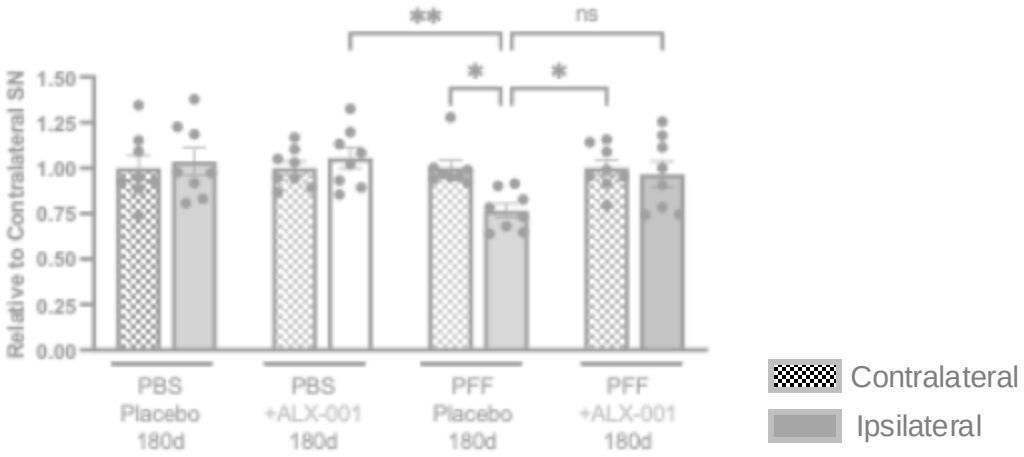
ALX-001 Treatment is Neuroprotective

- **Prevents PFF Driven Tyrosine Hydroxylase (TH) and TH Cell Density Loss**

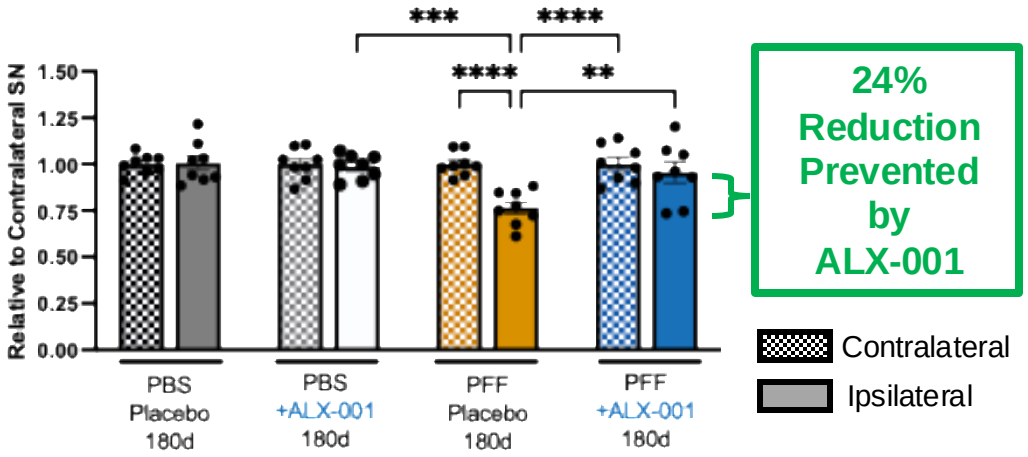
N = 8 animals per group
Evaluated DAT and TH via Immunohistology imaging as IR Area % ratio normalized to contralateral side ± SEM
One-way ANOVA with Dunnett's multiple comparison test

Treatment Effects of ALX-001 on Substantia Nigra (SN) Pathology

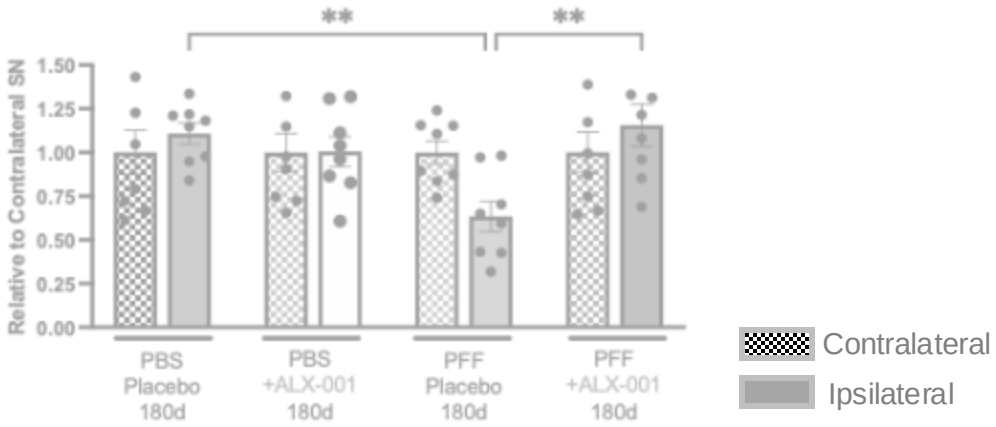
Tyrosine Hydroxylase (TH)
Via Immunoreactive Area Percent



Dopamine Transporter (DAT)
via Immunoreactive Area Percent



Tyrosine Hydroxylase (TH) Cell Density
Via Immunoreactive Area Percent

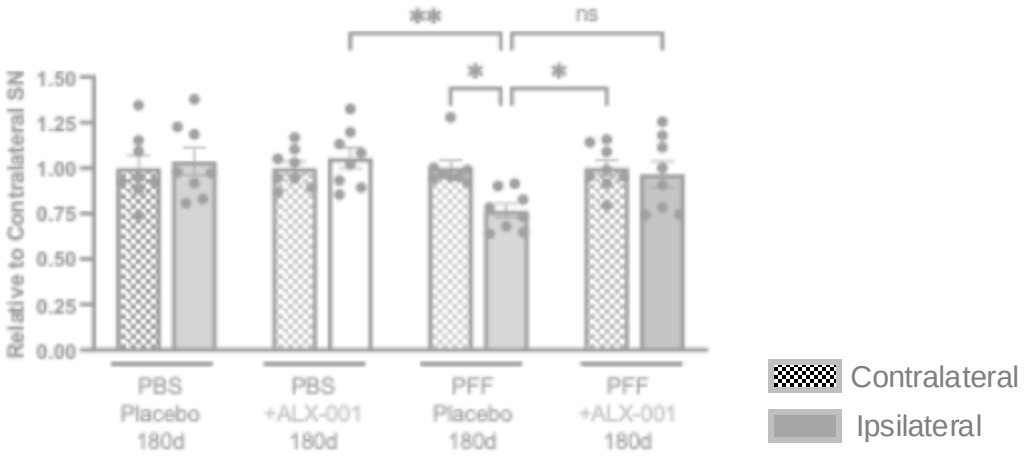


Dopamine Transporter Levels Confirm Therapeutic Benefit of ALX-001 to protect the Dopamine System in the Substantia Nigra

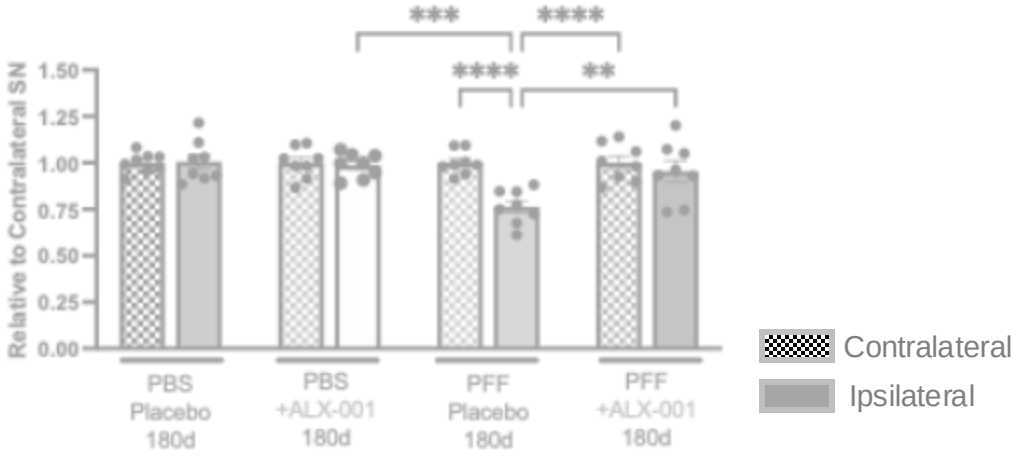
N = 8 animals per group
Evaluated DAT and TH via Immunohistology imaging as IR Area % ratio normalized to contralateral side ± SEM
One-way ANOVA with Dunnett's multiple comparison test

Treatment Effects of ALX-001 on Substantia Nigra (SN) Pathology

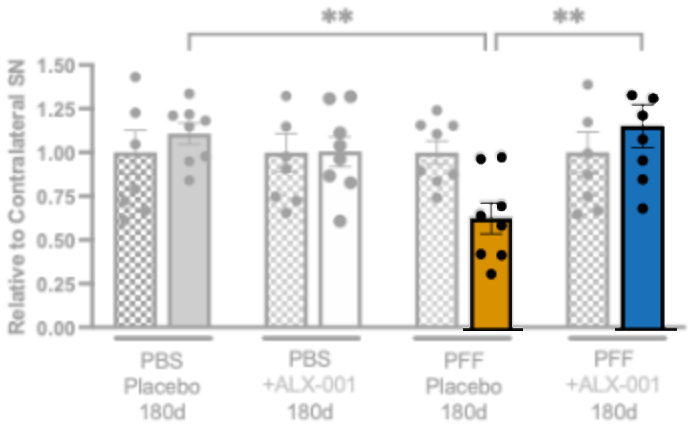
Tyrosine Hydroxylase (TH)
Via Immunoreactive Area Percent



Dopamine Transporter (DAT)
via Immunoreactive Area Percent

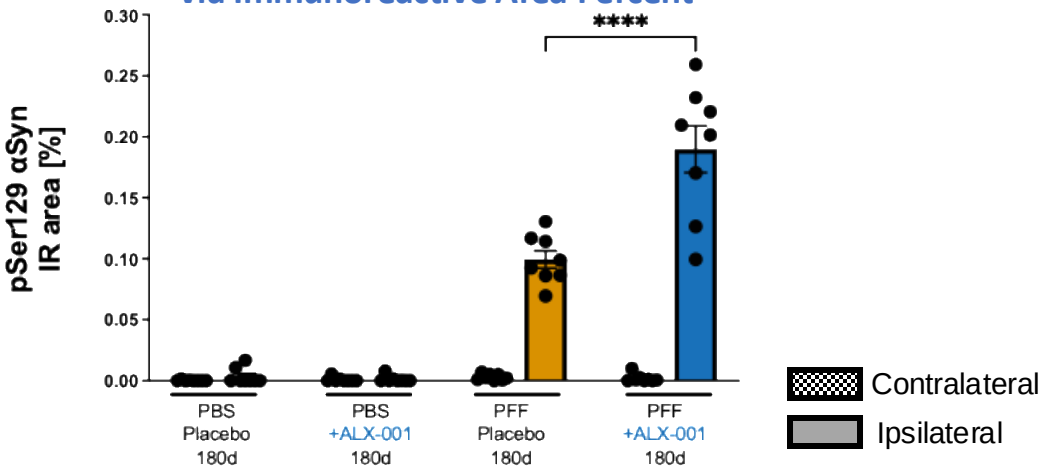


Tyrosine Hydroxylase (TH) Cell Density
Via Immunoreactive Area Percent



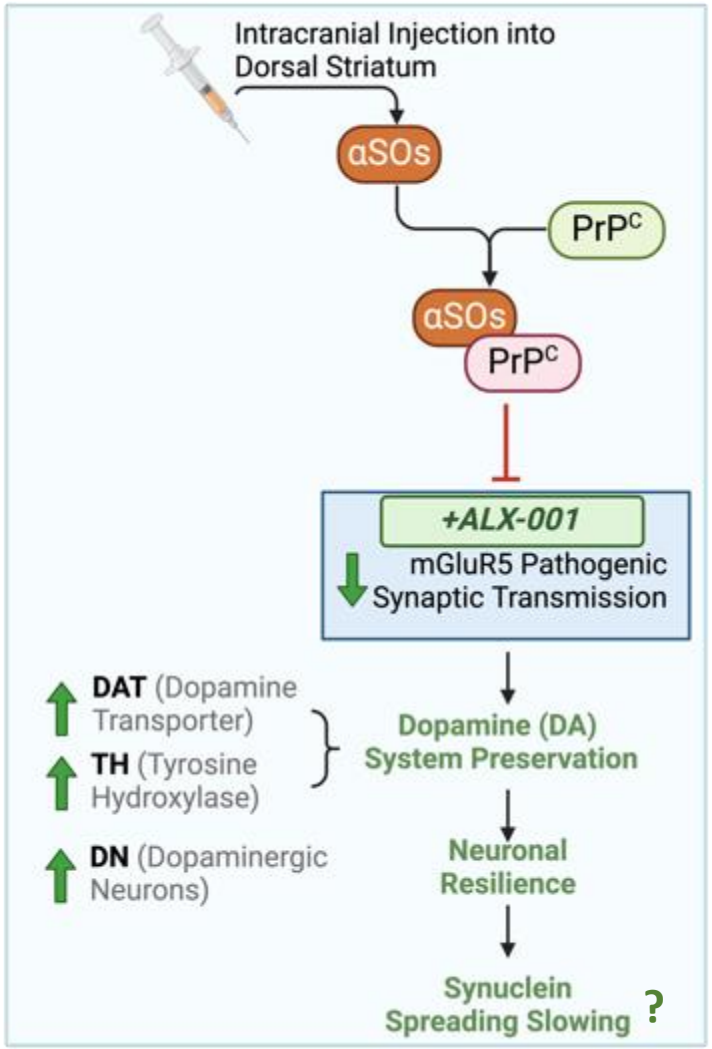
ALX-001 Treated Animals Have Higher α-Syn Levels Consistent with Higher Cell Density and Cell Number

pSer129 α-Syn Pathology
via Immunoreactive Area Percent



N = 8 animals per group
Evaluated DAT and TH via Immunohistology imaging as IR Area % ratio normalized to contralateral side ± SEM
One-way ANOVA with Dunnett's multiple comparison test

ALX-001 Demonstrates Beneficial Treatment Effect in PFF Model of PD



Hypothesis

Extracellular αSOs trigger synaptic damage and neurodegeneration in a PrP^C/mGluR5 dependent manner and ALX-001 treatment will provide therapeutic benefit by by blocking mGluR5 activation by αSO/PrP^C.

Results

- ALX-001 treatment prevents αSO driven TH and DAT loss in the Substantia Nigra.
- ALX-001 treatment is neuroprotective, preventing loss of TH cell density and neuron number in the Substantia Nigra.
- ALX-001 doesn't impact αSyn misfolding propensity, and effect on pathology spreading is not captured at in a single timepoint study.
- ALX-001 provides beneficial, disease modifying therapeutic effect in PFF model and holds promise for patients with PD.

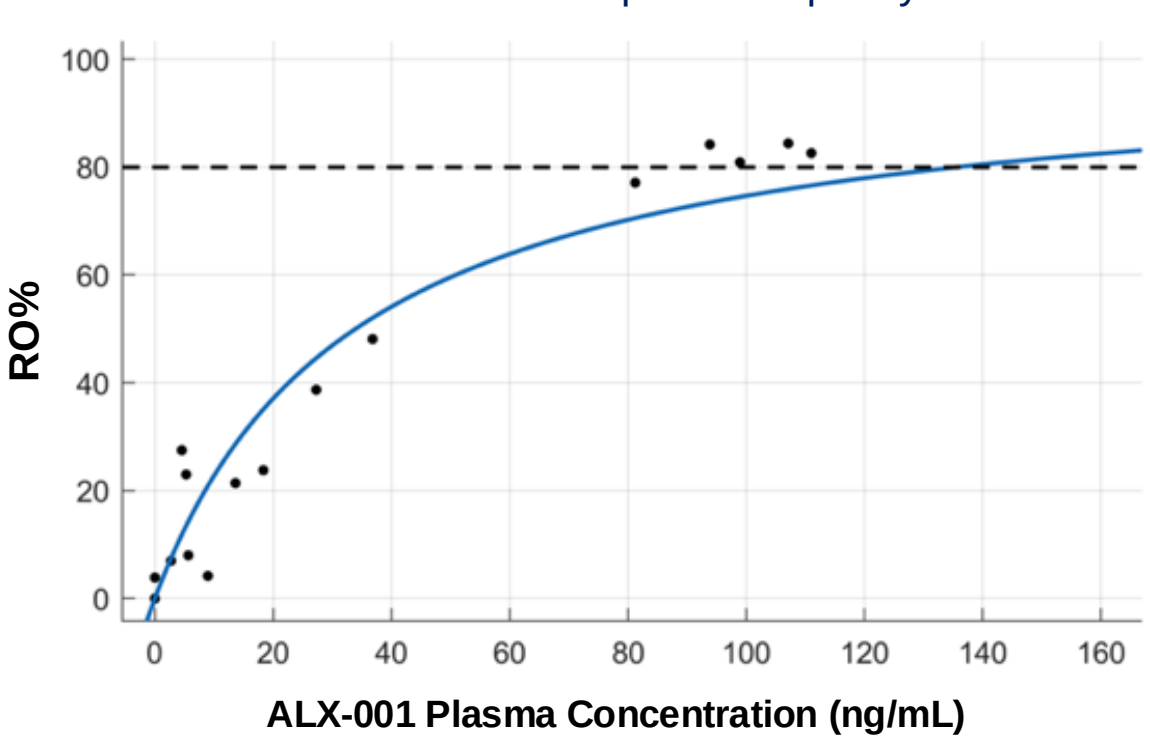
ADVANCEMENT OF ALX-001 TO PARKINSON'S DISEASE PATIENTS

ALX-001 Demonstrates a Strong Safety, Tolerability, Pharmacokinetics, and Target Engagement Profile in the Clinic

	Phase 1a Single Ascending Dose (SAD) (N=36)	Phase 1a Food Effect (FE) (N=12)	Phase 1b Multiple Ascending Dose (MAD) (N=32)
Population	Healthy adults aged 50-80, age matched for neurodegenerative disease population.		
Design	• Open label study of single dose administration at six consecutive increasing strengths.	• Randomized and double-blinded two group crossover.	• Randomized, double-blinded, placebo controlled (n = 6:2, active : placebo) • Twice Daily Oral Administration
Doses	10 mg up to 200 mg	150 mg	50 mg (10-Days), 100 mg (10- and 20-Days), 150 mg (20-Days)
Results Summary	✓ **Confirmed oral bioavailability.** ✓ **Confirmed blood brain barrier penetration and <u>full brain receptor occupancy.</u>** ✓ **ALX-001 safe and well-tolerated at all doses.**	✓ **Established modest impact of food on exposures.**	✓ **ALX-001 safe and well-tolerated at all doses.** ✓ **Achieve excellent target engagement coverage of IC_{80} at trough.**

ALX-001 Achieves High Target Engagement in Human Brain: mGluR5 Receptor Occupancy Measured with [^{18}F]FPEB PET

Brain Target Engagement Validated in Humans During Phase 1a SAD Study

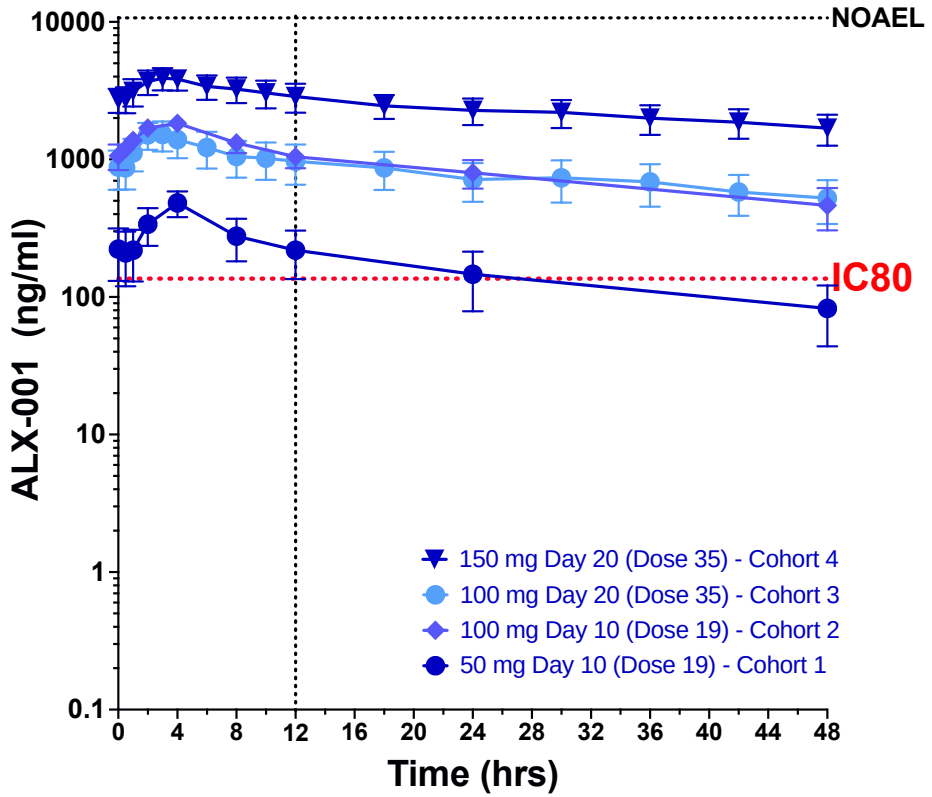


Receptor Occupancy

IC_{50} = 34 ng/mL

IC_{80} = 136 ng/mL

Final Dose Plasma Concentrations: Day 10 or 20



Low Dose 50 mg BID Capable of Achieving Target IC_{80} Levels at Day 10 of Dosing

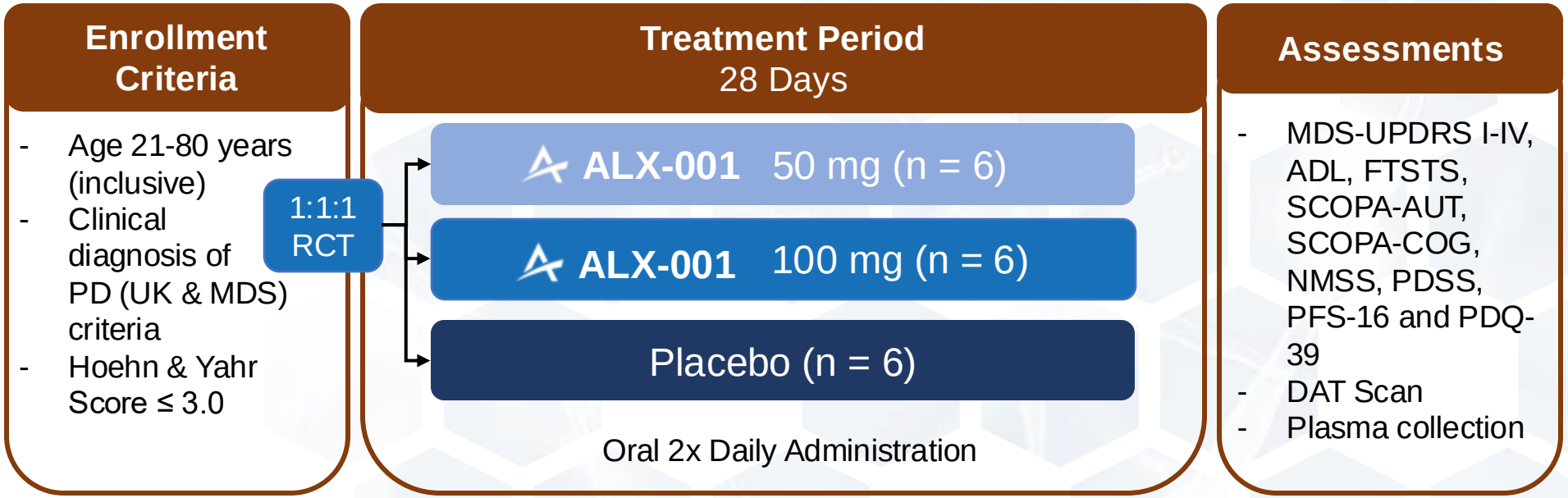
Phase 1b Parkinson's Disease First-in-Patient Safety Study (NCT06309147)

Duke Clinical Research Institute

Laurie Sanders, PhD.

Duke University School of Medicine

Kathryn Moore, MD



Primary Endpoint:
- Incidence of treatment-emergent adverse events (TEAEs)

Secondary Endpoints:
- Plasma PK analysis
- Change from baseline MSD-UPDRS Part III in "ON" state
- Change from baseline in Modified Schwab & England ADL
- Change from baseline PDQ-39

Exploratory Endpoints:
- Change from baseline MDS-UPDRS Parts I, II, and IV
- Change from baseline FTSTS
- Change from baseline SCOPA-AUT
- Change from baseline SCOPA-COG
- Change from baseline NMSS
- Change from baseline PDSS-2
- Change from Baseline PFS-16
- Change from baseline DaT SPECT
- Possible biomarkers including α-ssynuclein

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MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; ADL, Activities of Daily Living; PDQ-39, Parkinson's Disease Questionnaire; FTSTS, Five Times Sit to Stand; SCOPA, Scales for Outcomes in Parkinson's Disease; AUT, Autonomic Dysfunction; COG, Cognition; NMSS, Non-Motor Symptom Assessment Scale; PDSS, Parkinson's Disease Sleep Scale; PFS, Parkinson's Disease Fatigue Scale

Multiple Ongoing Clinical Studies of ALX-001

Study #:	ALX-923-102 Part B	ALX-923-107	ALX-923-108
NCT #:	NCT05804383	NCT06309147	NCT06632990
Study	28-Day Alzheimer's Disease (N = 18)	28-Day Parkinson's Disease (N = 18)	Clinical Metabolism Study (N = 36)
Goal	1. Evaluate safety of ALX-001 for 28-days in patients.	1. Evaluate safety of ALX-001 for 28-days in patients.	1. Characterize drug-drug interactions of ALX-001 on CYP1A2, CYP2D6, and CYP3A4 probe substrates. 2. Remove as many exclusionary concomitant medications as possible.
Population	MCI & early AD	Early PD	Healthy Volunteers
Design	18 patient, 3-arm, 1:1:1 randomized (n = 6/group), placebo controlled double blinded study with 28-Days of drug administration.	18 patient, 3-arm, 1:1:1 randomized (n = 6/group), placebo controlled double blinded study with 28-Days of drug administration.	36 subject, 1:1 randomized, open label study. Cocktail of probes administered on Day 1, ALX-001 BID administration starting on Day 3 for 20-days. Cocktail administered again on Day 20.
Doses	50 mg BID and 100 mg BID	50 mg BID and 100 mg BID	50 mg QD, 50 mg BID, & 100 mg BID

ALX-001 Holds Promise as a Disease Modifying Therapy for Neurodegenerative Disease and is Phase 2 Ready

- ✓ Synapse protection and neuroprotection observed in multiple preclinical models of Alzheimer's and Parkinson's disease.
- ✓ Completed chronic toxicology studies.
- ✓ Successfully manufactured Phase 2 GMP drug product supply.
- ✓ Open INDs in both AD and PD.
- ✓ Clinically confirmed mGluR5 target engagement in the brain.
- ✓ Characterized excellent safety profile out to 20-days with twice daily oral administration in healthy volunteers.
- ✓ Dosing AD and PD patients with multiple participants completing 28-day treatment course.

Thank You

- **Michael J. Fox Foundation Team**
- **Study Participants: including all healthy volunteers, Alzheimer's and Parkinson's disease patients**
- PsychoGenics Team for Collaborating on the Preclinical PFF Model.
- Yale PET Center
- **Adam Mecca, MD, PhD & Chris van Dyck, MD**
  Alzheimer's Disease Research Center
  Yale School of Medicine
- **Stephanie Post, MD & Team**
  Spaulding Clinical Research
- **Laurie Sanders, PhD & Team**
  Duke Clinical Research Institute
  Duke University School of Medicine
- **Kathryn Moore, MD**
  Burton Scott, MD, PhD
  Jeffery Cooney, MD
  Talita Rosa, MD
  Brian Dahlben, MD
  Erika Jacumin, PA
  Duke Neurology
  Duke University School of Medicine

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
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