A Phase 1b Multiple Ascending Dose Study Of The Safety, Tolerability, And Pharmacokinetics Of ALX-001, an mGluR5 Silent Allosteric Modulator, in Healthy Older Adults.

Clinical Trial Registry: NCT 05804383

Timothy Siegert[1], Patrick Simms[1], Stephanie Post[2], Adam Mecca[3], Chris van Dyck[3], Stephen Strittmatter[3]

[1] Allyx Therapeutics, Inc., New Haven, CT
[2] Spaulding Clinical Research, West Bend, WI
[3] Yale School of Medicine, New Haven, CT

ALLYX THERAPEUTICS

9 MAR 2024

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
Hybrid

Funding Support and Disclosures

NIA U01 AG058608
NIA R01 AG073117

NIA R44 AG069559

MJFF-021682

Disclosures

Yale University and S. Strittmatter (Yale) are equity holders in Allyx Therapeutics.
S. Strittmatter is a paid consultant of Allyx.

T. Siegert and P. Simms are full-time employees and equity holders in Allyx Therapeutics.

ALX-001 (*Formerly BMS-984923*): A First-in-Class Oral Drug to Preserve Synapses in Neurodegenerative Diseases

~6 M with Alzheimer's disease and ~1M with Parkinson's disease in the US.
Novel approaches are needed beyond amyloid or synuclein removal.

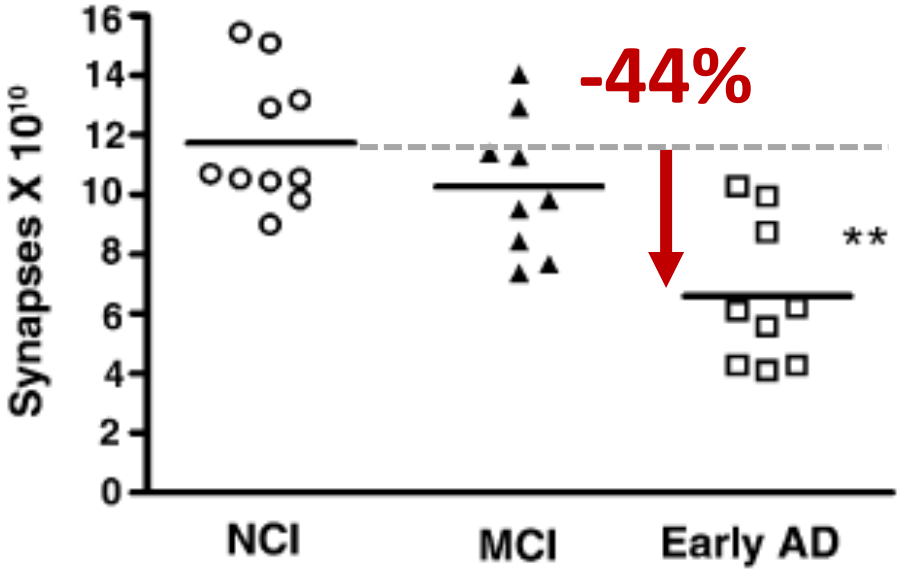
ALX-001: mGluR5 silent allosteric modulator (SAM) protects synapses from misfolded toxic protein oligomers.

First-in-class oral small molecule.
Validated brain target engagement in humans.

Active INDs with US FDA in Alzheimer's and Parkinson's diseases.
Phase 2 ready clinical program.

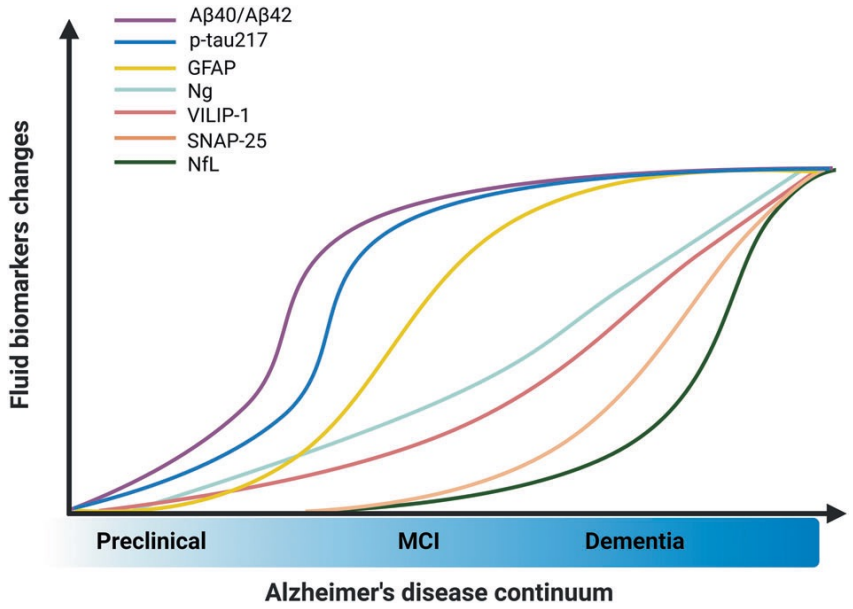
Synapse Loss Best Defines Alzheimer's Disease at the Symptomatic Stage

44% Reduction of Synapses in AD Subjects Compared to No Cognitive Impairment (NCI)



Scheff. S.W. et al *Neurobiology of Aging* 27 (2006) 1372

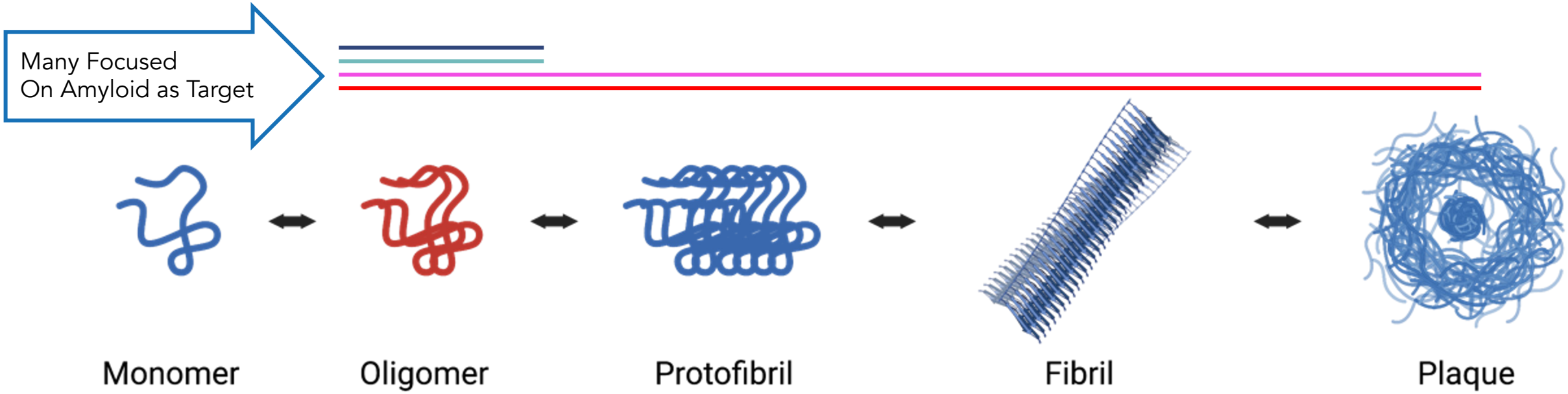
Synapse loss also measured longitudinally via protein biomarkers which best correlate to disease progression



Lista et al. *Molecular Psychiatry*. 2024

Our Allyx Mission: Develop a synapse targeting drug to halt synapse loss.

Amyloid-beta Oligomers (AβOs) are the Synaptotoxic Species in AD



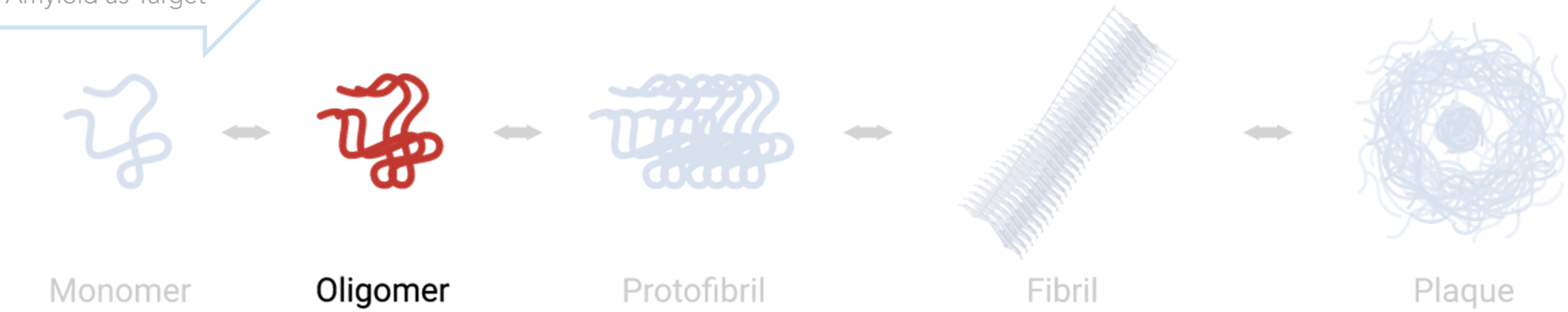
Anti-amyloid monoclonals have three major limitations:

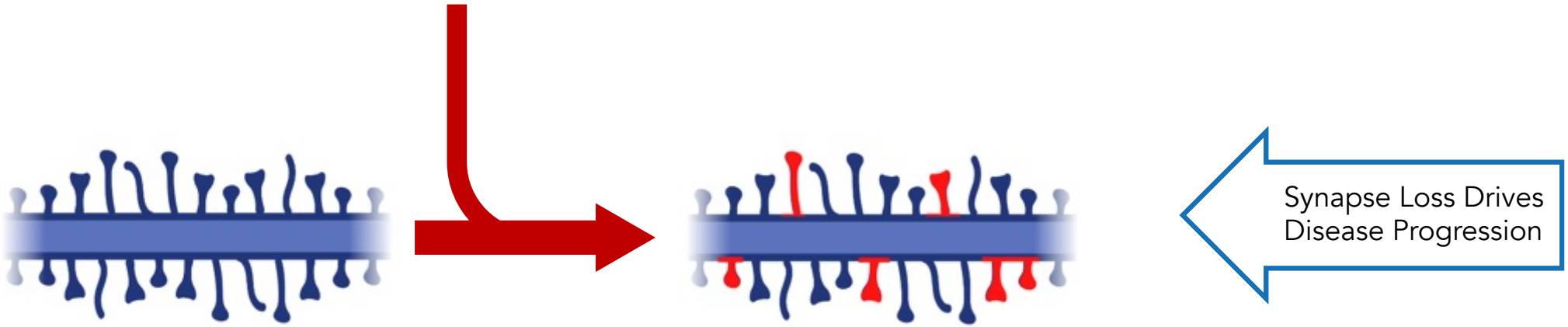
- Delivery
- Selectivity
- Toxicity

Limit Clinical Efficacy

Amyloid-beta Oligomers (AβOs) are the Synaptotoxic Species in AD

Many Focused
On Amyloid as Target

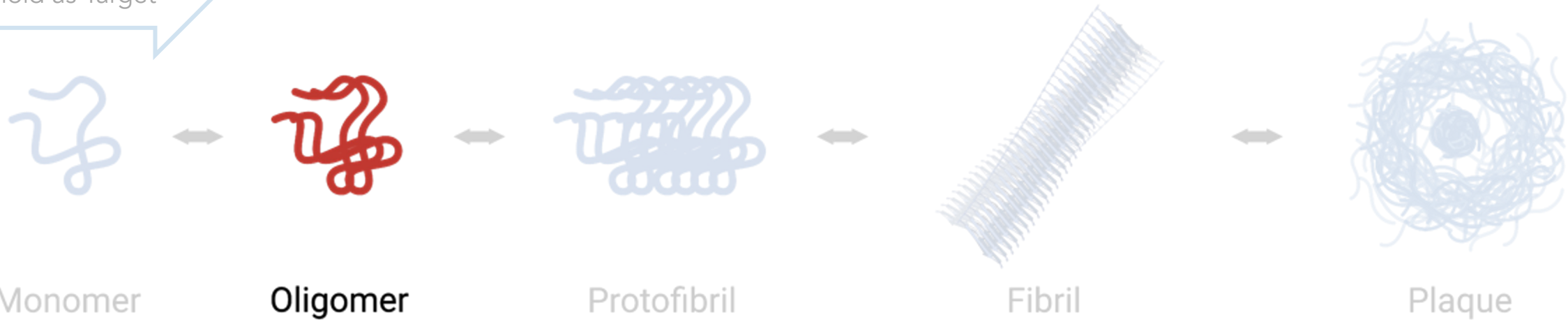


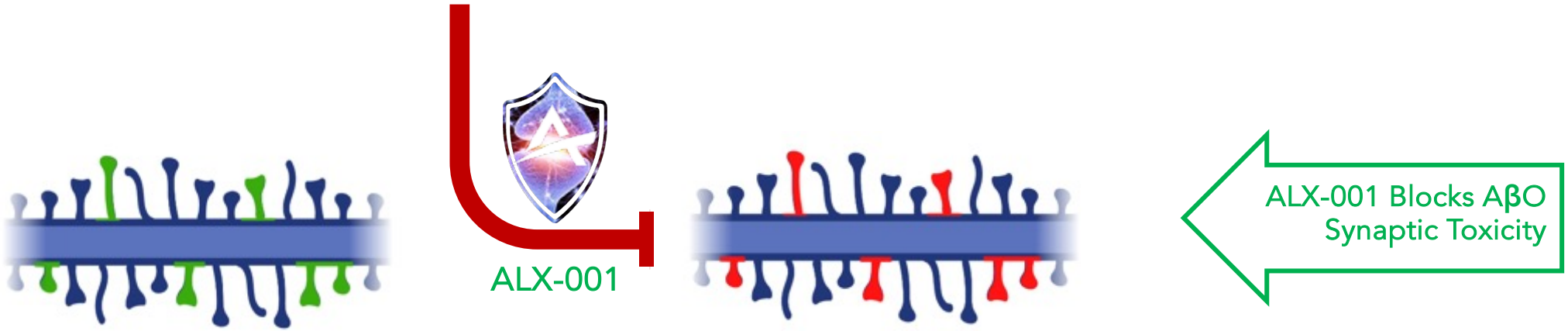


Synapse Loss Drives
Disease Progression

Amyloid-beta Oligomers (AβOs) are the Synaptotoxic Species in AD

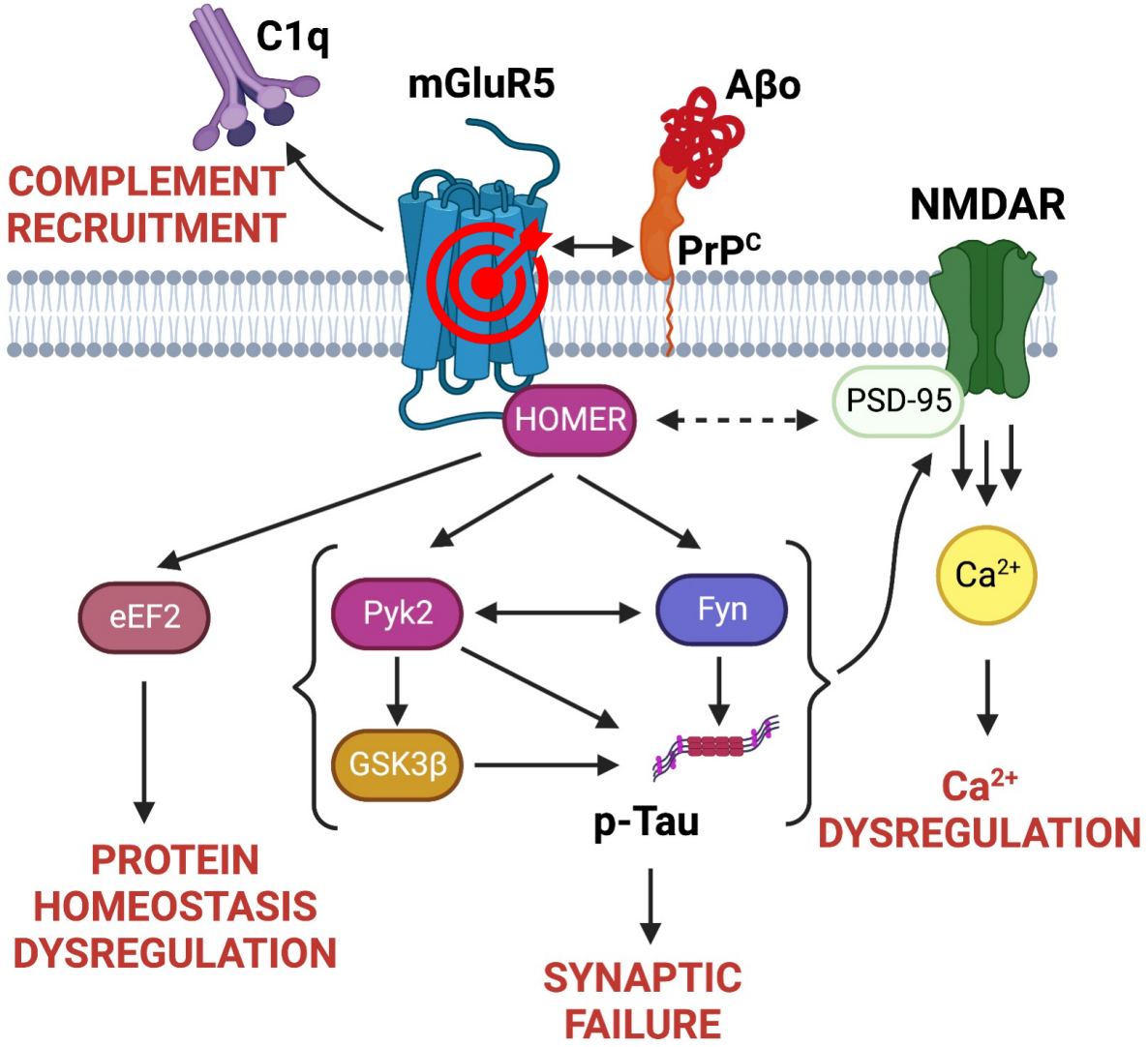
Competitors Focused
On Amyloid as Target





ALX-001 Blocks AβO
Synaptic Toxicity

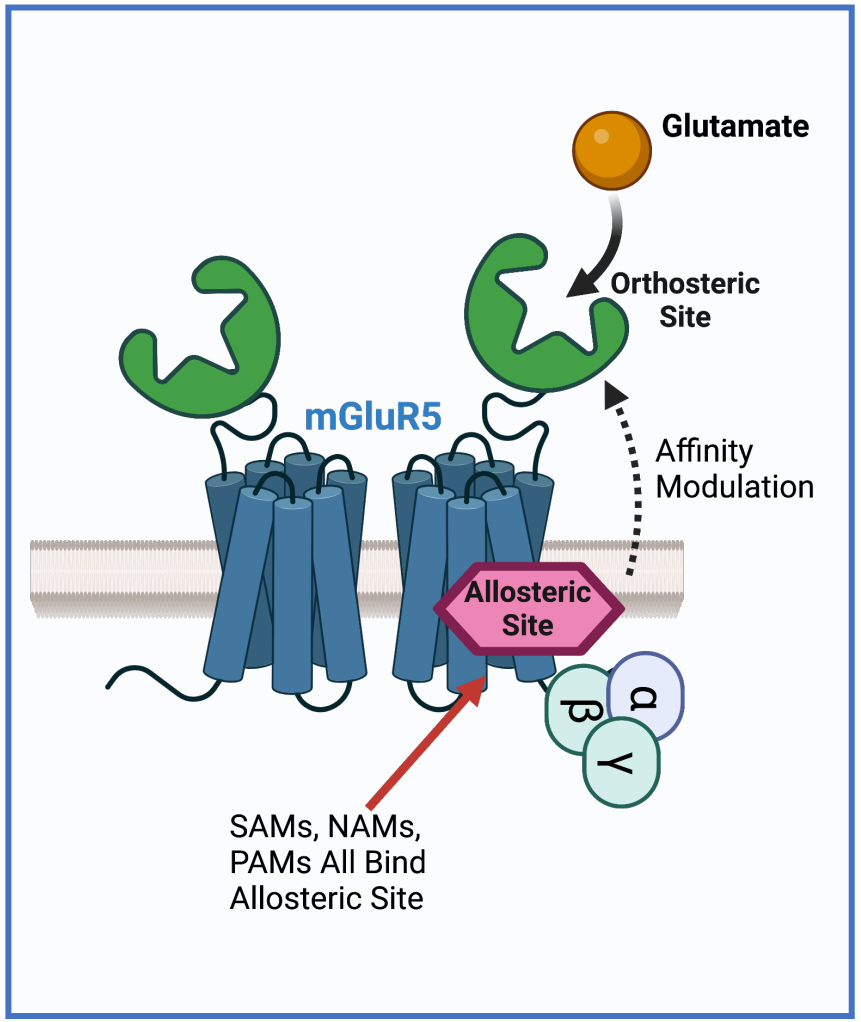
AβOs Drive Synapse Loss Through PrP^C/mGluR5 Co-Receptor



ALX-001 binds mGluR5 with high affinity and selectivity to normalize synapse function and prevent synaptic pruning.

Palmer, M.S. et al. *Nature*. 1991;352:340-342
Lambert, J.C. et al. *Nat. Genet*. 2013 (43): 1452-1458
Nalls, M. et al. Lancet Neurol. 2019; 18(12):1091-1102
Hong, S. et al. *Science*. 2016; 352 (6286):712-716.
Selkoe, D. Behav. Brain Res. 2008: 192(1):106-113.
Scheff, S. et al. Neurobiology of Aging. 2006: 27(10):1372-1384.
Cline, E. et al. J Alzheimers Dis. 2018; 64 (S1): 547-610.
Corbett, G. et al. Acta Neuropathol. 2020: 139(3): 503-526

ALX-001 is a First-in-Class Silent Allosteric Modulator, Delivering an Optimal Therapeutic Index for Neurodegenerative Diseases

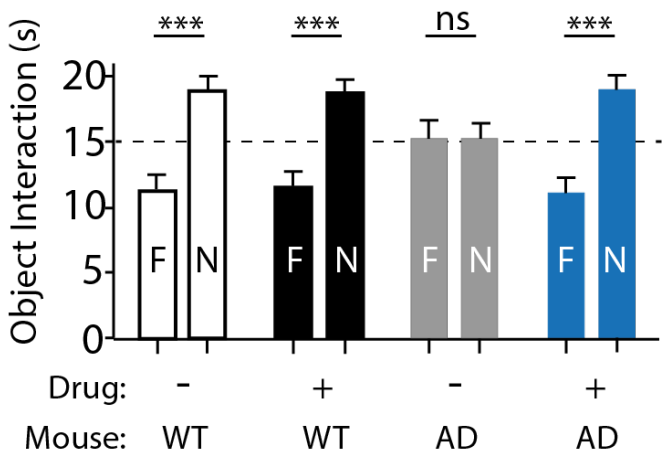


	Silent "Neutral" Allosteric Modulators	Negative Allosteric Modulators	Positive Allosteric Modulators
Binding Affinity	+	+	+
Glutamate Inhibition	-	+	-
Glutamate Activation	-	-	+
AβO/PrP^{C} Inhibition	+	+	-

Wide Therapeutic Window For AD Therapy

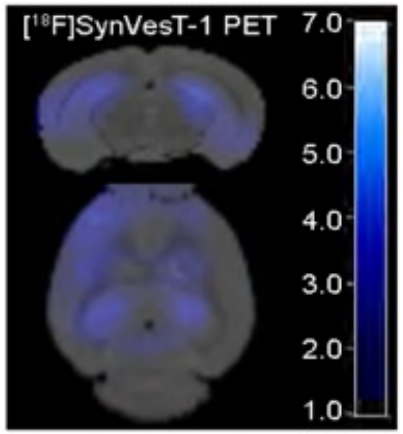
ALX-001 *Reverses* Memory Deficit and Synapse Loss in AD Models

Memory Rescued in Novel Object Recognition

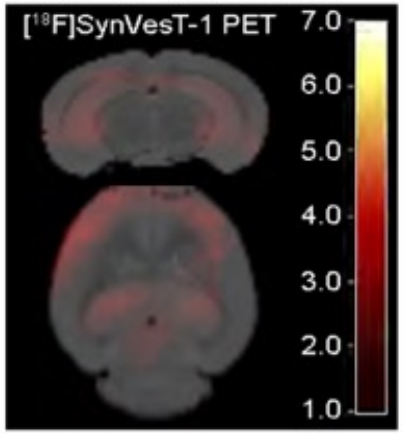


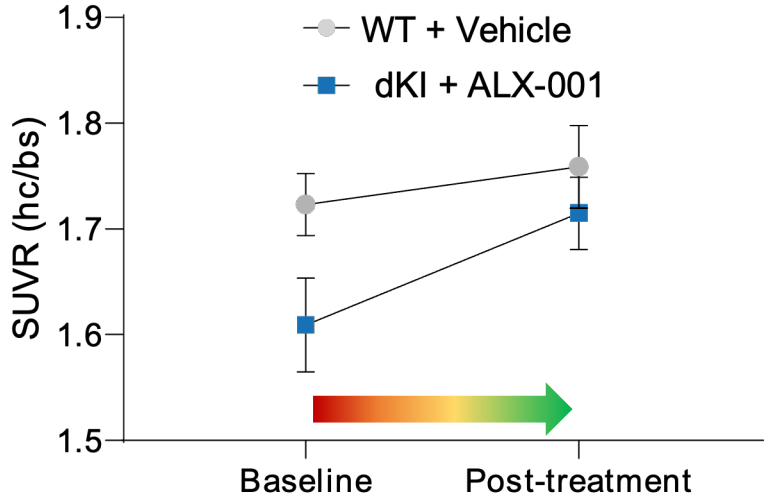
Synapse Recovery Observed Via SV2A PET Imaging

Synapse Loss Pre-Treatment



Synapse Recovery Post-Treatment





ALX-001 Efficacious in Multiple Animal Models of AD

ALLYX THERAPEUTICS

Left: 12-month old APP/PS1 mice treated with 3.75 mg/kg ALX-001, BID, 1-month
Middle & Right: 12-month old dKI mice treated with 3.75 mg/kg ALX-001, BID, 1-month

Haas et al, Cell Reports 20:76-88 (2017)
Spurrier et al, Science Translational Medicine *2022* 14(647)

ALX-001 was Safe & Well-Tolerated at All Doses in the Phase 1 SAD

Establish Preclinical Proof of Concept → IND Enabling Safety & Tox. → AD & PD IND Clearance from US FDA → **Phase 1a Single Ascending Dose** → Phase 1a Food Effect → Phase 1b Multiple Ascending Dose → Phase 2 Proof-of-Concept → Phase 2b/3

Completed

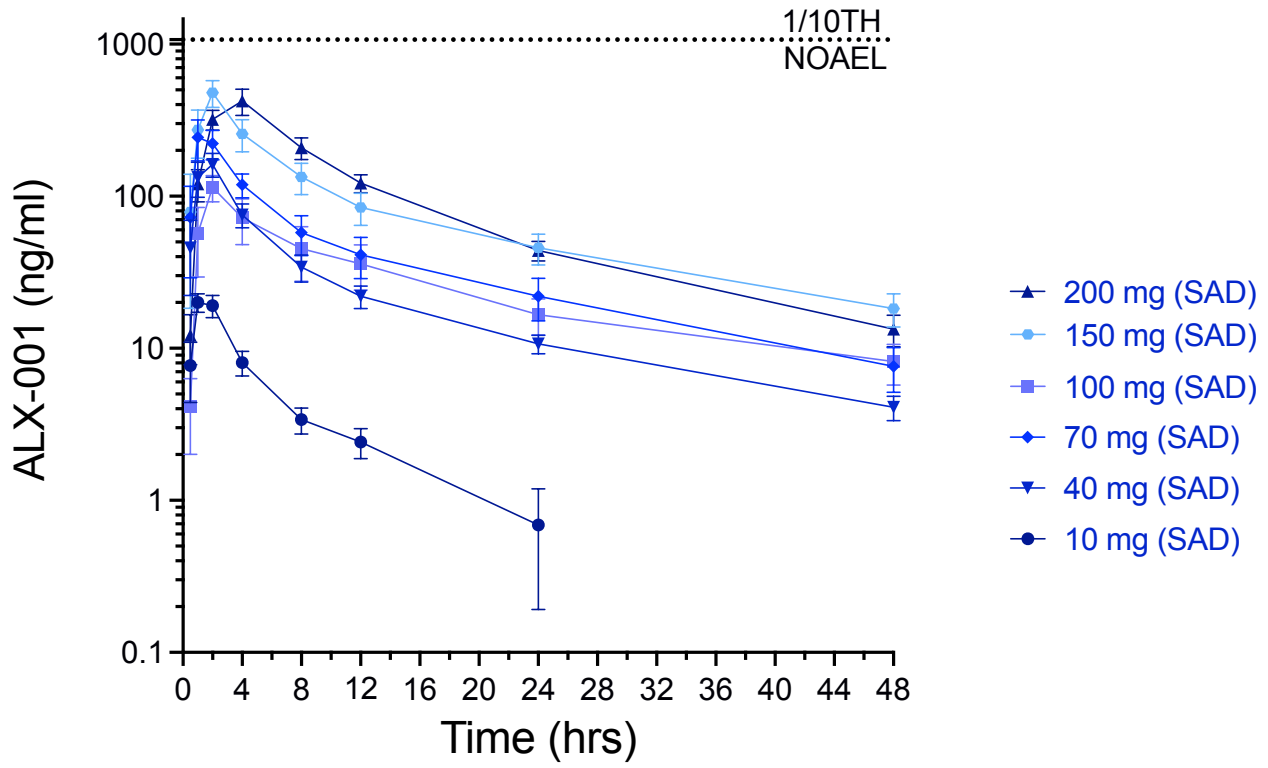
<u>Phase 1a SAD Study Results (Presented at CTAD 2023)</u>

- 6 dose cohorts (n=6 per group)
- 10 mg to 200 mg single doses
- Open label study in *healthy older adults*

- Safe and well tolerated at all doses.
  - 0 SAEs
  - 7 Mild Grade 1 Possibly Related AEs

- Characterized pharmacokinetics and confirmed oral bioavailability

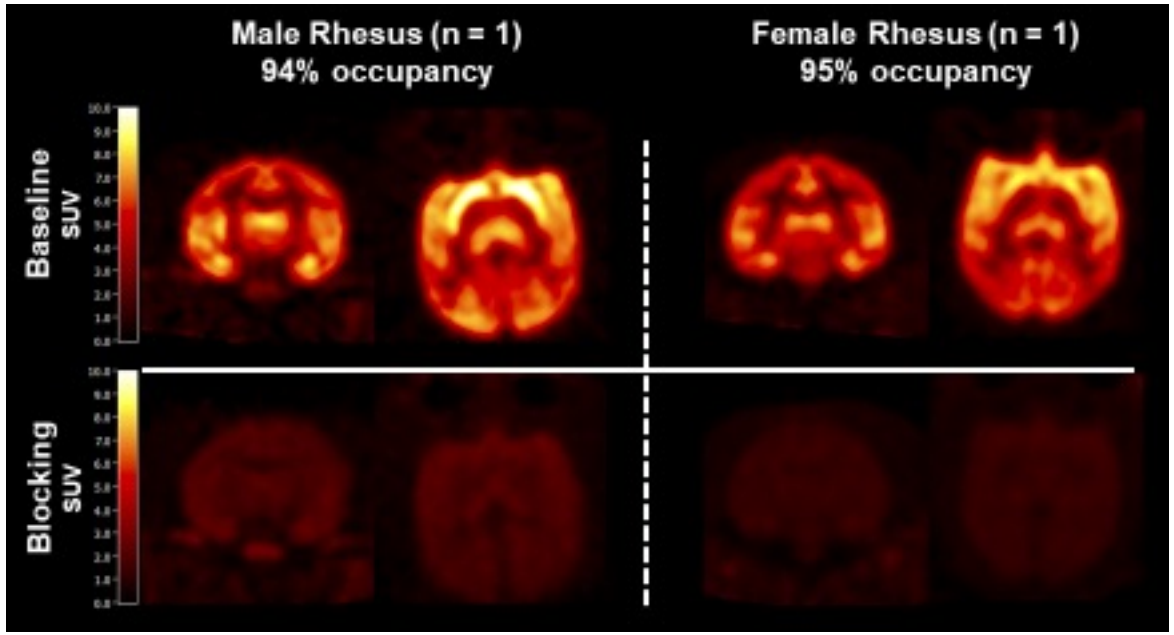
- Validated target engagement via mGluR5 PET imaging study.



Study Director: Adam Mecca, MD PhD (Yale University)

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

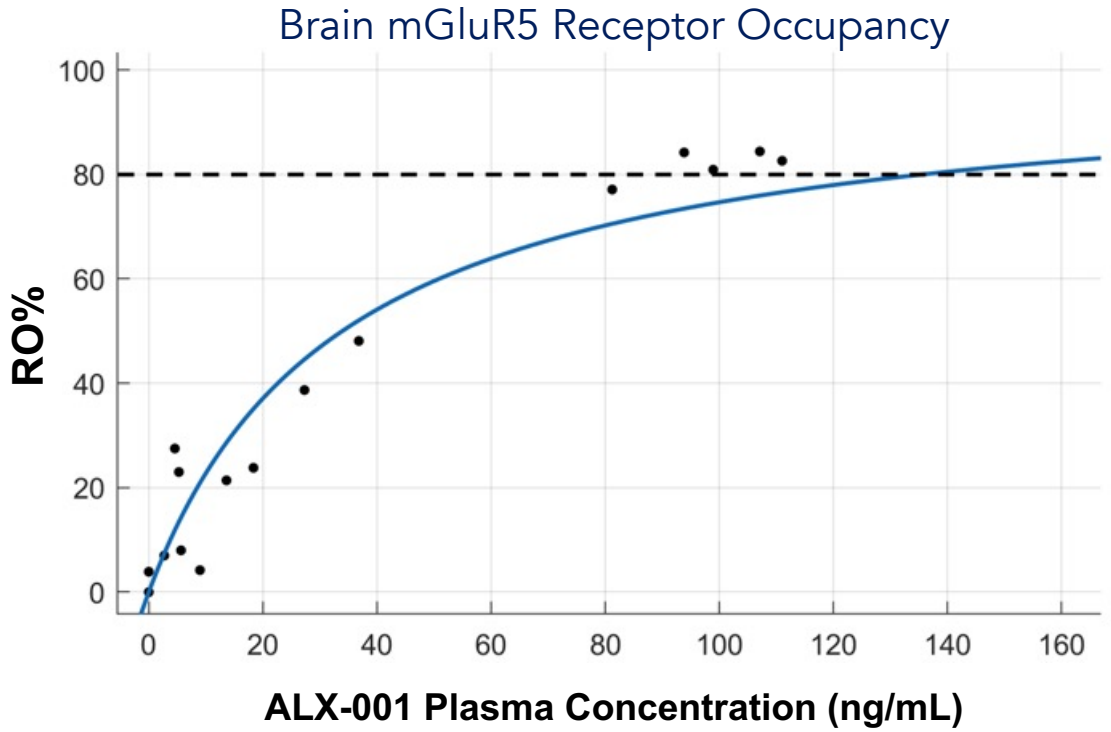
Brain Target Engagement Characterized in Primate PET Study



SUV (30 to 45 min) after infusion of 1 mg/kg ALX-001

Receptor Occupancy IC_{50} = ~25 ng/mL

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



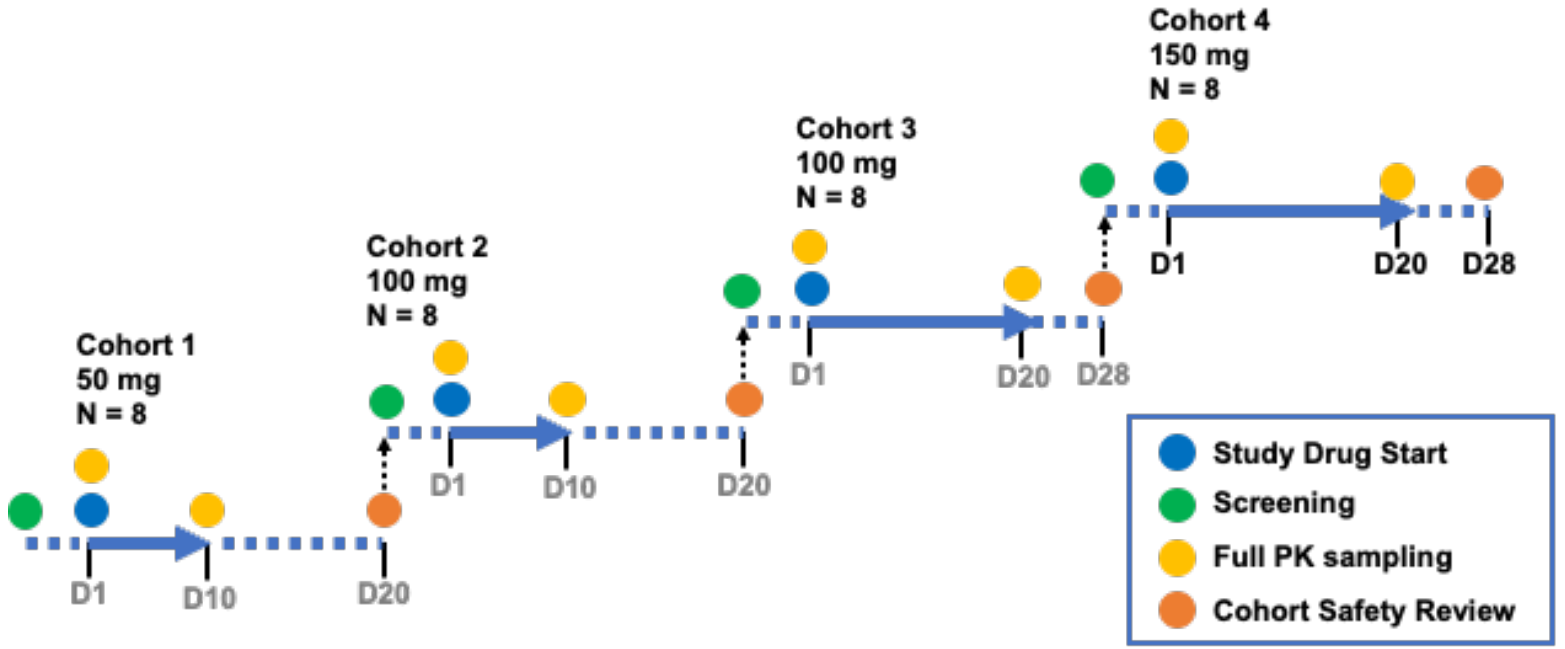
Receptor Occupancy IC_{50} = 34 ng/mL
IC_{80} = 136 ng/mL

A Phase 1b Multiple Ascending Dose Study of ALX-001

Establish Preclinical Proof of Concept → IND Enabling Safety & Tox. → AD & PD IND Clearance from US FDA → Phase 1a Single Ascending Dose → Phase 1a Food Effect → **Phase 1b Multiple Ascending Dose** → Phase 2 Proof-of-Concept → Phase 2b/3

Completed

Goal	• Establish safety, tolerability, and pharmacokinetics of ALX-001 administered twice daily (BID) drug at steady state.
Pop.	• Healthy adults aged 50-80, age matched for neurodegenerative disease population.
Design	• 32 participants total • Randomized, double-blinded, placebo controlled (n = 6:2, active : placebo)
Site	• Spaulding Clinical Research, West Bend, WI



Phase 1b MAD Demographics and Safety

Parameter	Mean (SD)
Age (years)	61 (7.26)
Weight (kg)	78.38 (13.739)
Body mass index (kg/m^2)	26.85 (4.109)

Parameter	Count (%)
Sex	
Female	15 (46.9)
Male	17 (53.1)
Race	
Asian	2 (6.3)
Black or African American	1 (3.1)
White	29 (90.6)
Ethnicity	
Hispanic or Latino	2 (6.3)
Not Hispanic or Latino	30 (93.8)

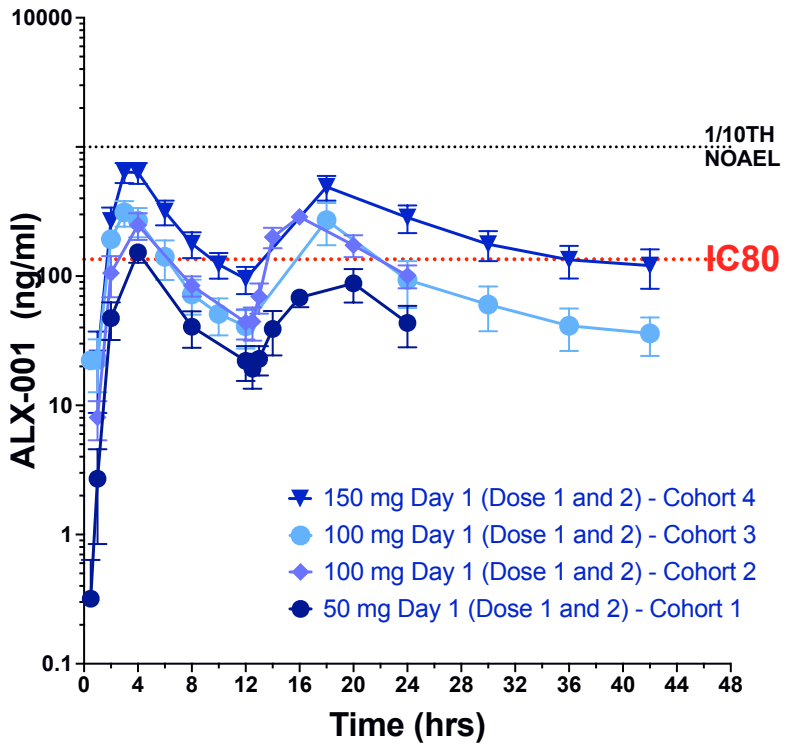
Favorable Safety Profile of ALX-001

	Cohort 1 ALX-001 50 mg (N=6)	Cohort 2 ALX-001 100 mg (N=6)	Cohort 3 ALX-001 100 mg (N=6)	Cohort 4 ALX-001 150 mg (N=6)	Pooled Placebo (N=8)	Overall (N=32)
Serious Adverse Events (SAEs)	0	0	0	0	0	0
Number of participants with at least 1 TEAE, n (%)	4 (66.7)	2 (33.3)	4 (66.7)	4 (66.7)	3 (37.5)	17 (53.1)
Number of TEAEs	8	9	11	9	7	44

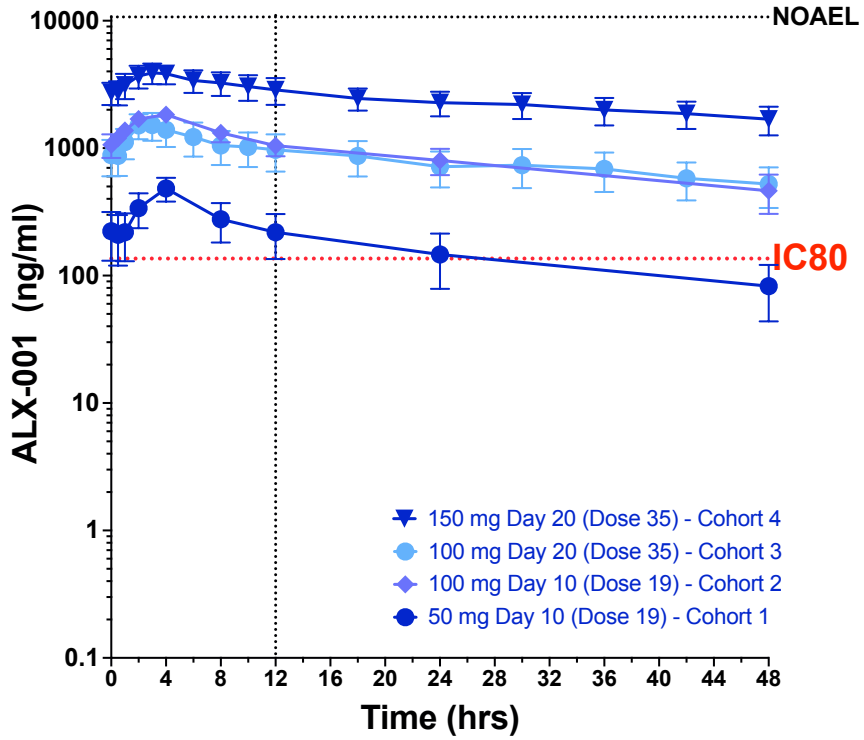
- Safety assessments included: vital signs, physical exams, ECGs, MoCA, NPI-Q, GDS, GCS, safety labs, adverse events.
- No clinically significant changes in cognitive or psychological symptom scales recorded.
- All AEs mild and fully recovered

Characterization of ALX-001 Pharmacokinetics of First and Last Day of Dosing

Day 1 Plasma Concentration: Dose 1 & 2



Final Dose Plasma Concentrations: Day 10 or 20



The studied dose range demonstrates a profile that maintains a 2.5-fold safety margin relative to the NOAEL and achieves a 2-fold coverage of the Receptor IC80

ALX-001 Achieves High Target Engagement while Avoiding mGluR5 Toxicity

	ALX-001	Dipraglurant	Mavoglurant	Basimglurant MR*
Class	SAM	NAM	NAM	NAM
Dose : Receptor Occupancy (%)	50 mg BID – 2-fold IC_{80} coverage 100 mg BID – 6-fold IC_{80} coverage 150 mg BID – 20-fold IC_{80} coverage	100 mg : 27% RO 200 mg : 44% RO 300 mg : 54% RO At 90 minutes post dose	25 mg : 27% RO 100 mg : 59% RO 200 mg : 74% RO 400 mg : 85% RO At 3-4 hrs post dose	0.5 mg : 25% RO 1.5 mg : 53% RO Estimated at steady state[1]
Adverse Events	No mGluR5 related AEs recorded to date at doses saturating the receptor	>88.5% treatment subjects experienced AE (Dizziness, nausea, fatigue, hypertension, asthenia, visual impairment, vertigo, feeling drunk, hallucinations, fall)	>82% patients at 100 mg BID experienced AE (Dizziness, Insomnia, Headache) 200 mg doses induced dizziness and hallucinations	Dizziness (24% at 1.5 mg, 4.5% at 0.5 mg and 5.5 % placebo), somnolence, headache
Max Tolerated Dose	150 mg BID to date	50 mg QD to 100 mg TID (<1 hr $t_{1/2}$)	100 mg BID Max	0.5 – 1.5 mg QD

ALLYX THERAPEUTICS

* Modified release required in order to reduce Cmax associated safety/tolerability limitations

[1] Quiroz, J. JAMA Pscyhiatry 2016 (73) 7, 673

Basimglurant: Lindeman, L. J Pharmacol. Exp. Ther. 353 (2015) 213-233

Mavolgurant: Vranesic, I. Bioorg. Med. Chem. 22 (2014) 5790

Beery-Kravis, E. Sci. Trans. Med. (2016) 8:321

Dipraglurant: Epping-Jorda, M. Cells 2023, 12*7), 1004

TMP-301: Christopher, J. J. Med Chem. 2015, 58, 6653-6664

Conclusions and Future Directions

- ALX-001 is a novel synapse targeted therapeutic approach to neurodegenerative disease.
- ALX-001 is advancing into Phase 2 development in both Alzheimer's and Parkinson's disease.
  - ALX-001 was safe in cognitively normal older adults at all doses investigated in the MAD out to 20-days with BID administration.
  - Characterized two viable doses for future patient studies:
    - 50 mg BID mean C_{Trough} provides 2-fold coverage of IC_{80} mGluR5 receptor occupancy.
    - 100 mg BID mean C_{Trough} provides 6-fold coverage of IC_{80} mGluR5 receptor occupancy.
- Two small grant funded pilot patient studies recently began screening:
  - 28-Day Study in AD Patients (NCT05804383)
    - Grant Funding Source → NIH R01 AG073117 (PI: Adam Mecca, MD, PhD – Yale University)
    - 3-arm parallel dose design at 50 mg BID, 100 mg BID & Placebo
  - 28-Day Study in PD Patients
    - Grant Funding Source → MJFF (PI: Laurie Sanders, PhD – Duke University)
    - 3-arm parallel dose design at 50 mg BID, 100 mg BID & Placebo

Thank You!

Study Participants

Yale PET Center
- Phase 1a SAD RO Study

Yale ADCR
- Adam Mecca, Chris van Dyck & Team
- Phase 1a SAD RO Study
- Phase 1b MAD Medical Monitoring

Spaulding Clinical Research
- Stephanie Post & Team
- Clinical trial site Phase 1a Food Effect
- Clinical trial site Phase 1b MAD

Strittmatter Lab – Yale University

Funding
NIA U01 AG058608
NIA R01 AG073117
NIA R44 AG069559
MJFF-021682

Contact: tsiegert@allyxthera.com
Website: www.allyxthera.com

Headquarters:
555 Long Wharf Drive,
New Haven, CT 06511

Labs:
UConn TIP Incubator
400 Farmington Ave,
Farmington, CT 06032