One-month Oral Treatment with PTI-125, a New Drug Candidate, Reduces CSF & Plasma Biomarkers of Alzheimer's Disease

Late Breaking Oral Communication

12th Clinical Trials on Alzheimer's Disease (*CTAD*)

December 5, 2019 - San Diego, CA

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Disclosures and Contributions

- PTI-125 is a proprietary compound of Cassava Sciences, Inc.
- Lindsay H. Burns, PhD; Nadav Friedmann, PhD, MD; and Carrie Crowley are employees of Cassava Sciences.
- Michael Marsman, PharmD and Hoau-Yan Wang, PhD are consultants to Cassava Sciences.
- Hoau-Yan Wang, PhD; Zhe Pei, PhD; and Kuo-Chieh Lee performed biomarker assays and are affiliated with City University of New York School of Medicine.
- *J Neurosci, Neurobiol Aging* and *Neuroimmunol Neuroinflammation* publications on PTI-125 are online: *www.CassavaSciences.com.*

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Phase 2a Clinical Trial of PTI-125

I. Background

II. Clinical Results

III. Mechanism of Action

IV. Conclusions

PTI-125 – A Novel Drug for Alzheimer's disease

- **PTI-125 is our proprietary, small molecule drug candidate to treat Alzheimer's disease (AD) and other dementias.**
  - Our AD program benefits from significant, long-term scientific and financial support from the National Institutes of Health (NIH).
- **By binding a single target, PTI-125 reduces both neurodegeneration and neuroinflammation.**
- **Clinical results from a first-in-patient study support PTI-125's mechanism of action.**
  - Clinical biomarker results are consistent with > 10 years of basic science and preclinical data.

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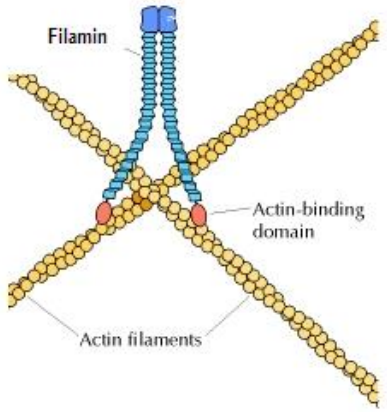
The Target of PTI-125 is *Altered* Filamin A (FLNA)

FLNA is an intracellular scaffolding protein anchored in the cell membrane.

FLNA interacts with > 90 proteins, influencing many signaling pathways.



The AD brain carries an *ALTERED* conformation of FLNA.

Altered FLNA is critical to amyloid beta's toxicity.

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PTI-125 Mechanism of Action

- **Altered FLNA enables $A\beta_{42}$ signaling via two different receptors:**
  - i. **α7-nicotinic acetylcholine receptor (α7nAChR)** → hyperphosphorylates tau
  - ii. **Toll-like receptor 4 (TLR4)** → releases inflammatory cytokines

- **PTI-125 preferentially binds *altered* FLNA, restores its proper shape/function, potently suppressing $A\beta_{42}$ signaling via α7nAChR and TLR4.**
  - Through a single target, PTI-125 reduces both neurodegeneration and neuroinflammation.

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Phase 2a Clinical Trial of PTI-125

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Phase 2a Study Design

- **Objective:** Safety, PK and biomarkers under an IND filed by Cassava Sciences
- **Study Design:** First-in-patient, open-label treatment at 5 sites in the US
- **Patients:** Mild-to-moderate AD, MMSE ≥ 16 ≤ 24, age 50-85
- **Key Inclusion:** CSF Total tau/$A\beta_{42}$ ≥ 0.30
- **Enrollment:** Thirteen (13) patients
- **PTI-125 Dose:** 100 mg oral tablets, b.i.d. for 28 days
- **Biomarkers:** CSF samples collected at screening and Day 28
  Blood samples for plasma/lymphocyte markers at Days 1, 14 and 28

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Phase 2a Safety and Pharmacokinetics

- Drug was well-tolerated, no drug-related adverse events observed
- PK parameters of PTI-125 100 mg b.i.d. in AD patients:

Day	C_{max} (ng/mL)	T_{max} (h)	C_{last} (ng/mL)	T_{last} (h)	λz (1/h)	AUC_{last} (h*ng/mL)	$T_{1/2}$ (h)	CSF/ plasma
Day 1	1,020	2.00	176	12	0.176	5,320	4.51	---
Day 28	1,100	2.06	238	12	0.174	6,700	4.35	0.61

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CSF Biomarker Methods

- CSF biomarkers were measured by CUNY using commercial ELISA kits (LifeSpan BioSciences, Inc.) according to manufacturer's instructions.
- Samples were pre-treated with protease and phosphatase inhibitors.
- Screening and Day 28 samples were run in the same ELISA plate, in triplicate, for each biomarker.
- Assays used 50 µl CSF per well (YLK40 used 100 µl), subtracting background for chromogen and the no-CSF control.
- Values were fit to standard curves; standard curves had R^2 values of 0.85-0.99.
- CSF samples were tested blind to Baseline/Day 28.
- Statistical analyses were conducted by an independent biostatistician.

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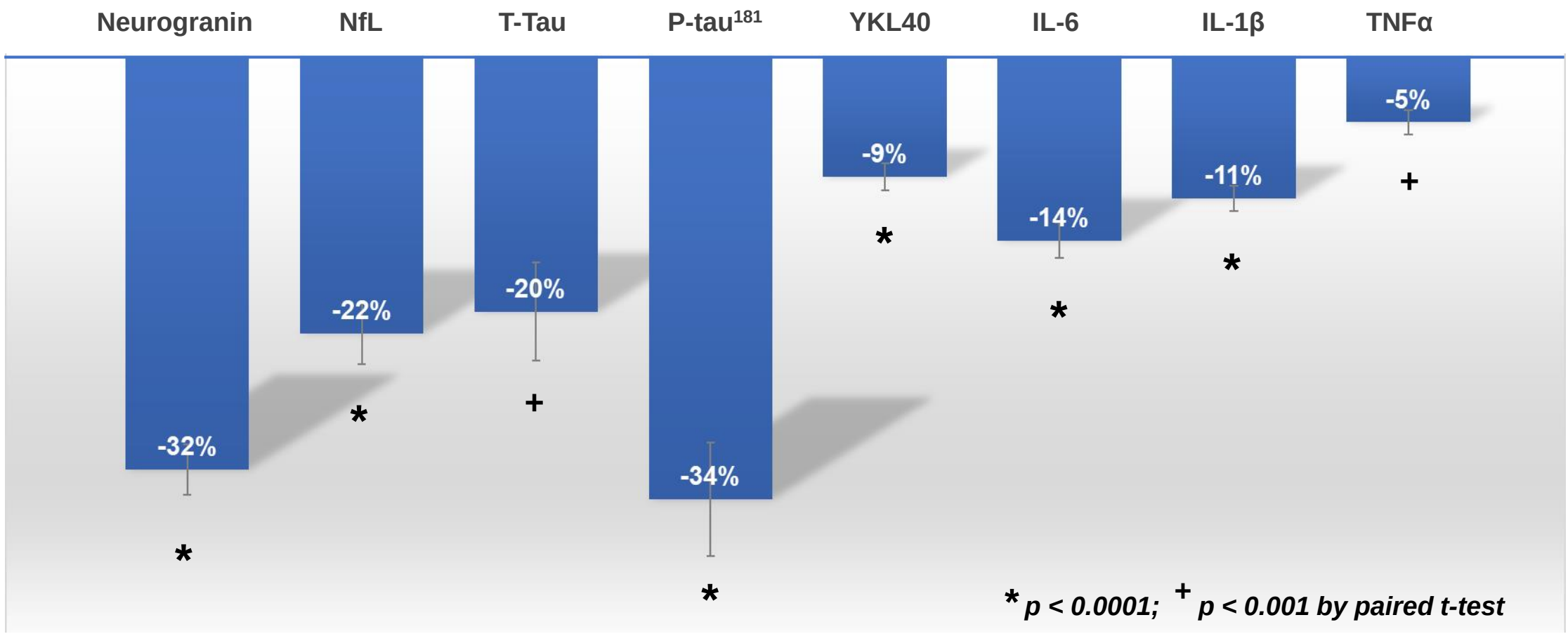
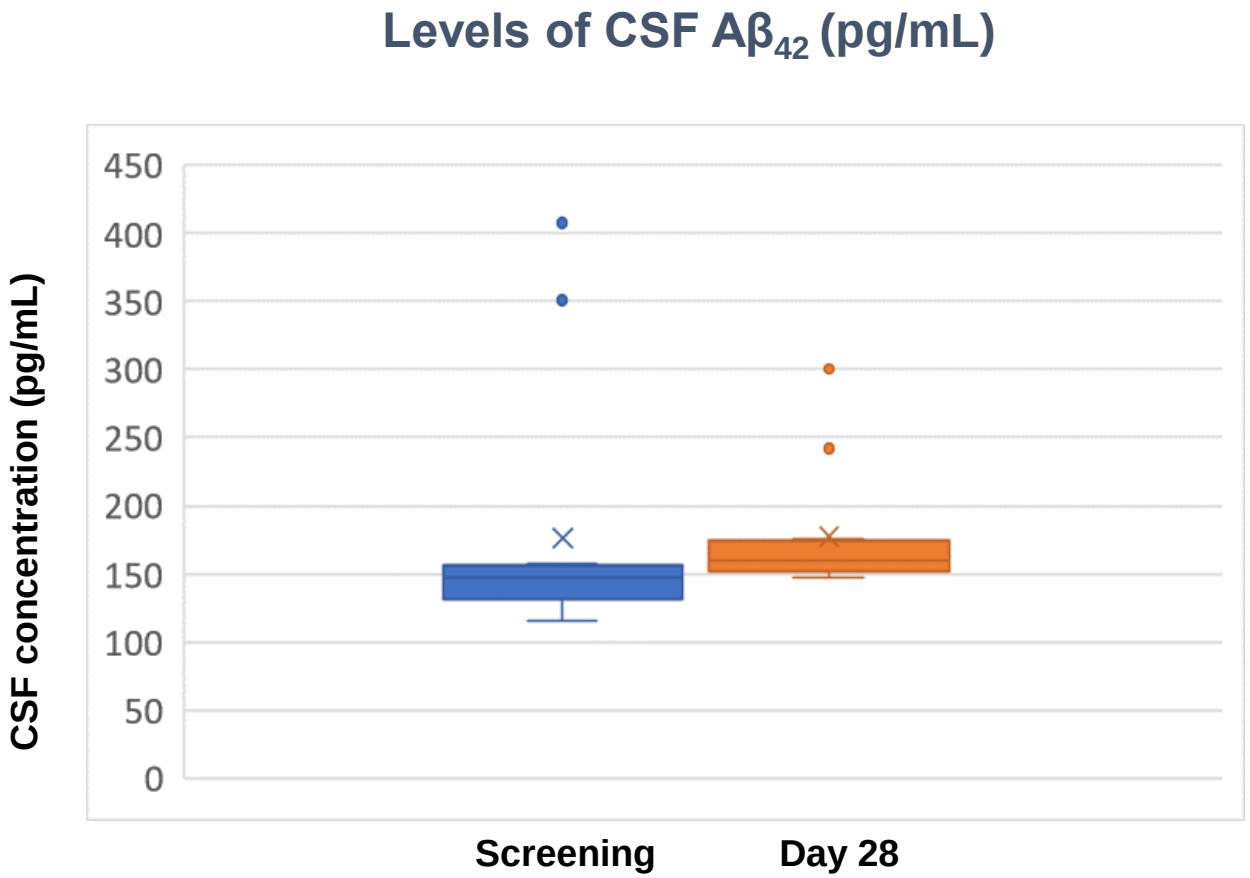
Phase 2a Summary Results - CSF Biomarkers

Change from Baseline to Day 28

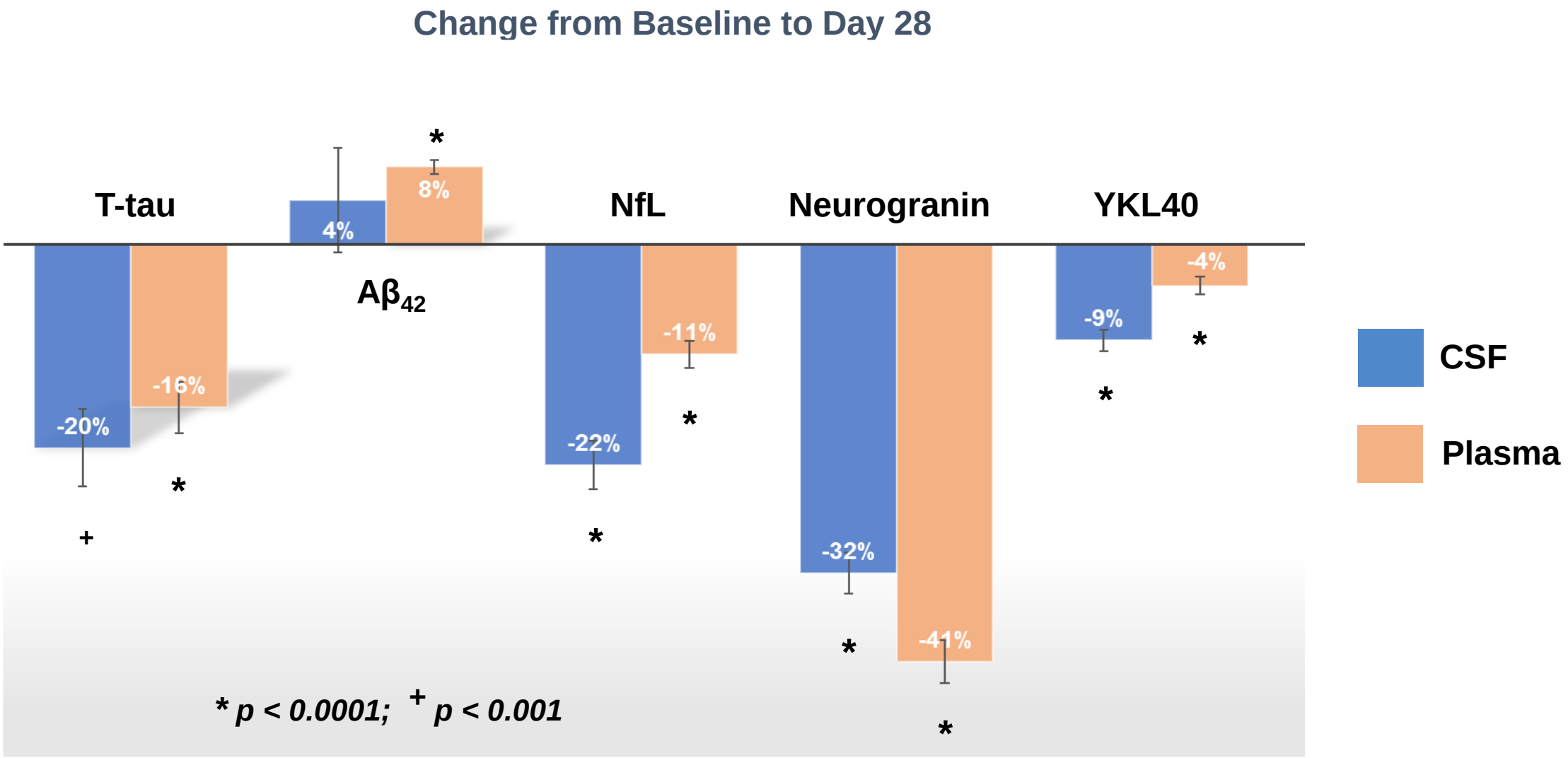


Slight Increase in CSF Amyloid-beta ($A\beta_{42}$)

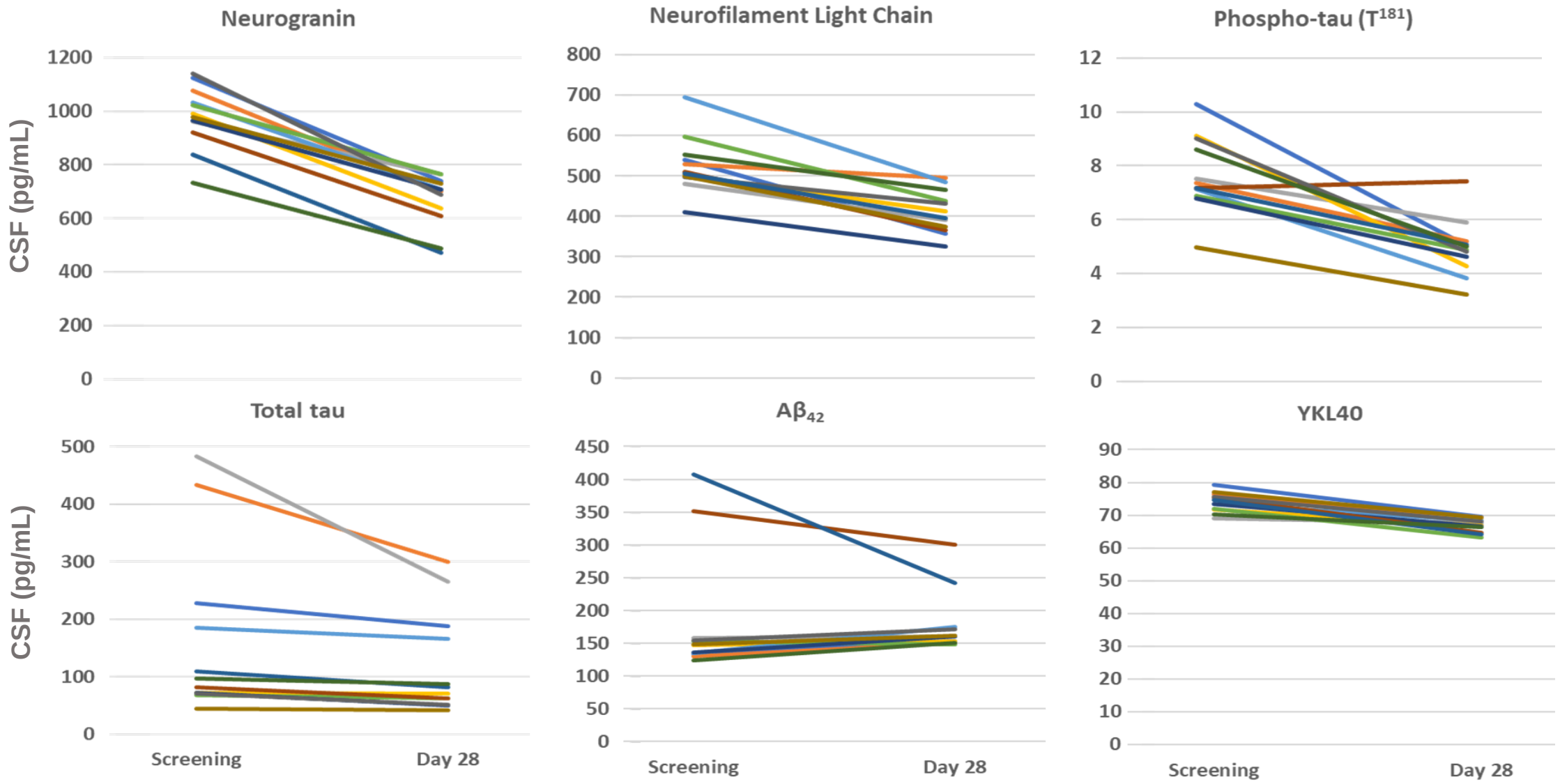


Note: Low CSF levels of $A\beta_{42}$ indicates Alzheimer's disease.

Phase 2a Biomarkers – CSF vs. Plasma



CSF Biomarkers – Individual Patient Responses



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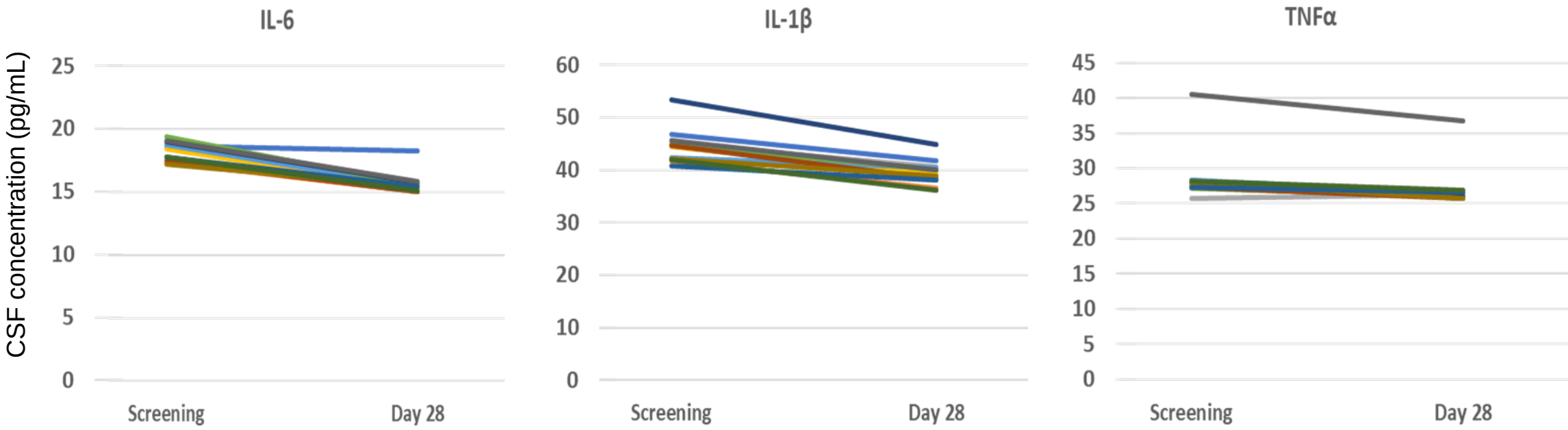
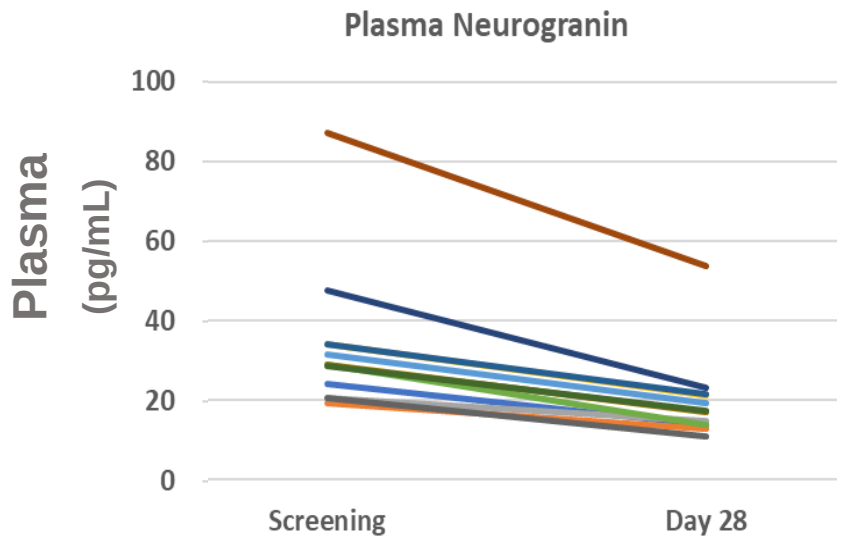
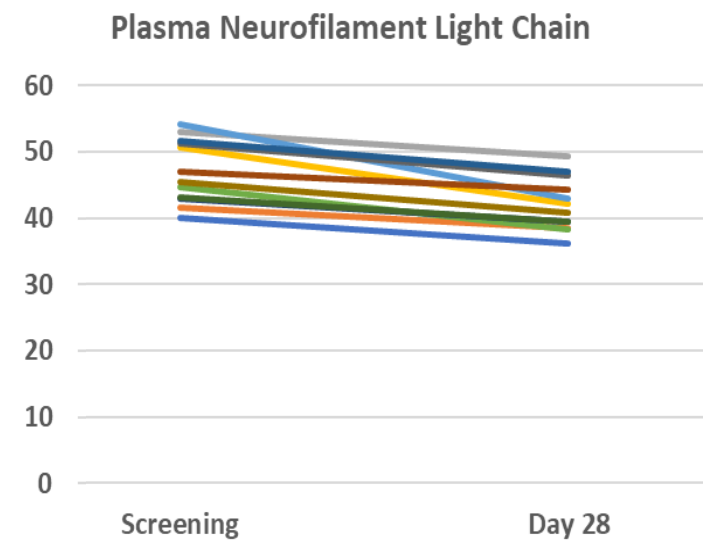
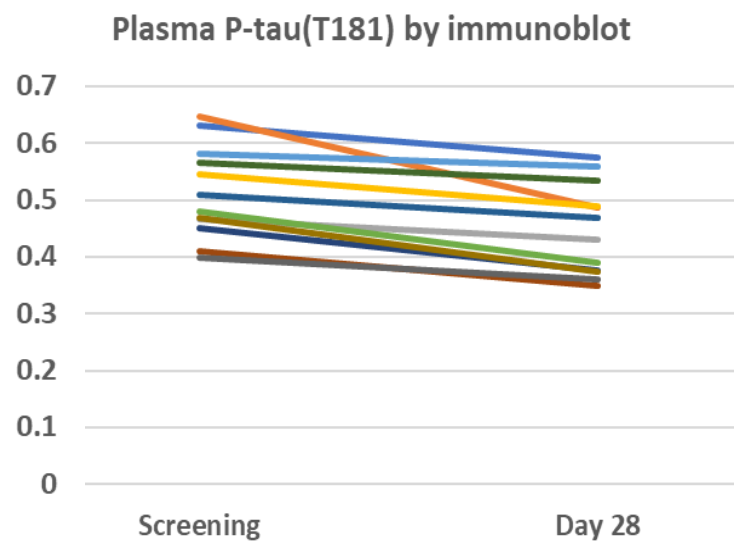
CSF Cytokines – Individual Patient Responses

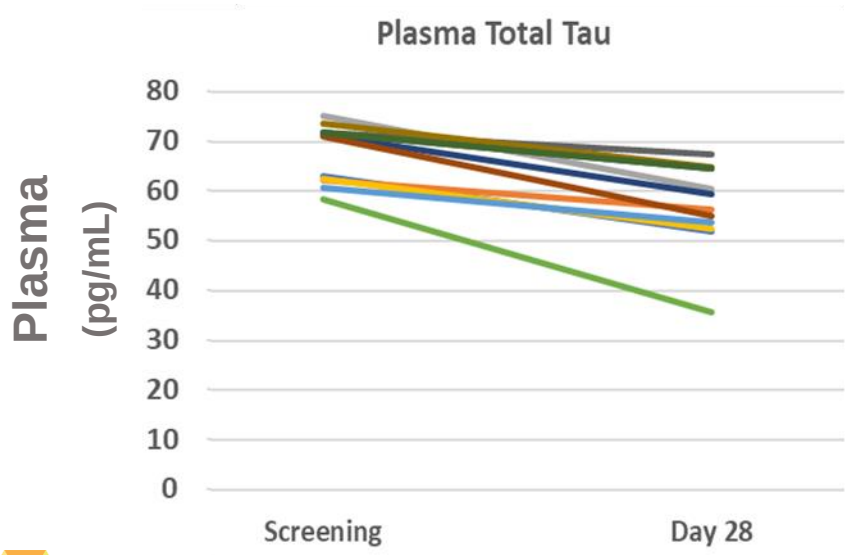


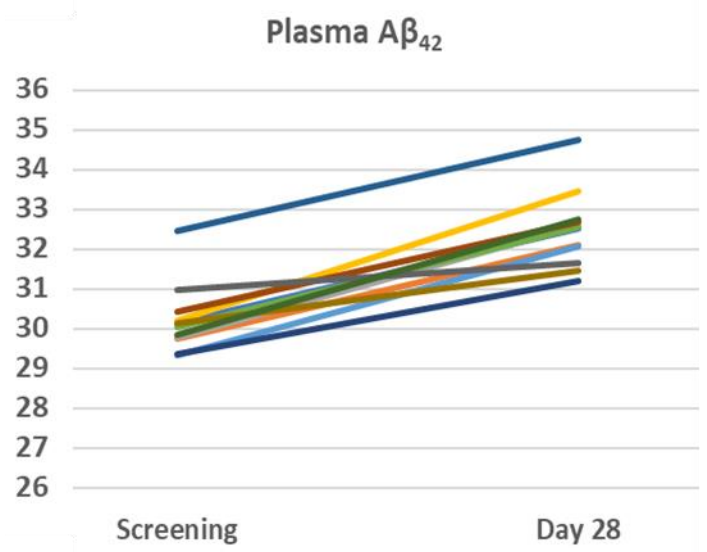
Plasma Biomarkers – Individual Patient Responses

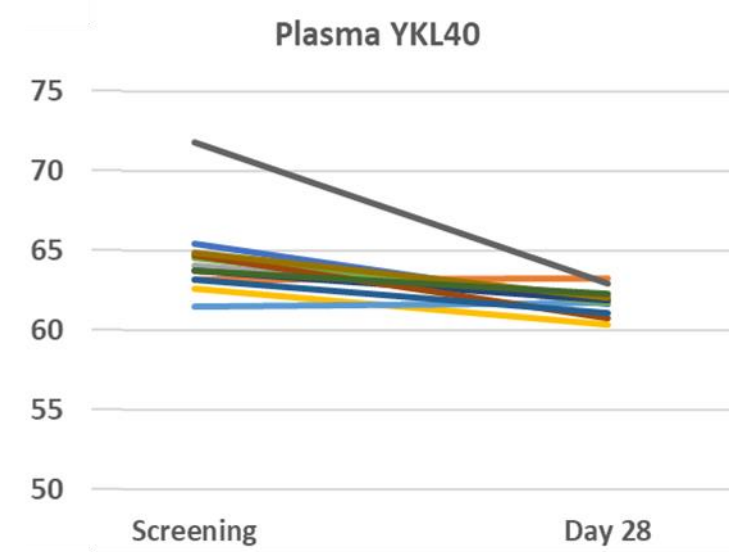












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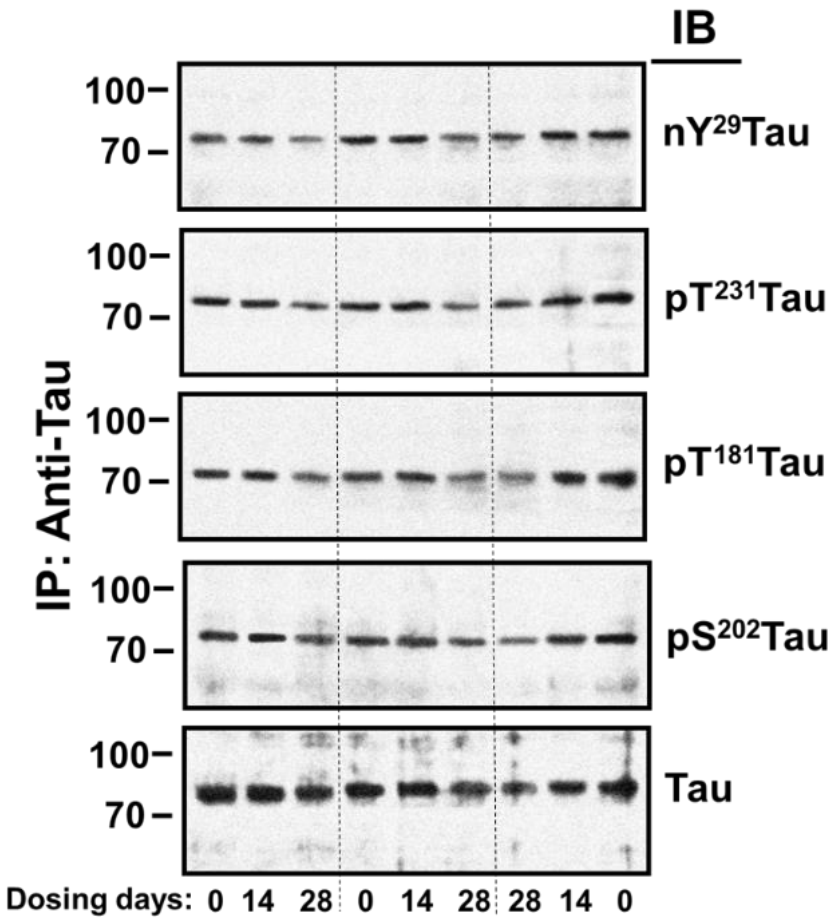
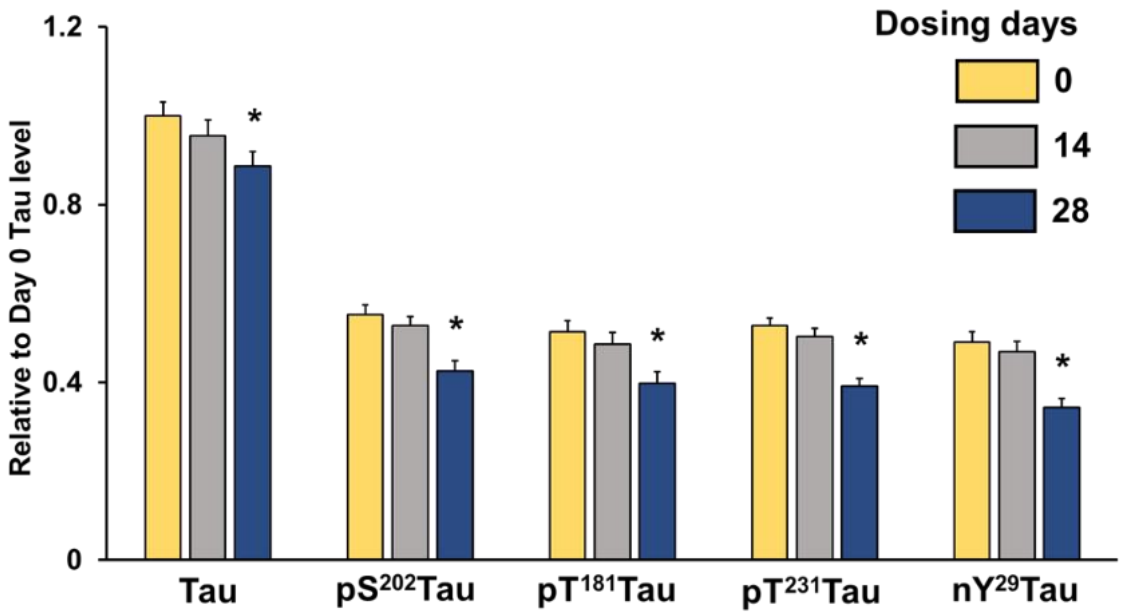
P-Tau and Nitrated Tau Reduced in Plasma



Reductions in Tau, P-tau and N-tau:
Baseline to Day 14 & Day 28



*** p < 0.001 Baseline vs. Day 28**

Phase 2a Clinical Trial of PTI-125

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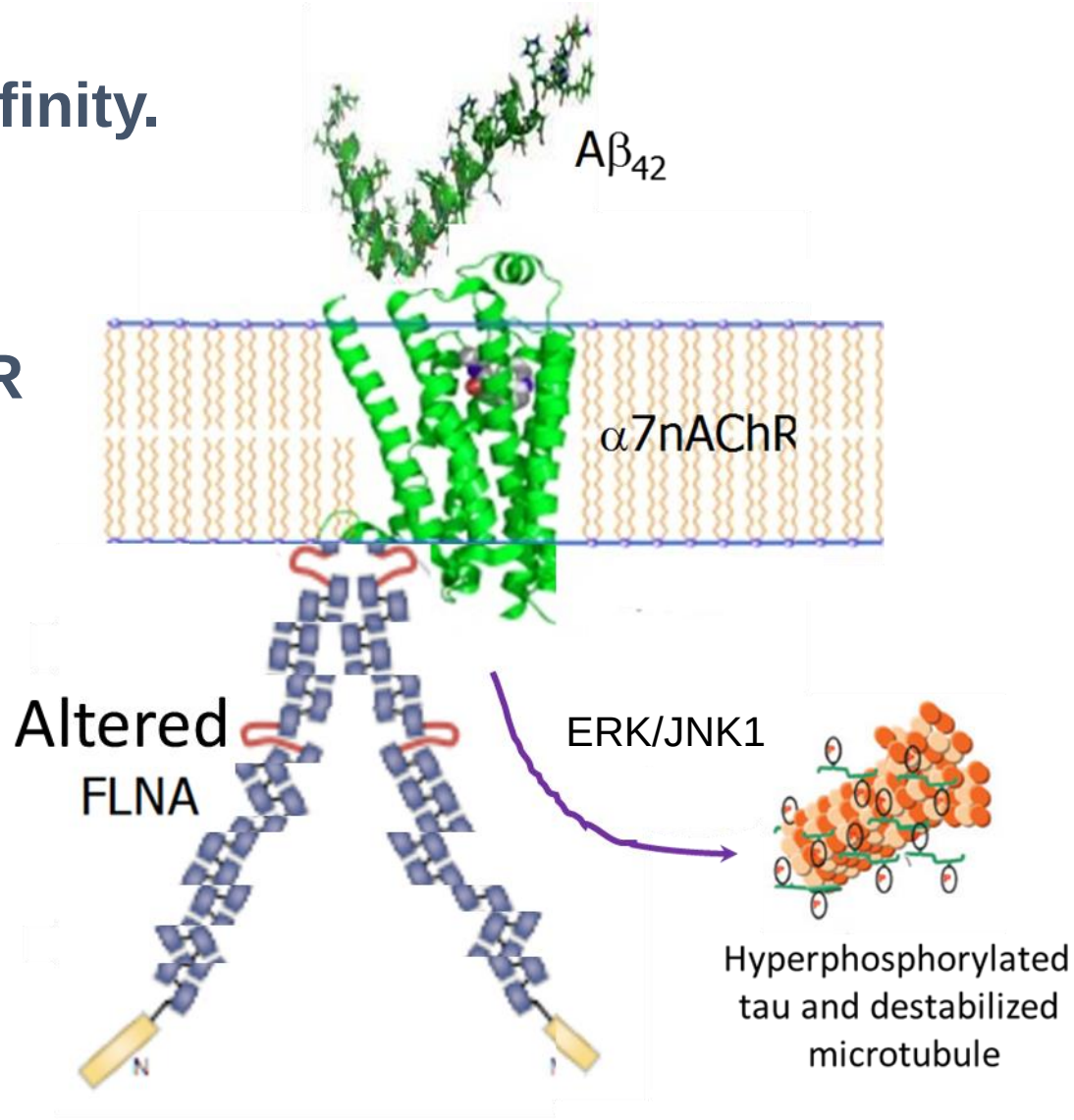
Altered FLNA links to α7-nicotinic acetylcholine receptor

- $A\beta_{42}$ binds α7nAChR with femtomolar affinity.
- Altered FLNA linkage to α7nAChR enables $A\beta_{42}$ signaling through α7nAChR to hyperphosphorylate tau.



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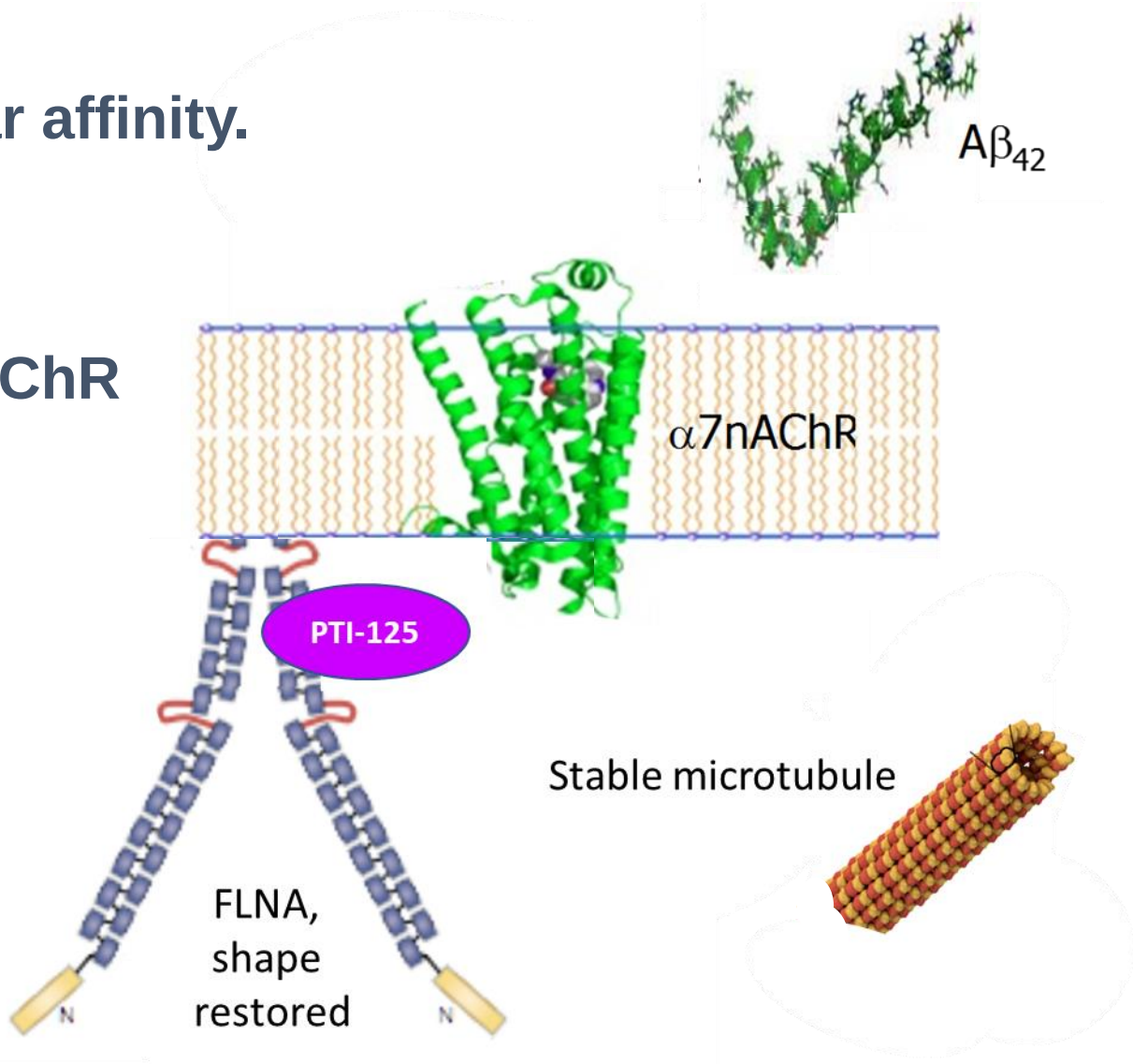
- ***PTI-125 binds altered FLNA, restores its normal shape, stops $A\beta_{42}$ signaling and tau hyperphosphorylation.***



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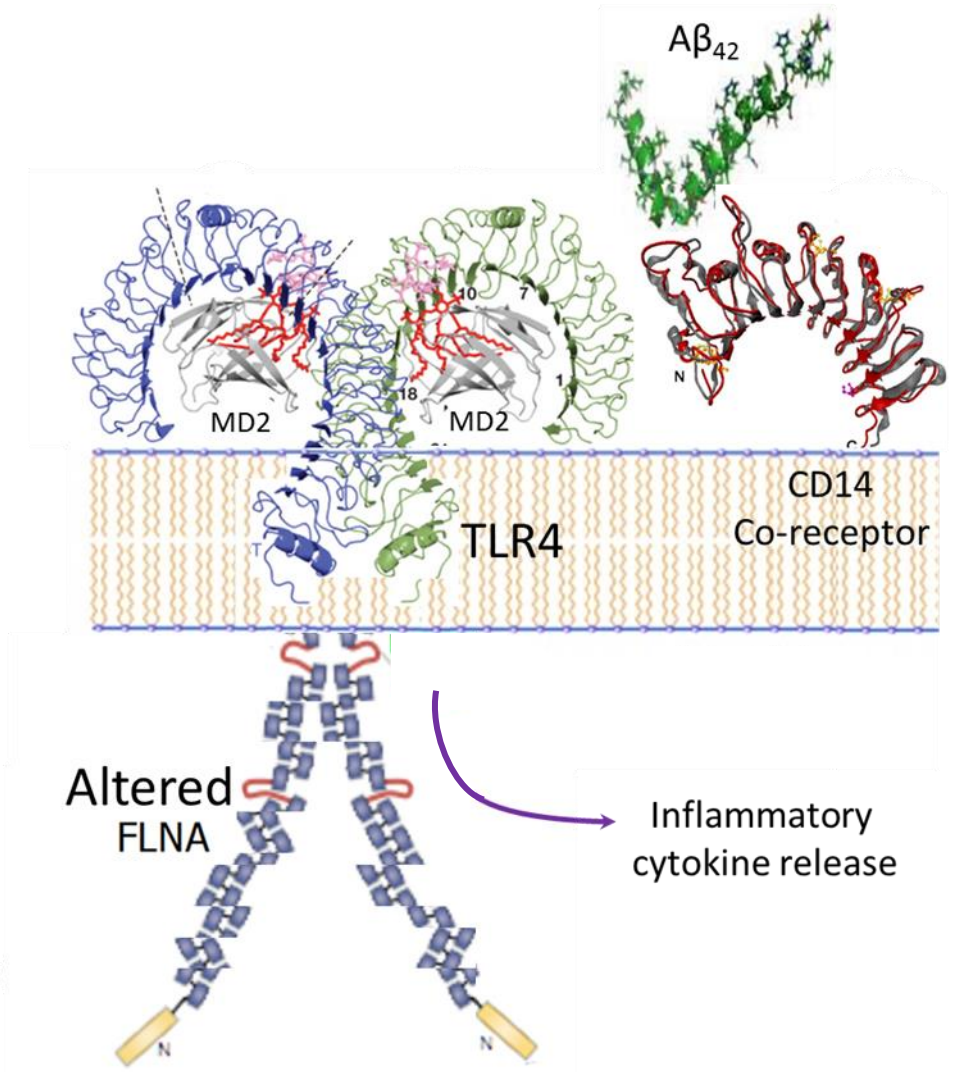
Altered FLNA links to Toll-like Receptor 4 (TLR4)

- **Altered FLNA linkage to TLR4 enables $A\beta_{42}$ to activate TLR4.**
- **Persistent TLR4 activation results in chronic neuroinflammation.**



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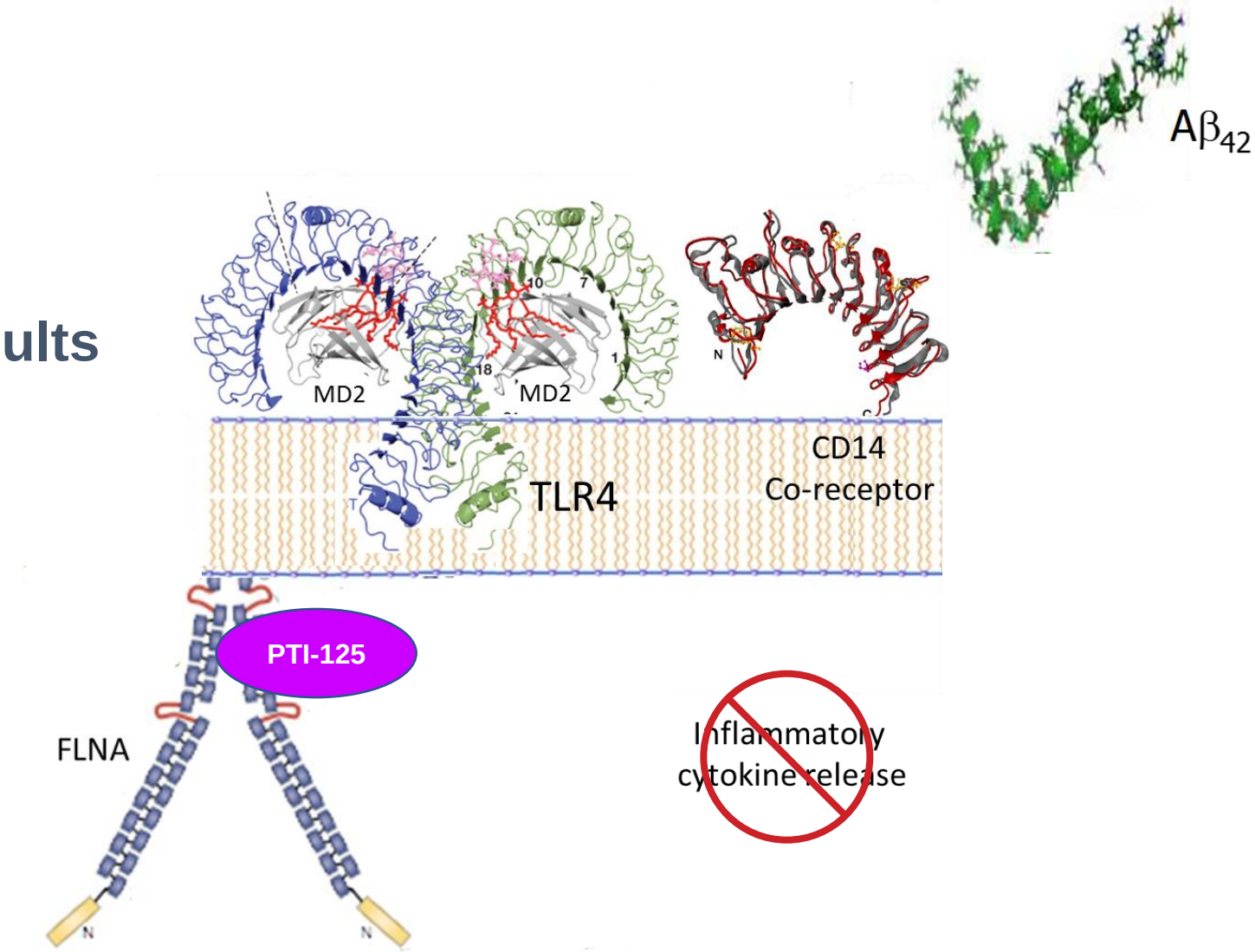

Target Engagement & Mechanism of Action

Evidence in patient lymphocytes from Day 0 to 14 to 28 by three methods:

i. Reversal of altered conformation of FLNA
   Assessed by isoelectric focusing point

ii. Reduced FLNA linkages to α7nAChR and TLR4
   Assessed by co-immunoprecipitation

iii. Reduced $A\beta_{42}$ complexed with α7nAChR and CD14
   Assessed by co-immunoprecipitation

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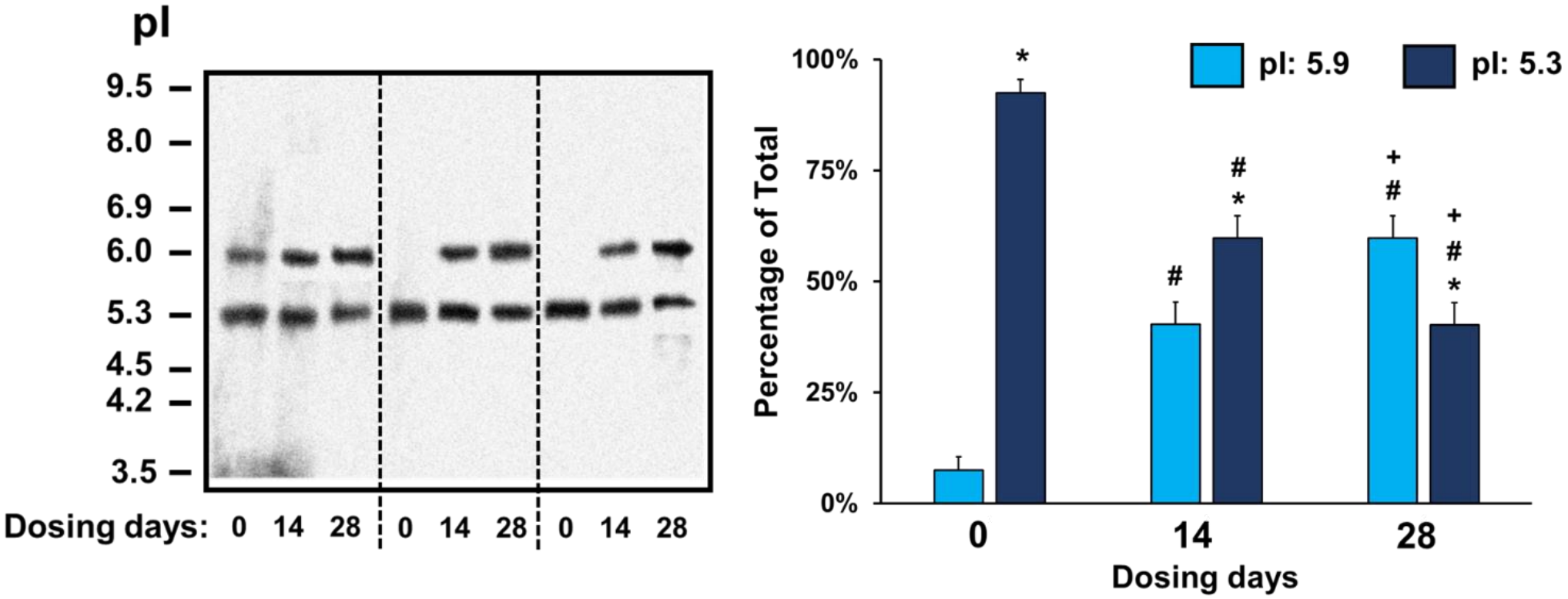
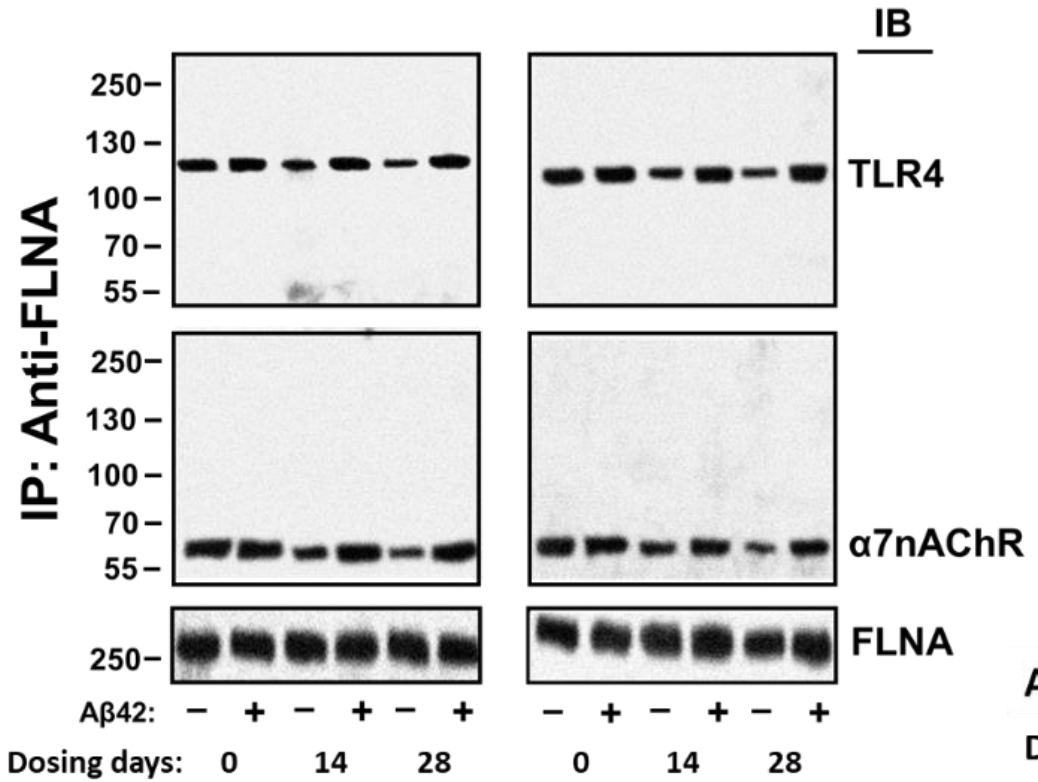
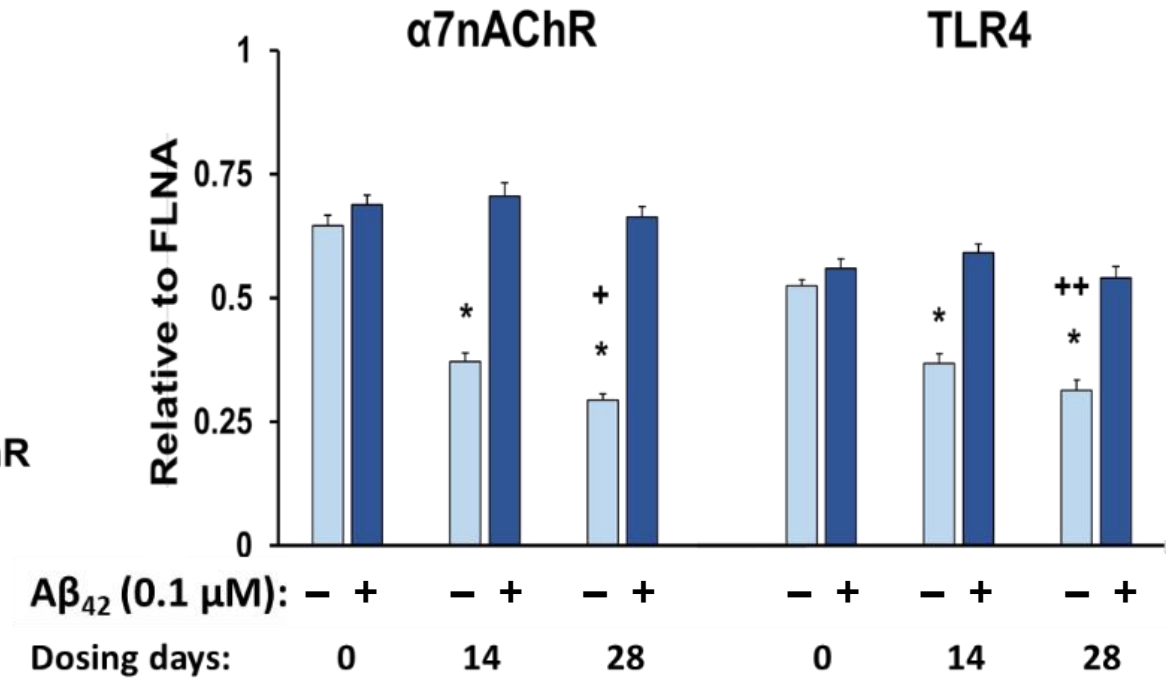
FLNA's Native Shape Restored in Patient Lymphocytes



**** p < 0.0001 vs. pI 5.9; # p < 0.0001 vs. Day 0; + p < 0.0001 vs. Day 14***

FLNA Linkages to α7 and TLR4 Reduced in Lymphocytes





**** p < 0.001 vs. Day 0; $^{+}$ p < 0.01, $^{++}$ p < 0.05 vs. Day 14***

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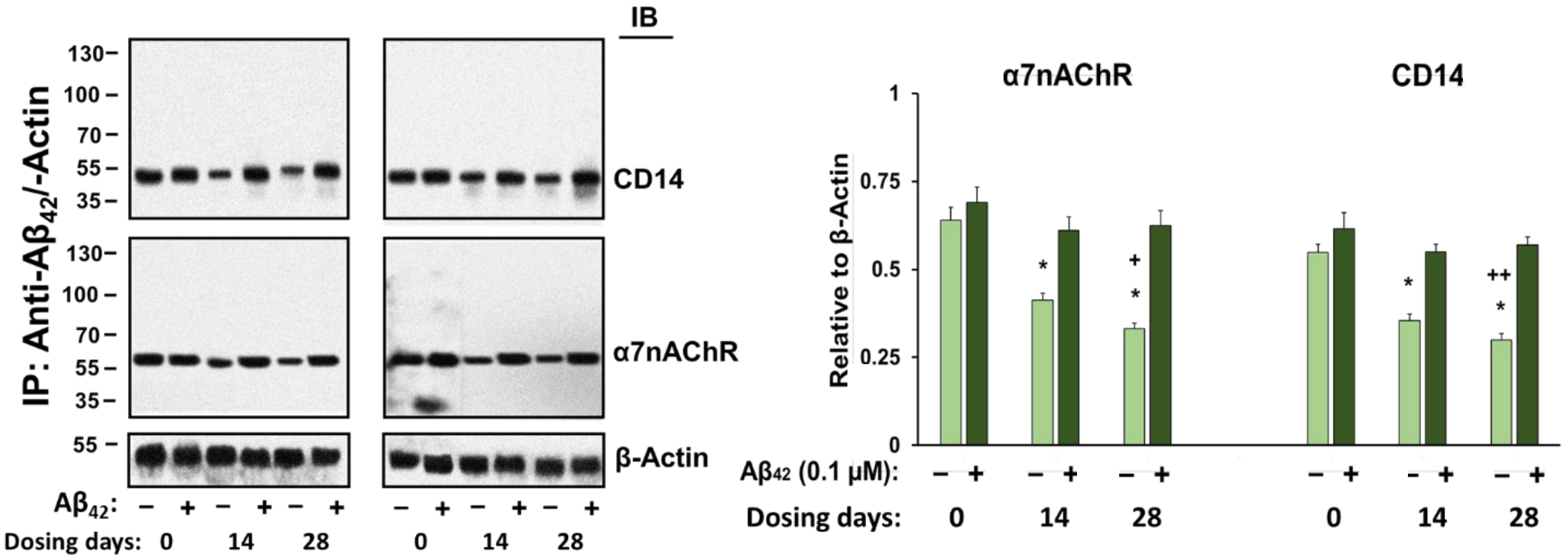
$A\beta_{42}$ Bound to α7nAChR or CD14 Reduced in Lymphocytes



** p < 0.001 vs. Day 0; + p < 0.01, ++ p < 0.05 vs. Day 14*

Phase 2a Clinical Trial of PTI-125

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Summary of PTI-125 Effects

- **Validated CSF biomarkers of AD pathology improved in all patients treated with PTI-125:**
  - Reduced post-synaptic damage: Neurogranin -32%
  - Reduced tau: Total tau -20%, P-tau -34%
  - Reduced axonal degeneration: Neurofilament light chain -22%
  - Reduced neuroinflammation: YKL40, IL-6, IL-1β, TNFα reduced 5-14%
- **Consistent improvements in biomarkers across CSF, plasma and lymphocytes.**

PTI-125 at 100 mg b.i.d. for 28 days appeared to slow the rate of neurodegeneration and suppress neuroinflammation, consistent with the drug's mechanism of action and preclinical data.

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Phase 2a data are…..

Promising because:

- **PTI-125 improved all biomarkers of AD pathology, neurodegeneration and neuroinflammation.**
  - Consistent effects across CSF, plasma, lymphocytes
  - All patients responded to PTI-125
  - Drug was safe and well-tolerated
- **Clinical results are consistent with PTI-125's mechanism of action and > 10 years of basic science.**
- **Biomarker data imply disease-modifying effects.**

Viewed conservatively because:

- **Treatment was open-label.**
- **The number of patients is small.**
- **Dose-response remains undefined.**

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Conclusions

This first-in-patient study of PTI-125, a new drug candidate, demonstrated:

- ✓ **Evidence of target engagement and mechanism of action in AD patients**
- ✓ **Significant improvements in biomarkers of AD**
- ✓ **Clinical validation for FLNA as a target for AD drug development**

These data highlight PTI-125's potential as a disease-modifying drug therapy for Alzheimer's disease.

Clinical results are being confirmed in an ongoing 60-patient, blinded, randomized, placebo-controlled clinical trial.

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