Early Clinical Results with SavaDx, an Investigational Blood-based Diagnostic/Biomarker for Alzheimer's Disease

Biomarkers for Alzheimer's Disease Summit

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Disclosures

- SavaDx and PTI-125 are proprietary product candidates of Cassava Sciences.
- Lindsay H. Burns, PhD and George (Ben) Thornton, PhD are employees of Cassava Sciences.
- Hoau-Yan Wang, PhD is a consultant to Cassava Sciences and is affiliated with City University of New York (CUNY) School of Medicine.
- Research reported in this presentation was supported by the National Institute on Aging of the NIH under award AG057329 and other research grant awards.
- The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of NIH, CUNY or any other third-party.

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THE CITY UNIVERSITY OF NEW YORK

Lindsay H. Burns, PhD

- SVP Neuroscience, Cassava Sciences; employee 2002-present
- Previously, Neurex/Elan Pharmaceuticals and Abgenix/Amgen
- Harvard BA, University of Cambridge PhD, post-doc Harvard Med School
- Publications in neurodegeneration; reward processing; discriminative learning; Parkinson's and Huntington's disease; and mu opioid receptor signaling

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SavaDx

I. Introduction

II. Diagnostic Data

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SavaDx – A Novel Diagnostic/Biomarker for AD

- **SavaDx is a blood-based diagnostic/biomarker for Alzheimer's disease (AD).**
  - Program benefits from significant financial support from the National Institute on Aging (NIA).
- **SavaDx was discovered in collaboration with Prof. Hoau-Yan Wang, PhD (CUNY) under academic research funding provided by Cassava Sciences.**
  - Worldwide commercial rights owned exclusively by Cassava Sciences.
- **SavaDx is an investigational product candidate.**
  - The U.S. Food and Drug Administration has not reviewed or approved SavaDx for its proposed use as a diagnostic/biomarker of AD, or any other clinical indication.

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SavaDx Detects an AD Proteopathy

- **A ‘proteopathy’ refers to a protein that become structurally abnormal, and disrupts the normal function of cells, tissues and organs.**

- **We discovered a new proteopathy in AD: an altered form of the scaffolding protein, Filamin A (FLNA).**

- **SavaDx detects protein changes in blood from altered FLNA.**
  - Detects abnormal protein-protein interactions in lymphocytes
  - Detects unique proteolytic products in plasma

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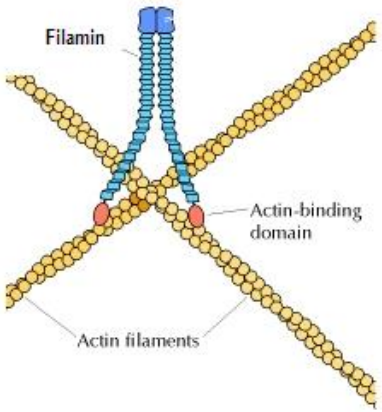
SavaDx Detects the Filamin A (FLNA) Proteopathy

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.

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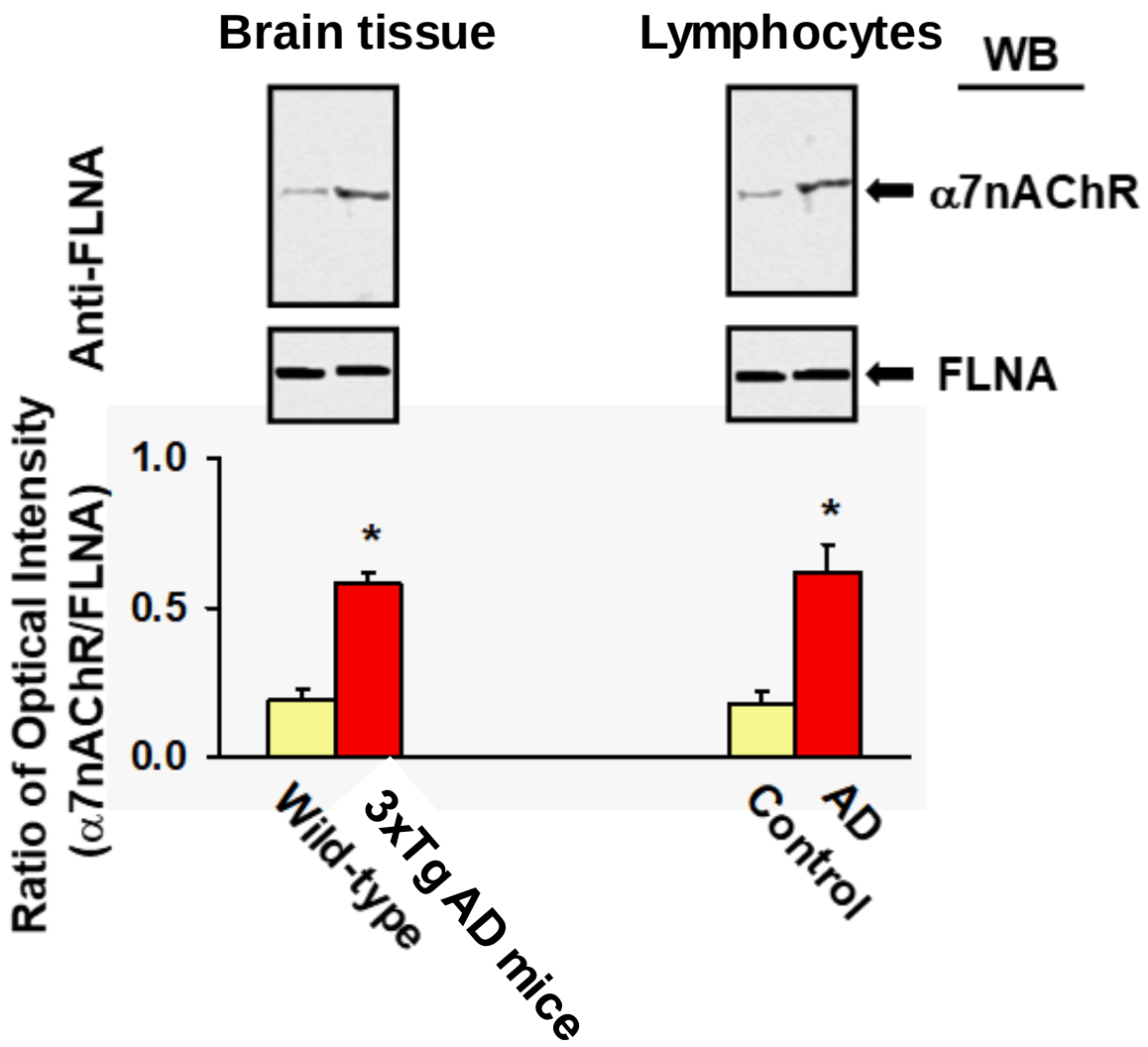
The FLNA Proteopathy in AD Brain

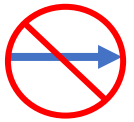
- **Altered FLNA links to two different receptors to enable $A\beta_{42}$ signaling:**
  - i. **α7-nicotinic acetylcholine receptor (α7nAChR)** → hyperphosphorylates tau
  - ii. **Toll-like receptor 4 (TLR4)** → releases inflammatory cytokines

FLNA – α7nAChR Increases in 3xTg AD Mice & AD Patients



PTI-125 Reverses the FLNA Proteopathy

- **PTI-125 is our investigational drug candidate for AD.**

- **PTI-125 binds *altered* FLNA, restores its native shape, un-links FLNA from:**
  - i. **α7-nicotinic acetylcholine receptor (α7nAChR)**  hyperphosphorylates tau
  - ii. **Toll-like receptor 4 (TLR4)**  releases inflammatory cytokines

- **Through a single target, PTI-125 suppresses $A\beta_{42}$ signaling, reducing both neurodegeneration and neuroinflammation.**

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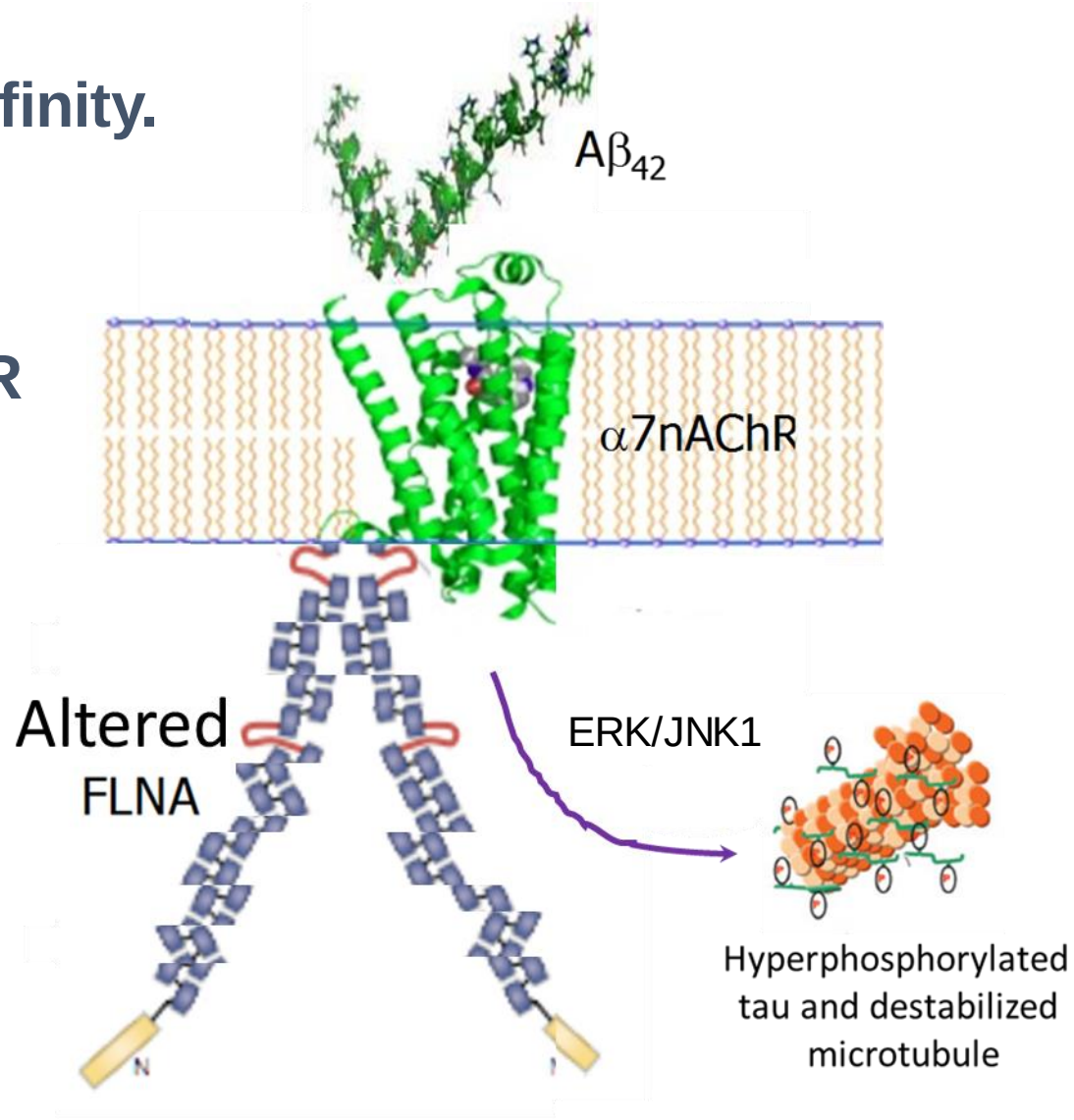
Altered FLNA links to α7-nicotinic acetylcholine receptor

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



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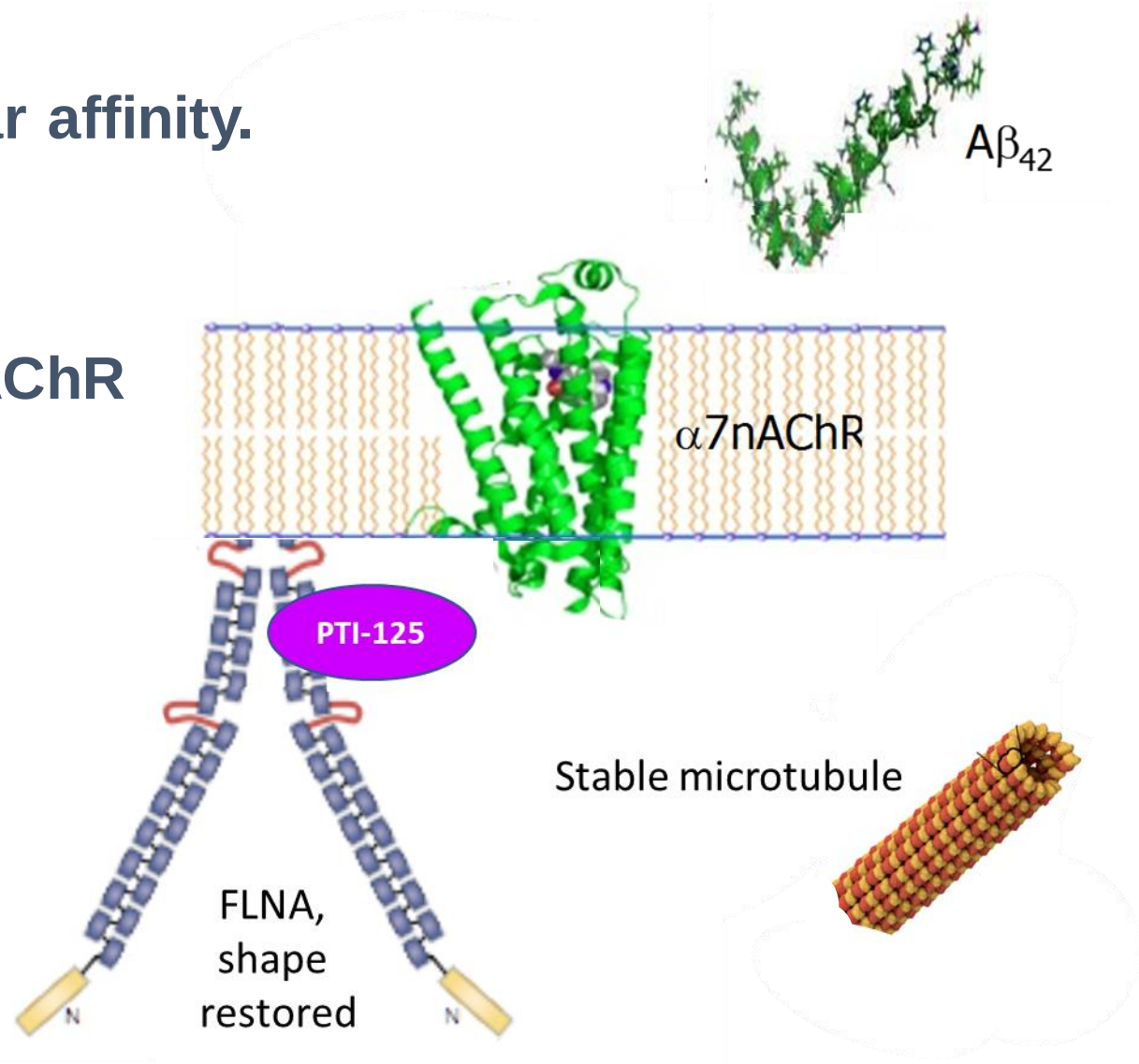
Altered FLNA links to α7-nicotinic acetylcholine receptor

- $A\beta_{42}$ binds α7nAChR with femtomolar affinity.

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

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



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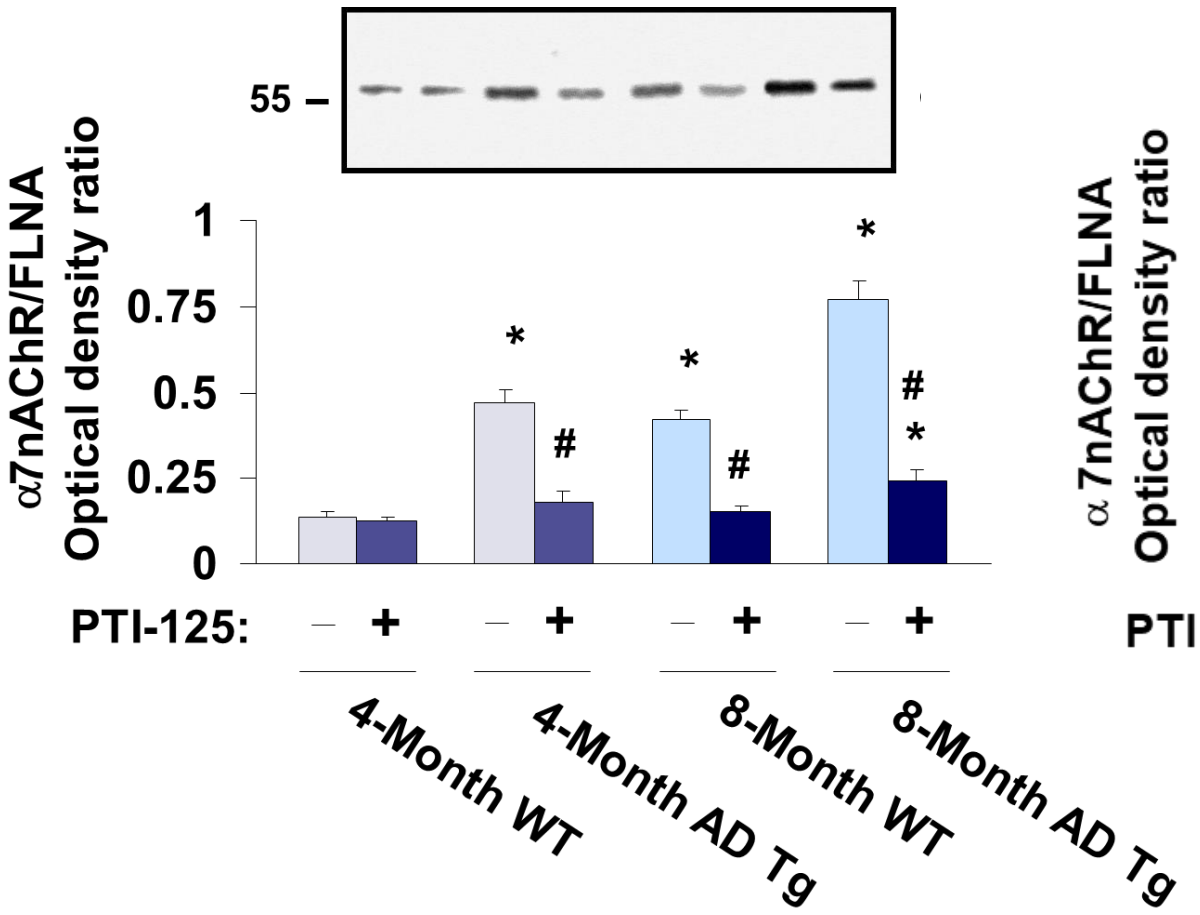
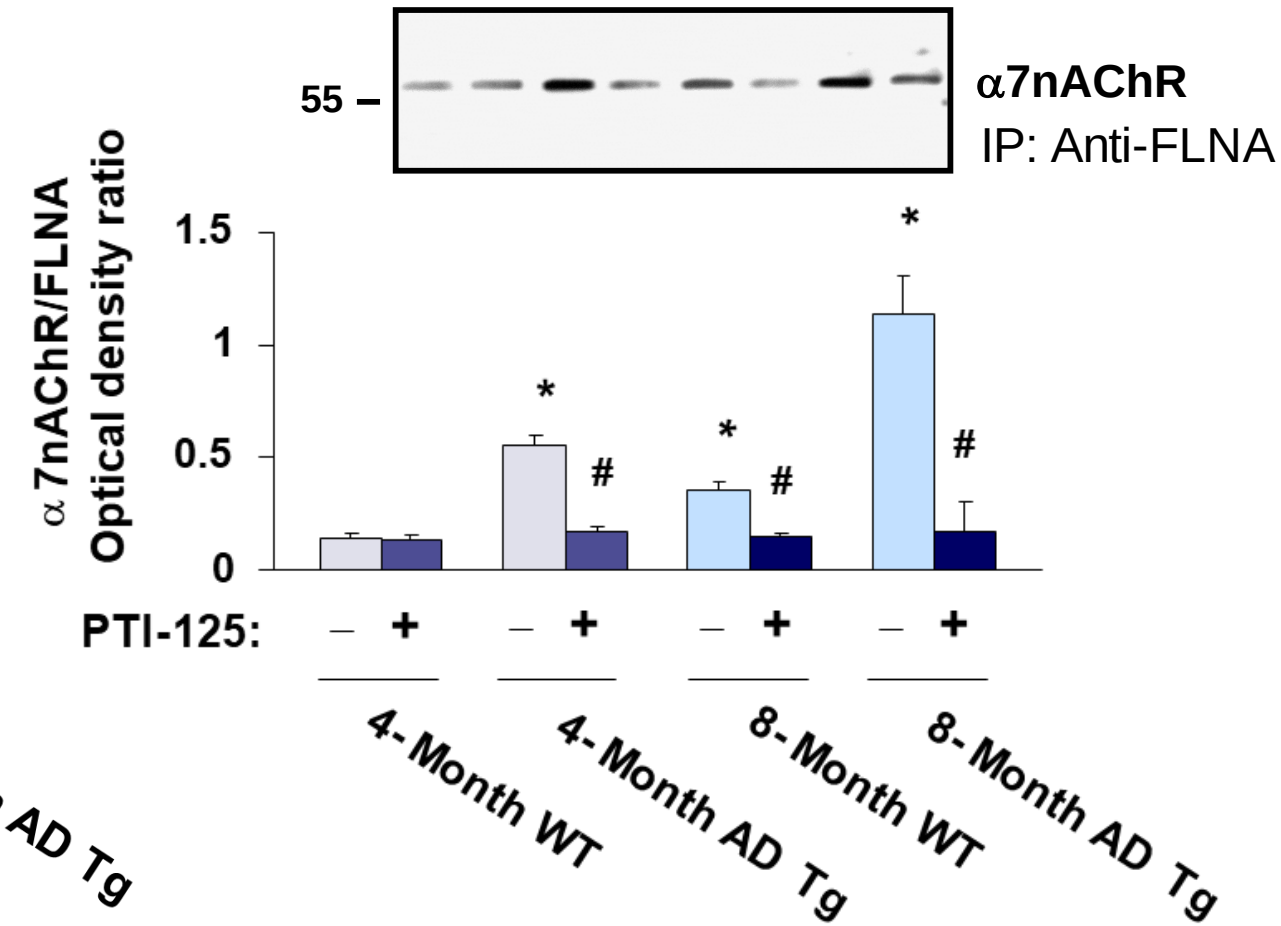
α7 – FLNA Linkage in Brain and Lymphocytes in Tg Mice

Hippocampus



Lymphocytes



SavaDx

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SavaDx - Pilot Diagnostic Studies

Study A (n=44; Dr. Joel Ross; AD confirmed by Amyvid or FDG-PET)

	AD	MCI-AD	MCI-SNAP	Elderly Normal Controls
n	15	2	8	19
Age	75.3 (11.9)	77.5 (3.5)	77.4 (4.6)	75.6 (4.3)
Sex	9M, 5F (1 na)	1M, 1F	5M,3F	13M, 6F
MMSE	19.9 (3.3)	25.0 (0.0)	27.0 (2.5)	29.2 (0.7)
Protein 1	10906 (3698)	6722 (4717)	1183 (944.70)	1127 (1124)
Protein 2	50 (0.0)	381 (468)	8215 (3551)	7222 (1995)
Ratio 1 / 2	218.1 (73.96)	102 (138)	0.172 (0.188)	0.148 (0.136)

Study B (n=78; Dr. Steven Arnold; AD confirmed by CSF Tau/pTau)

	AD	MCI-AD	MCI-SNAP	Elderly Normal Controls	Young Normal Controls
n	20	13	14	21	10
Age	68.27 (8.6)	71.51 (6.750	73.64 (16.46)	70.24 (5.99)	23.2 (4.32)
Sex	12F, 8M	6F, 8M	4F, 9M	14F, 7M	5F, 5M
MMSE	16.9 (7.1)	24.3 (3.3)	28.1 (2.4)	29.3 (1.0)	na
Protein 1	10201 (2691)	6293 (3735)	2451 (2972)	217.5 (379.8)	50 (0.0)
Protein 2	122.4 (323)	2348 (2784)	7184 (3155)	7815 (3705)	50 (0.0)
Ratio 1 / 2	193.5 (67.82)	41.44 (73.24)	0.4258 (0.54)	0.02798 (0.04)	1 (0.0)

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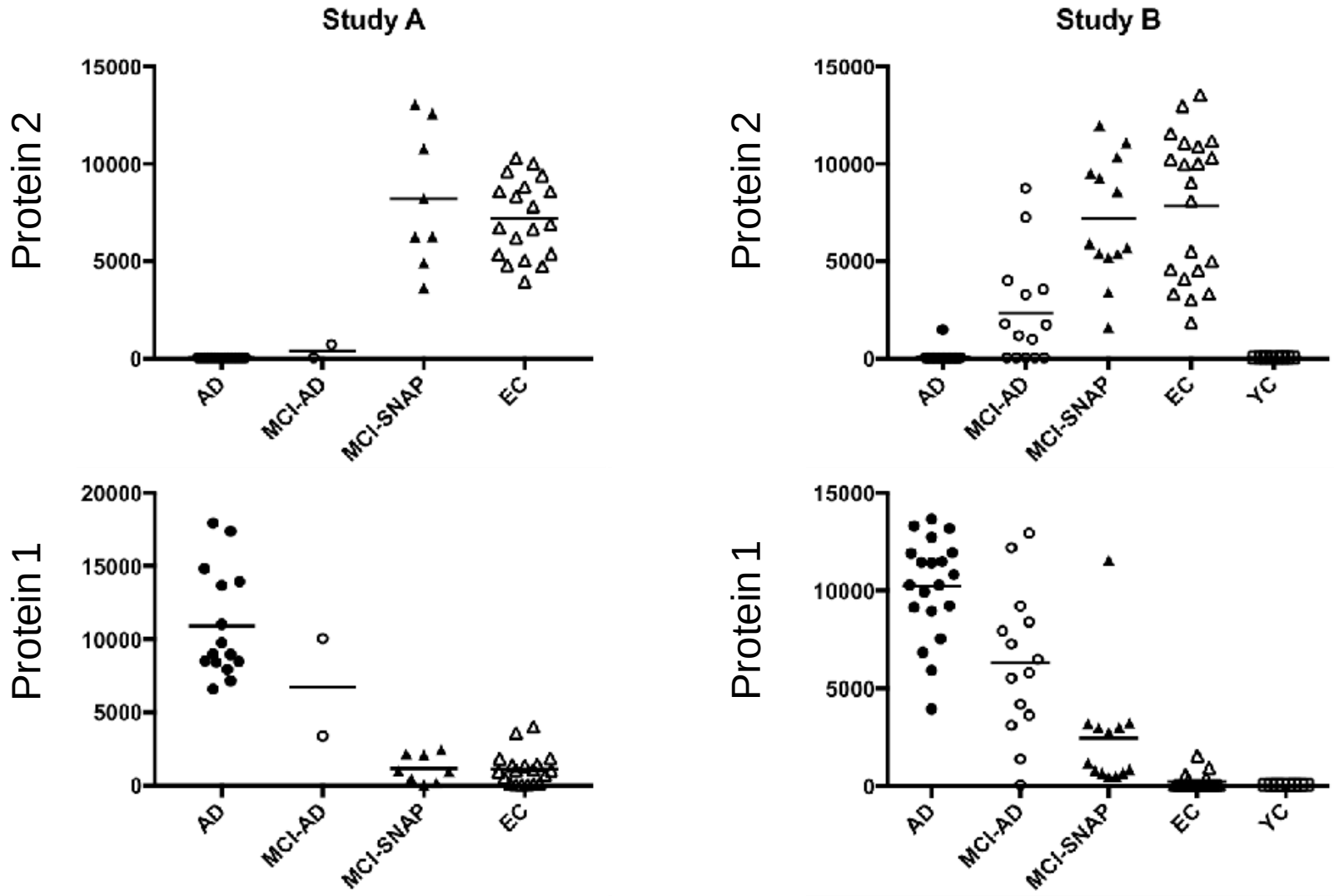
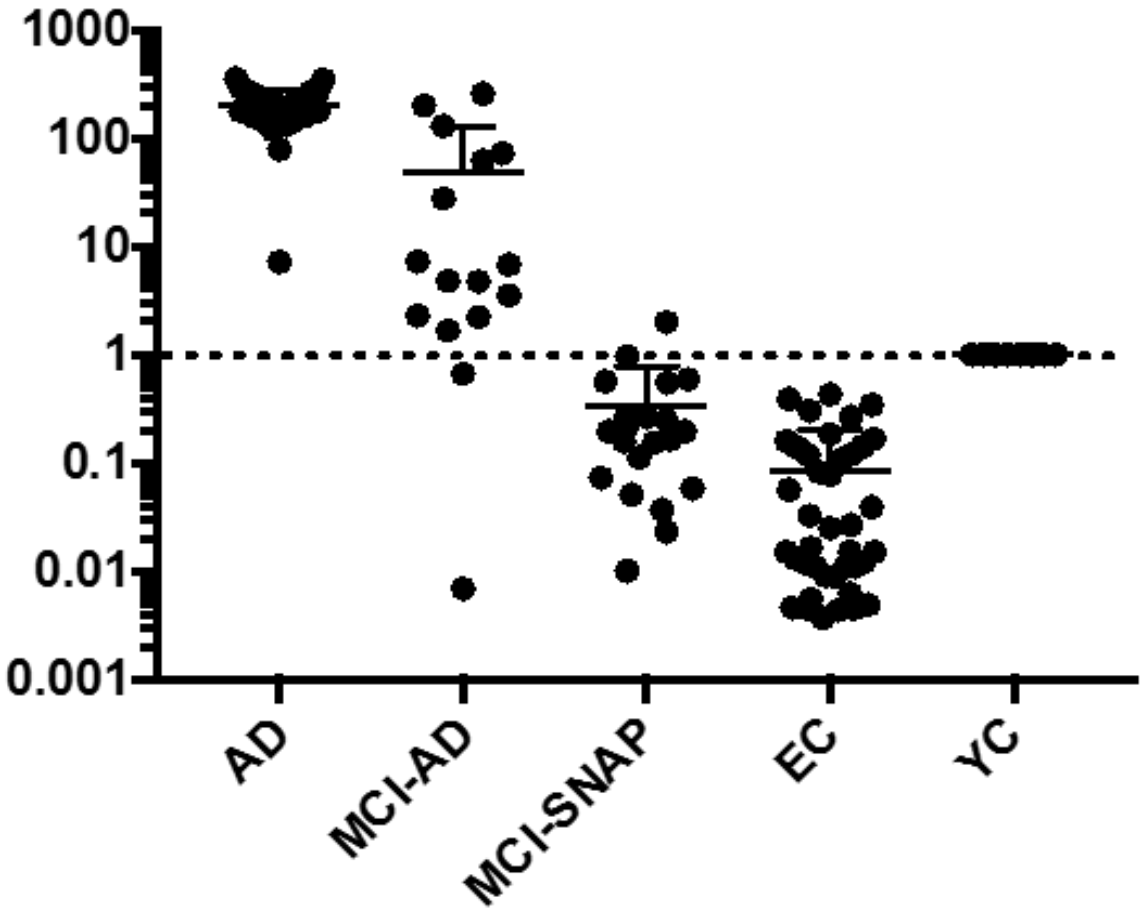
Western Blot Band Densities



SavaDx – Positive Results in Studies A & B Combined (N=122)

SavaDx identified and stratified blood samples from:



- AD patients
- Mild Cognitive Impairment due to AD (MCI-AD)
- MCI with Suspected Non-Amyloid Pathology (MCI-SNAP)
- Elderly Controls (EC)
- Young Controls (YC)

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Lessons Learned

- **Additional samples tested with SavaDx showed meaningless results.**
  - Samples were analyzed using commercial antibodies.
- **Lot-to-lot variability of commercial mAbs, differences in affinity and avidity.**
  - We are developing proprietary antibodies, with funding provided by NIH.
- **Variability in sample handling/processing between sites.**
  - We are standardizing collection procedures.
    - PGE1 added to plasma could have affected results.
    - Keeping whole blood at room temperature until centrifugation may disrupt results.

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SavaDx and PTI-125

- PTI-125 is our investigational drug candidate for AD.
- PTI-125 targets and reverses altered FLNA.
- SavaDx is a biomarker to track treatment effects of PTI-125 because SavaDx detects protein changes in blood from altered FLNA.

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PTI-125 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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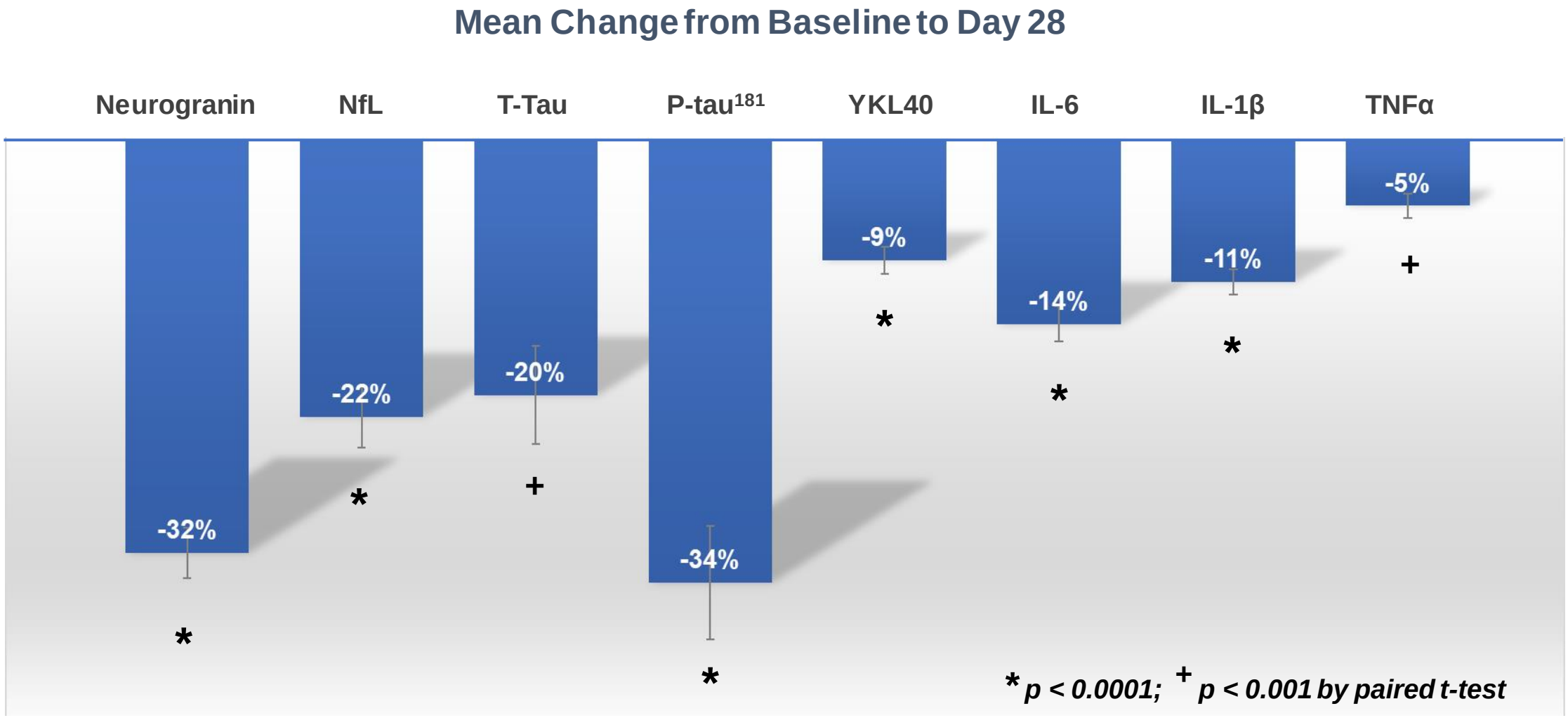
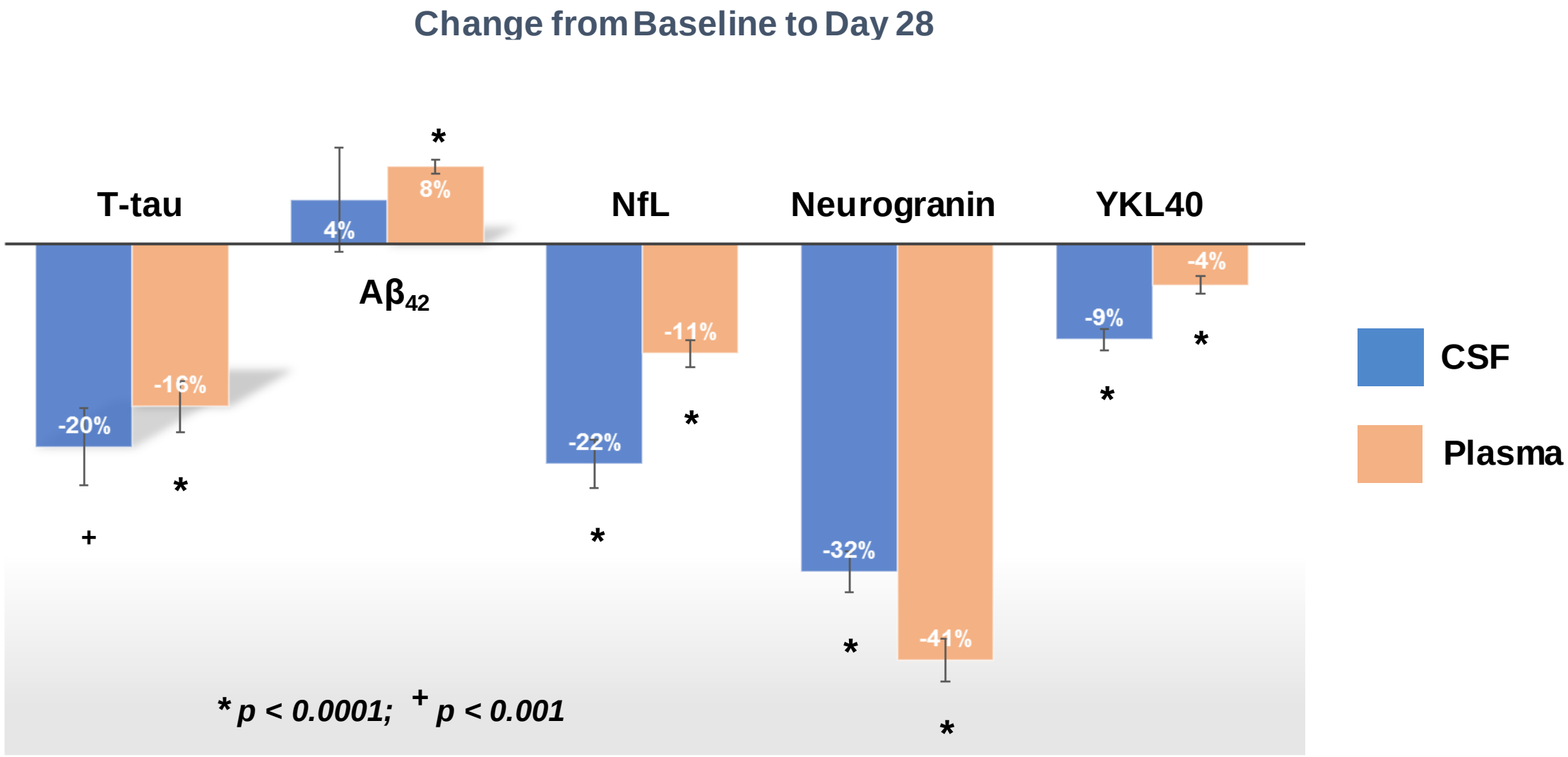
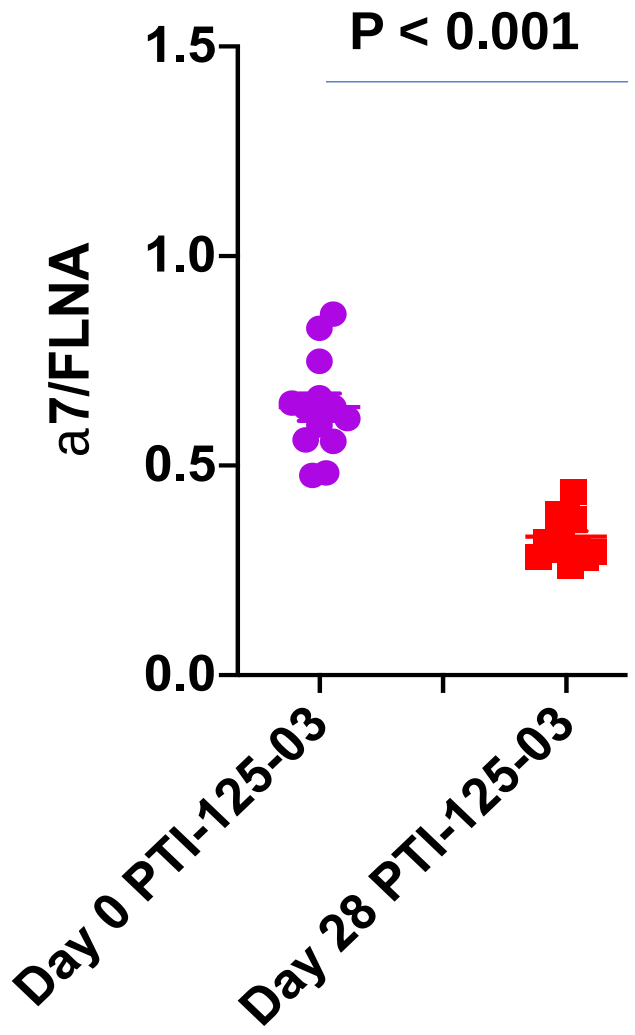
Phase 2a Summary Results - CSF Biomarkers



Phase 2a Biomarkers – CSF vs. Plasma



Phase 2a Biomarkers – SavaDx in Lymphocytes



PTI-125 significantly reduced SavaDx values over 28 days, demonstrating target engagement and treatment effect of PTI-125 in AD.

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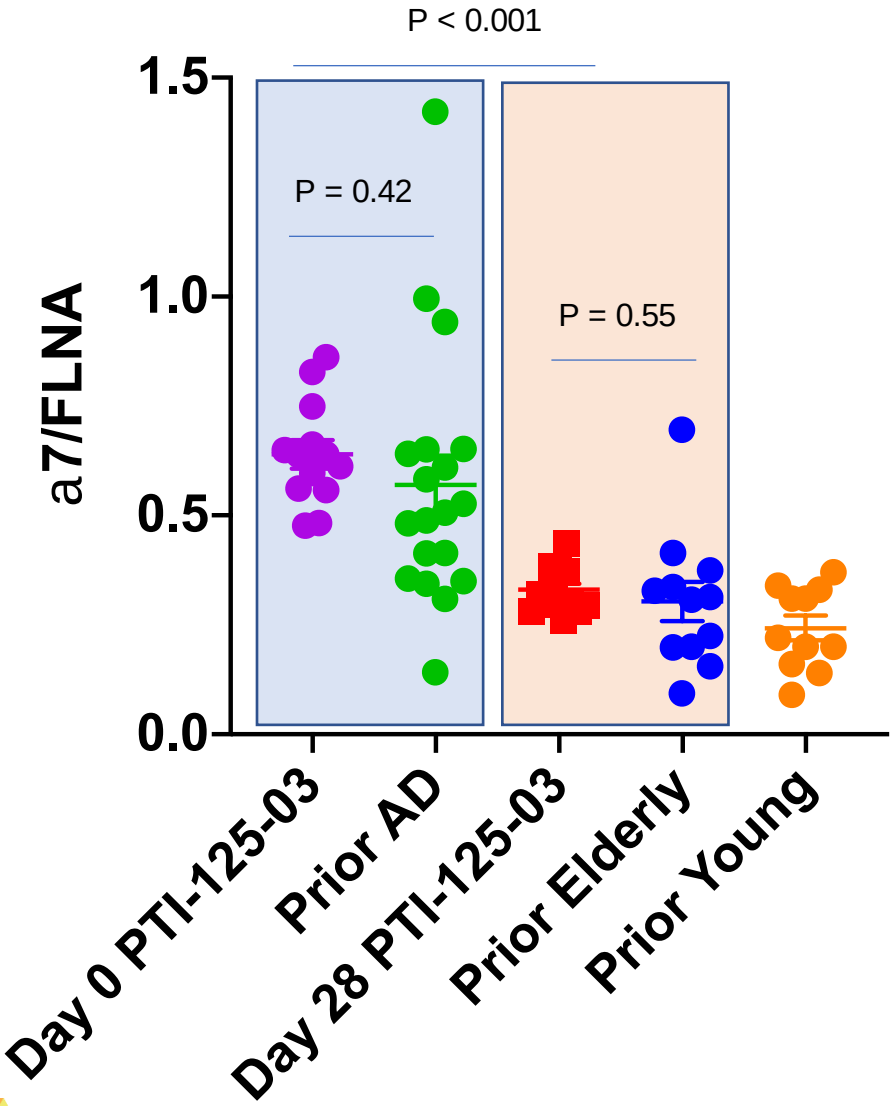
Phase 2a Biomarkers – SavaDx in Lymphocytes



- Before dosing (i.e., Day 0), patients showed SavaDx values in lymphocytes that matched our historical AD values.
- After 28 days of dosing with PTI-125, patients showed SavaDx values that matched historical values for both Elderly and Young controls, illustrating the magnitude of treatment effect of PTI-125 in AD.

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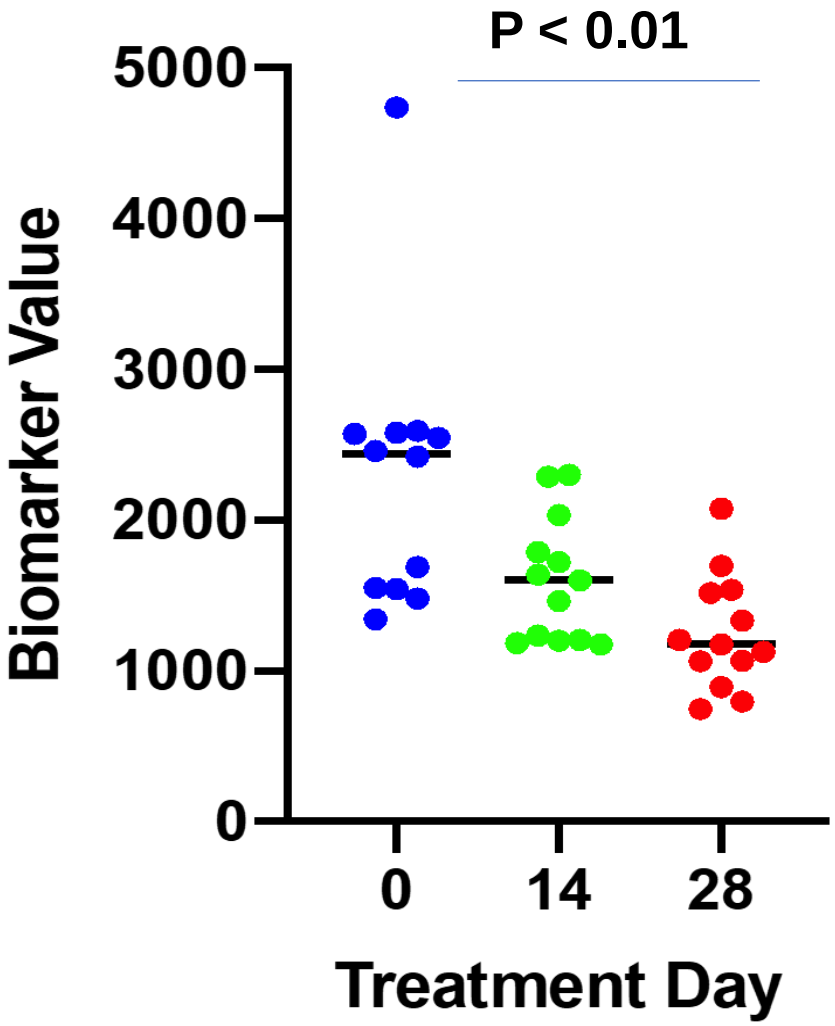
Phase 2a Biomarkers – SavaDx in Plasma



SavaDx values in plasma were significantly reduced (p<0.01) in AD patients dosed with PTI-125 for 28 days, demonstrating additional evidence of target engagement and treatment effect.

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Phase 2a Clinical Trial of PTI-125

I. Introduction

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III. Clinical Trial Treatment Effects

IV. Conclusions

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Next Steps

- **Future studies with SavaDx intend to demonstrate sensitivity and specificity as a diagnostic/biomarker of AD.**
  - We are developing proprietary antibodies for use with SavaDx, with funding by a research grant award from NIH.
  - Validation studies are planned for 2nd half 2020 and beyond.

- **SavaDx will be used to evaluate treatment effects of PTI-125 in a recently completed randomized, placebo-controlled Phase 2b study in AD.**

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Conclusions

- **SavaDx is a simple blood test for AD, funded by NIH.**

- **Early data are encouraging!**
  - **SavaDx diagnosed AD patients vs. non-AD subjects in 122 samples.**
  - **SavaDx stratified AD patients into distinct groups.**
  - **SavaDx demonstrated target engagement/treatment effect of PTI-125 in a Phase 2a study.**

SavaDx shows potential as a simple, non-invasive tool to diagnose and stratify AD, and to confirm treatment effects of PTI-125.

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