SavaDx Exposed

A revolutionary diagnostic for Alzheimer's Disease
or
a scam of scientifically illiterate investors?

What is SavaDx?

About SavaDx

SavaDx is Cassava Sciences' investigational diagnostic to detect Alzheimer's disease. The goal of SavaDx is to make the detection of Alzheimer's as simple as getting a blood test, possibly years before the appearance of any overt clinical symptoms. SavaDx was substantially funded by a peer-reviewed research grant award from the National Institutes of Health (NIH).

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.

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

A simple blood test that can detect AD before symptom onset

How good is SavaDx?

Amyloid Pathology). In 122 samples, the assay distinguished AD from EC with 98% accuracy and MCI-AD from MCI-SNAP with 92% accuracy. In an additional 100+ plasma samples with APOE genotyping, PTI-125-DX was 100% accurate in diagnosing control, MCI and AD. PTI-125-DX also split the MCI patients into MCI-AD and MCI-SNAP.

42 (A?42) hijacks to hyperphosphorylate tau protein. We have tested over 220 plasma samples and show two orders of magnitude significant differences between patients with AD diagnoses (confirmed by imaging or CSF markers) and age-matched normal controls. These two groups are distinguished with 98-100% accuracy. In one of two blinded studies, PTI- 125-DX distinguished MCI with confirmed AD pathology (MCI-AD) from MCI with suspected non-amyloid pathology (MCI-SNAP) with 92% accuracy; in the other, this distinction needs confirmation by imaging. In this

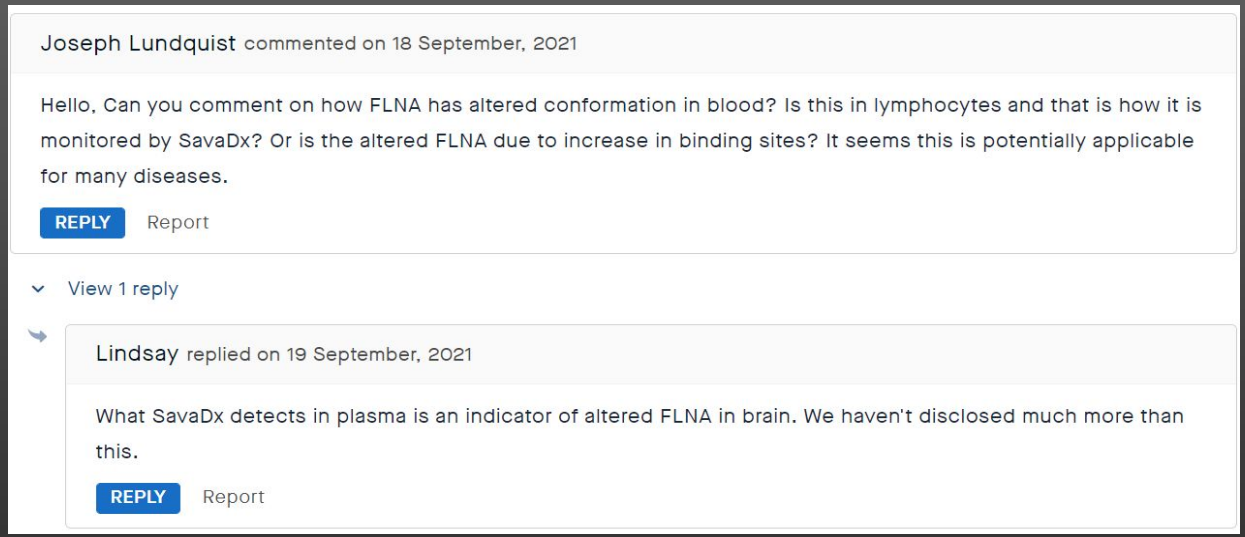
In blinded studies, our investigational diagnostic, SavaDx, detected >10-fold differences between patients with Alzheimer's and age-matched normal controls or young cognitively intact subjects (N=232).

SavaDx can distinguish:

-Healthy elderly from Alzheimer's patients with **98%** accuracy

-Mild impaired (MCI) from Alzheimer's patients **92%** accuracy

So how does SavaDx work?



Joseph Lundquist commented on 18 September, 2021

Hello, Can you comment on how FLNA has altered conformation in blood? Is this in lymphocytes and that is how it is monitored by SavaDx? Or is the altered FLNA due to increase in binding sites? It seems this is potentially applicable for many diseases.

REPLY Report

View 1 reply

Lindsay replied on 19 September, 2021

What SavaDx detects in plasma is an indicator of altered FLNA in brain. We haven't disclosed much more than this.

REPLY Report

SavaDx is not protected by patents, so the details are secret.

The company has not disclosed how **brain** FlnA is measured in **blood**.

Seriously, how does SAVADx work?

Company grants refer to a ratio of two protein fragments,

but data are presented as a single protein band?

2017

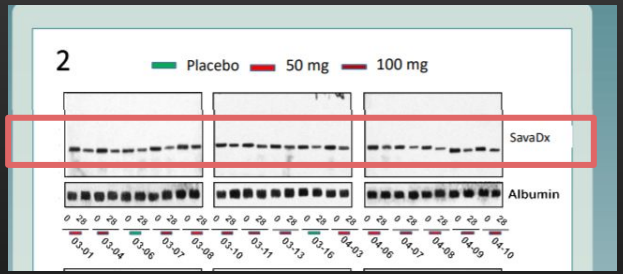
Western blot. Although certain details are still being optimized, I am confident in both versions of this assay for diagnosis. The lymphocyte assay was tested in a clinical trial of 70 samples, which showed a 7-fold difference between AD patients (confirmed by imaging or CSF biomarkers) and age-matched controls. The plasma assay, relying on a ratio of fragments that flips, has demonstrated differences of two orders of magnitude between confirmed AD and elderly controls. For the proposed clinical trial, I will assess both versions of PTI-125-DX before

2019

PTI is developing PTI-125-DX, a novel, quantitative blood-based diagnostic candidate for Alzheimer's disease (AD). A non-invasive and inexpensive AD diagnostic is sorely needed, particularly one with the ability to detect early pathological changes that precede cognitive symptoms. PTI-125-DX measures the ratio of two protein fragments in plasma and is a companion diagnostic/biomarker for our therapeutic candidate PTI-125. PTI-125 disrupts and

2021

Immunoblots of the SavaDx assay show changes from Day 1 to Day 28 in plasma samples from 30 study subjects in placebo, 50 mg and 100 mg treatment arms (**Fig. 2**).

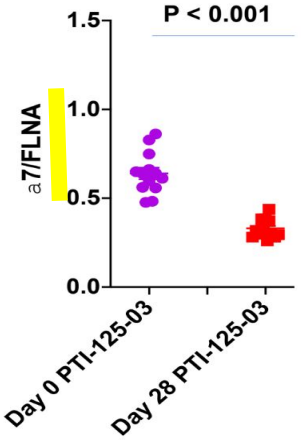


Do we have a winner?

A company presentation labels SavaDx as the ratio of the Alpha-7 nicotinic receptor to FLNA

Which ties in with Dr Wang's discovery in a grant for SavaDx

Phase 2a Biomarkers – SavaDx in Lymphocytes

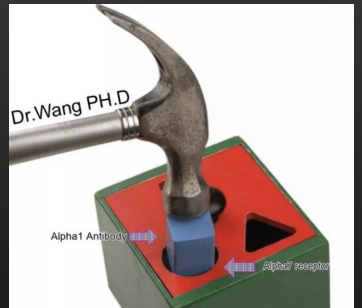


PTI-125 significantly reduced SavaDx values over 28 days, demonstrating target engagement and treatment effect of PTI-125 in AD.

CASSAVA

initially tested under a research agreement with your company. The original lymphocyte assay takes advantage of my finding that the association of filamin A with the alpha7 nicotinic acetylcholine receptor is elevated in both brain and lymphocytes of AD patients, and that PTI-125 treatment effects on this association in brain are mirrored in lymphocytes of PTI-treated mice. Both PTI and I have contributed significant effort to optimize procedural details of

It would all make sense, except there are no working antibodies for alpha-7



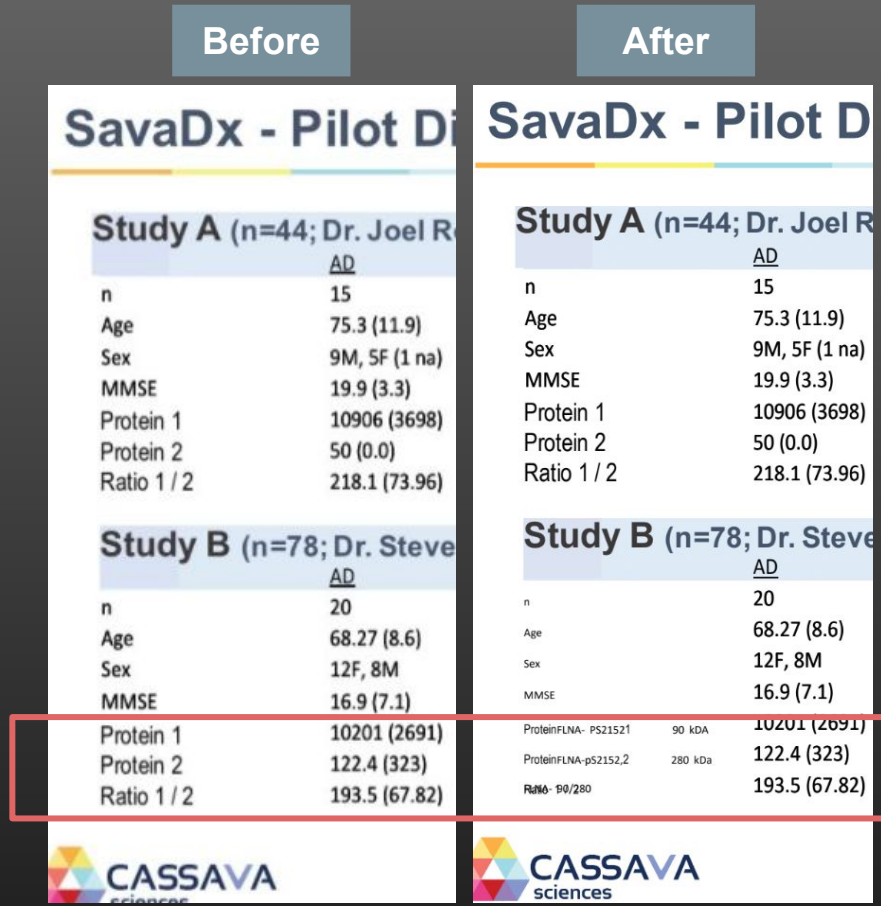
What's under the hood?

We found a clue of the proteins Cassava claims to measure in SavaDx (which they've tried to hide)

Looking at Cassava's NIH grant, one page had an unredacted reference to 90kDa FLNA

The "FLNA 90kDa" reference is indexed by Google to a PDF.

Opening up that PDF and removing the labels revealed the true labels in **a hidden layer!**



Confirmation received in the email

Email between Drs Wang & Xu contains results of a Western Blot analysis of **two proteins of 90 & 280 kDa**

FLNA lysate is used as a positive control, therefore the assay targets the 90 and 280kDa fragments of FLNA

In the analysis we see the 90/280 kDa ratio calculations, plus the 28d vs 0d ratio

Finally, we have the answer to **what** SavaDx actually is: **the ratio of 90/280 kDA FLNA**

But more questions arise...

FIOA of Email Communications of Dr. Wang

From: Qiang Xu <qxx07a@acu.edu>
Sent time: 01/24/2021 10:48:30 PM
To: Ben Thornton <gthornton@cassavasciences.com>; Ben Thornton <gbt20a@acu.edu>; Hoau-Yan wang <[redacted]@gmail.com>; Hoau-yan Wang
Subject: [EXTERNAL] 20210124 results
Attachments: 20210124 Western blot results.xlsx

Hi Ben and Hoau,

Hope you are well! Attached is today's results and analysis.

Xu Lab 2021-01-24 16h31m11s M2WSHR					
Lane	Band No.	Band Label	Mol. Wt. (KDa)	Relative Front	Adj. Volume (Int)
1: 0.5 ug of FLNA lysate (LC419924)	1		280	0.131815	6410581
2: 20 ul Bio-Rad 1/60unstained MW Marker					
3: 60ng 1740 + 60ng A3 + 60ng A4 Peptides	1		90	0.606625	211317080
4:1 uL of Sample 05-005 Day 0	1		280	0.128364	830502
4	2		90	0.596273	1911642
5:1 uL of Sample 05-005 Day 28	1		280	0.113872	520208
5	2		90	0.585921	2702336
6: 1 uL of Sample 06-002 Day 0	1		280	0.10559	464724
6	2		90	0.583161	3329352
7: 1 uL of Sample 06-002 Day 28	1		280	0.102139	166852
7	2		90	0.58109	809480
8: 1 uL of Sample 06-005 Day 0	1		280	0.097308	174440
8	2		90	0.58109	335405
9:1 uL of Sample 06-005 Day 28	1		280	0.091787	29298
9	2		90	0.57971	204315

Miraculous Wang: the one-band man

While SavaDx is the ratio of two protein fragments - only a single band was presented in the AAIC poster

The blots presented used **SavaDx Ab1** - which we now know to be the 90kDa FlnA fragment (see slide 7)

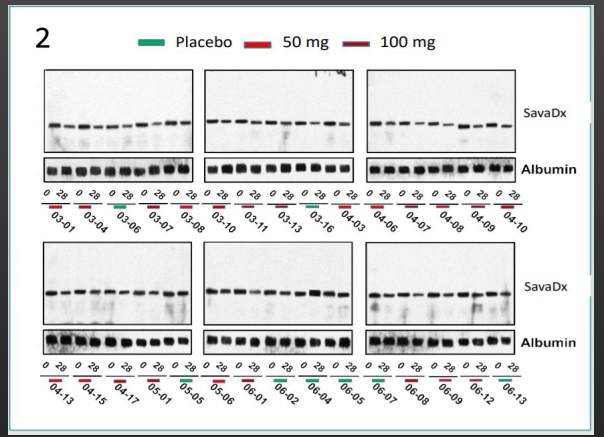
The company removed its own description from a subsequent version of the poster available on their website

AAIC

Immunoblots of the SavaDx assay show individual changes from Day 1 to Day 28 in plasma samples from 30 of the 64 study subjects across treatment arms (**Fig. 2**). These blots used SavaDx Ab1.

Web

Immunoblots of the SavaDx assay show changes from Day 1 to Day 28 in plasma samples from 30 study subjects in placebo, 50 mg and 100 mg treatment arms (**Fig. 2**).



If only we had some FlnA Western blots from those patients...

Xu did those experiments?

An email exchange between Dr Qiang Xu - a co-author of the AAIC Poster - and Dr Wang was included in FOIA'd material

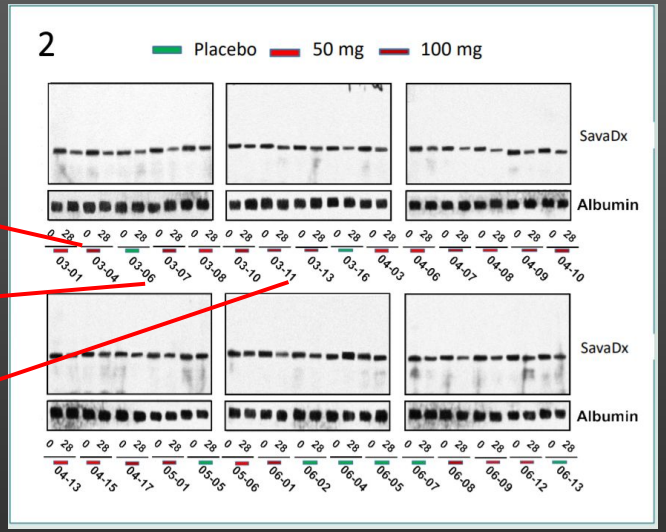
The Xu lab email contains the original **Western blot films** along with the quantification results for 12 patients - plus identification numbers

7 of those numbers match the IDs in the SavaDx poster presented at AAIC

FOIA'd email

3: 60ng 1740 + 60ng A3 + 60ng A4 Peptides	1
4:1 uL of Sample 03-004 Day 0	1
4	2
5:1 uL of Sample 03-004 Day28	1
5	2
6: 1 uL of Sample 03-006 Day 0	1
6	2
7: 1 uL of Sample 03-006 Day 28	1
7	2
8: 1 uL of Sample 03-011 Day 0	1
8	2
9:1 uL of Sample 03-011 Day 28	1
9	2

AAIC Poster Presentation



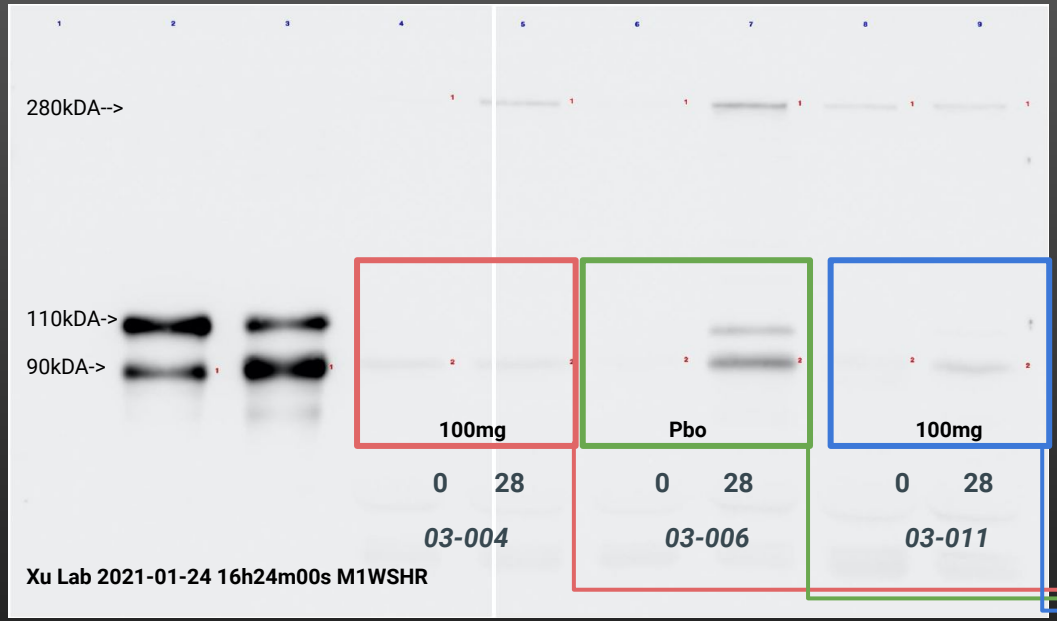
Presto! We are unblinded!

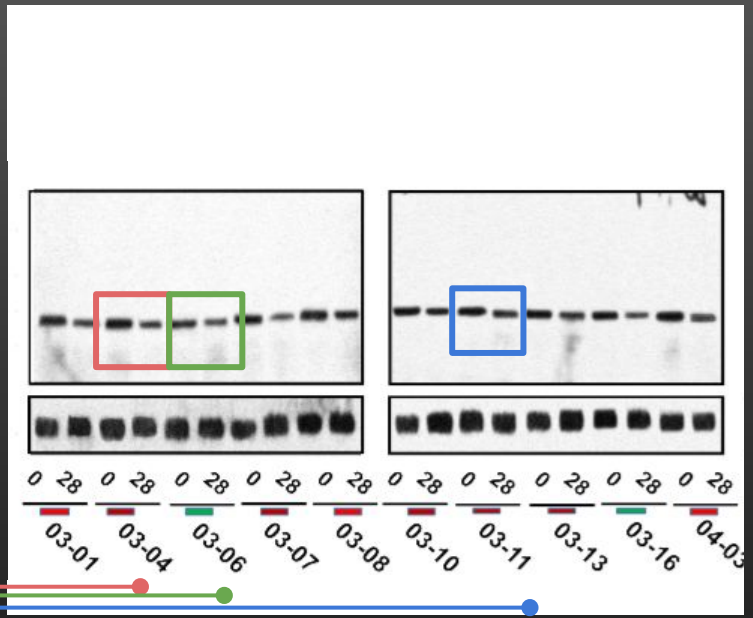
You are never going to guess what happened next...

Xu lab raw data directly contradicts Cassava poster

1/4

We see an entirely different band for FlnA detected with much weaker staining...



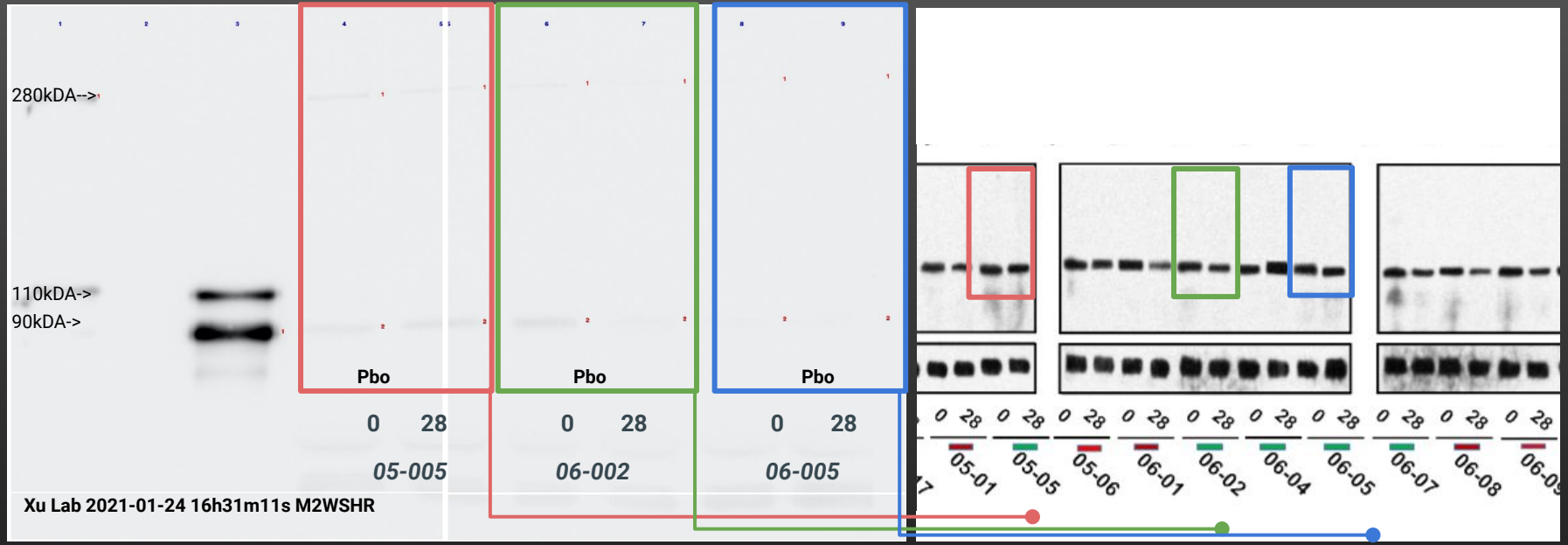


*The raw gel includes both 90 and 280kDA FLNA fragments whereas the poster only shows 90kDA protein

Xu lab raw data directly contradicts Cassava poster

2/4

...while the pattern of FlnA reduction that Cassava claims is not confirmed either visually (below) or by Xu's image quantitation (slide 14)...

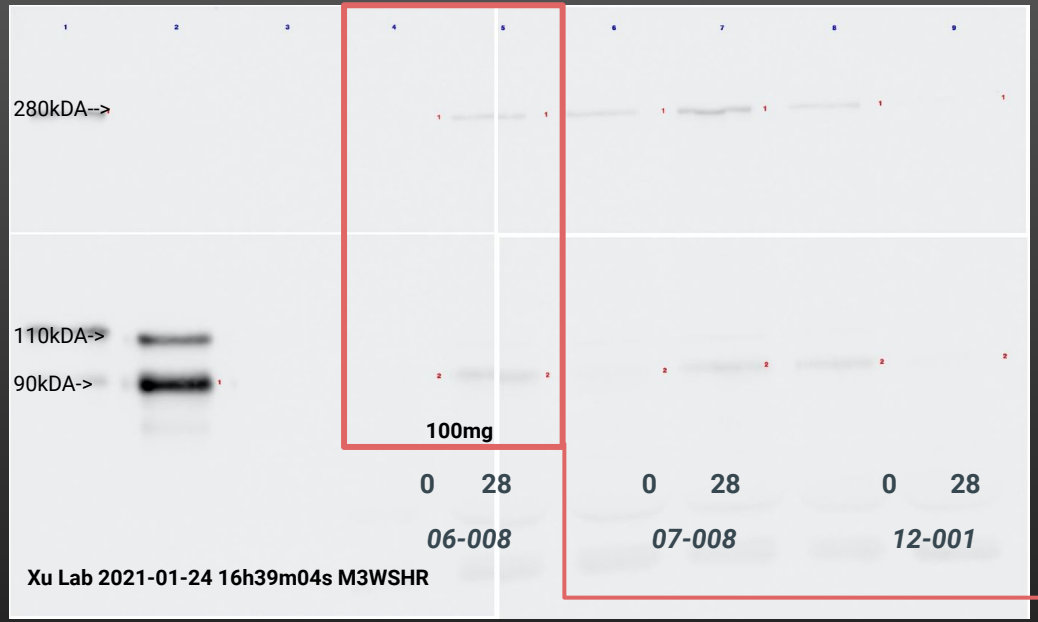


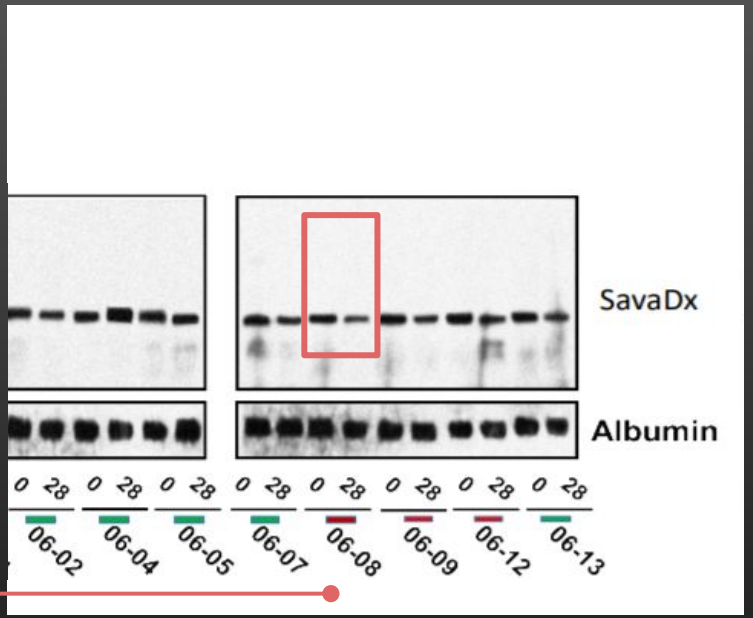
*The raw gel includes both 90 and 280kDA FLNA fragments whereas the poster only shows 90kDA protein

Xu lab raw data directly contradicts Cassava poster

3/4

...and no 110kDa pre-cursor in the blot presented in AAIC 2021





*The raw gel includes both 90 and 280kDA FLNA fragments whereas the poster only shows 90kDA protein

Xu lab raw data directly contradicts Cassava poster

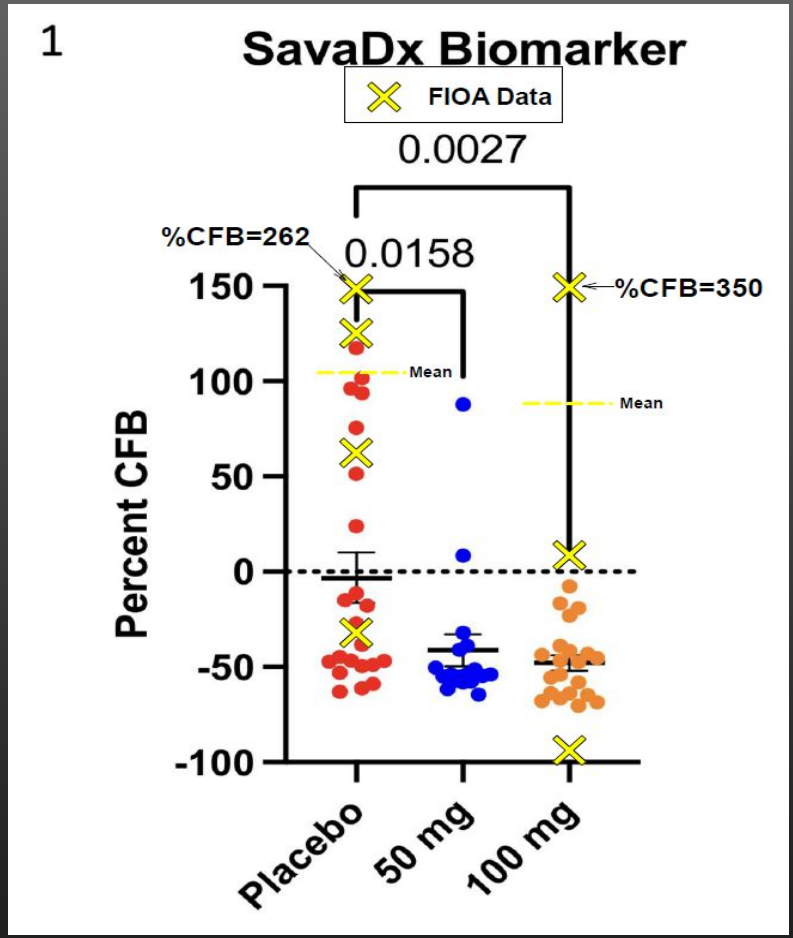
4/4

Using Xu's own quantification from email:

- Xu data doesn't overlap for ANY patients
- 2/7 patients off the scale (262 & 350%)
- SavaDx assay does not categorize by treatment

Xu FOIA data injects some REALITY

into Cassava's UNREAL success story



Summary: The State* of SavaDx

- Based on Western Blot quantification = outdated
- Not patented and not a trade secret = $0
- “Validation” clinical trial for 2021 = Cancelled
- Does not show effect of Simufilam treatment = 0% accurate
- Discovered emails suggest numbers totally fabricated = Fraud?

*Stay tuned, more FIOA emails by Christmas!

Contributors

- Jesse Brodkin
- Enea Milioris
- Adrian Heilbut
- Patrick Markey

References

- FOIA email exchange
- Cassava's SavaDx story
- Xu lab data table

How does this revelation relate to Simufilam MOA?

Taking SavaDx results at face value suggests dysregulation of FlnA cleavage in AD patients

This core hypothesis has never been reported by Cassava or ANY OTHER labs

In AD, 280kDa FlnA appears cleaved to 90kDA in excess

If so, the Poster (slide 14) suggests that:

- simufilam acts by blocking the cleavage of FlnA to a 90kDa fragment

This can be easily tested by checking whether simufilam blocks the activity of Calpain, the cleaving enzyme that turns 280kDA Flna to 90kDa

We find the implied MOA and scientific rationale

- Laughably unsubstantiated
- Inconsistent with Cassava claims so far
- Contrary to FlnA functions in literature