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?

SavaDx can distinguish:

- Healthy elderly from Alzheimer’s patients with 98% accuracy
- Mild impaired (MCI) from Alzheimer’s patients 92% accuracy

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 (A42) 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).
So how does SavaDx work?

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?

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

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

Immunoblot 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.

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!
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...
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.

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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.

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

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

...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

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
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● Adrian Heilbut
● Patrick Markey

References
● FOIA email exchange
● Cassava’s SavaDx story
● Xu lab data table
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