

# Cassava Sciences: *A Shambolic Charade*

3 November 2021

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# DISCLOSURE

The authors of this presentation and the associated letter to FDA hold stock and options positions that may benefit from a decline in Cassava Sciences' stock price.

# Cassava Sciences is an unprecedented Scientific Charade

- An astonishing story of sleazy drug development that potentially endangers AD patients
- With all the ingredients of:
  - A web of shady characters and cronies
  - Nefarious development
  - Fabrication & manipulation of data
  - Excessive unsubstantiated claims

**Our analysis is entirely based on publicly available information and visible for everyone to see and challenge**



# Cassava Outdoes the Greatest Biomedical Dumpster Fires

Dr. Fiddes: Clinical researcher fabricated data & falsified records; FDA ignored early warnings → Prison

BioCryst: Cancer clinical trial studies falsified; reported by an insider → Prison

Potti: Duke MD made up genomics data, detected by outside statisticians; allegations initially denied

Theranos: Holmes lied to investors, but **even Theranos** didn't submit fake data to FDA → Indictments

Cassava pulls together an **unprecedented** combination of circumstances and behavior:

**Both pre-clinical and clinical data are compromised, starting from IND submission**

**Cassava still denies issues**

**Received ~\$20M in NIH funding**

**Misleading results were hyped to investors to sell equity**

***Cassava's ongoing clinical charade makes a mockery of scientific standards, clinical trial conduct, and the regulators who are entrusted to protect the integrity of the medical research system and rights of patients***

# Overview

Our concerns arise from an assessment of virtually every aspect of Cassava's programs available for public scrutiny. Beyond the misconduct documented in the [Citizen's Petitions](#) we reveal a pattern of deliberate, coordinated misconduct involving both Cassava Sciences and their academic collaborator at CUNY, Dr. Hoau-Yan Wang.

Our complete letter to FDA is available at <http://www.cassavafraud.com>

We offer a brief background and summary of the key issues and questions that we have identified, including:

- fabrication of pre-clinical and clinical evidence across the entire Simufilam program
- inadequate and unreliable safety studies
- improper and opaque study conduct by Cassava and their collaborators
- serious misconduct in the analysis and reporting of clinical trial data

We first review Cassava's suspicious history and the **obvious scientific misconduct pervading all of Cassava's preclinical science underlying the "discovery" of Simufilam.**

Next, we present highlights from our full letter of the egregious data anomalies and manipulation of both the **biomarker** and **cognitive** measurements from Cassava's Phase 2 trials.

Finally, [as Remi Barbier likes to say](#), we "**connect the dots**" and present a honest account of what Cassava did, and theory of why they did so, and the **serious consequences** that await.

# Shady Players and Shady History

[A Tormented Corporate History](#)

[Impotent, Conflicted Scientific Advisory Board](#)

[Claims Too Good to be True](#)

[Dr. Wang's Fantasy](#)














# Pain Therapeutics to Cassava

- Pain Therapeutics (PTIE): Founded in 1998 by Remi Barbier, with Dr Friedmann
- Early preclinical research in analgesia, including studies of low-dose Naloxone
- In-licensed Remoxy, a supposedly tamper-resistant version of Oxycodone
- Remoxy was first rejected by FDA in 2008
- Nevertheless, Remi persisted.. and Remoxy was rejected again and again
- Remoxy was rejected for the last time in 2018, leading to 'disoriented' Remi's famous diatribe against the 'shambolic regulations' at the FDA
- In 2017 Cassava begins a pivot to Alzheimer's Disease (AD) based on Wang's 2008 research with Pain Therapeutics and their novel drug: Simufilam
- The rebranded company miraculously hits milestone after milestone in a record of unprecedented clinical success in AD - both in the treatment and diagnosis of the disease

# The Cassava Gang: back together for one last heist..

Pain Therapeutics / Cassava Sciences insiders have worked together for over 20 years (generating nothing of value in that time), with connections going back to the 1980s 1990s at XOMA, Robertson Stephens, and J&J R&D

Few “outsiders” hired into senior roles at Cassava, and company has no internal scientific research capabilities

	<p><b>Remi Barbier - Chairman, President &amp; CEO</b>    </p>		<p><b>Lindsay H. Burns, PhD - SVP Neuroscience</b>    </p>												
	<p><b>Nadav Friedmann, PhD/MD - CMO, Board member</b>  <i>Eight FDA drug approvals prior to Cassava Sciences.</i>    </p>		<p><b>Michael Zamloot - SVP Technical Operations</b>  <i>Four FDA drug approvals prior to Cassava Sciences.</i>   </p>												
	<p><b>Jim Kupiec, MD – Chief Clinical Development Officer</b>  <i>Two FDA drug approvals prior to Cassava Sciences.</i>    </p>	<p style="text-align: center;"><b>Independent Directors</b></p> <table border="0"> <tr> <td data-bbox="1217 885 1299 992">  </td> <td data-bbox="1312 885 1745 978"> <p><b>Sanford Robertson</b>                      Founding Partner - Francisco Partners and Robertson Stephens &amp; Company</p> </td> <td data-bbox="1821 871 1931 978">  </td> <td data-bbox="1770 978 1987 1092"> <p><b>Richard Barry</b>                      Founding Partner, Portfolio Manager, Eastbourne Capital</p> </td> </tr> <tr> <td data-bbox="1217 1013 1299 1120">  </td> <td data-bbox="1312 1013 1719 1099"> <p><b>Robert Gussin, PhD</b>                      Formerly, CSO &amp; Corporate VP, Science and Technology, Johnson &amp; Johnson</p> </td> <td data-bbox="1860 1106 1974 1220">  </td> <td data-bbox="1745 1220 2012 1278"> <p><b>Michael O'Donnell</b>                      Partner, Orrick LLP</p> </td> </tr> <tr> <td data-bbox="1217 1135 1299 1242">  </td> <td data-bbox="1312 1135 1681 1220"> <p><b>Patrick Scannon, MD/PhD</b>                      Formerly, Founder &amp; CSO/CMO - XOMA Corporation</p> </td> <td colspan="2"></td> </tr> </table>			<p><b>Sanford Robertson</b>                      Founding Partner - Francisco Partners and Robertson Stephens &amp; Company</p>		<p><b>Richard Barry</b>                      Founding Partner, Portfolio Manager, Eastbourne Capital</p>		<p><b>Robert Gussin, PhD</b>                      Formerly, CSO &amp; Corporate VP, Science and Technology, Johnson &amp; Johnson</p>		<p><b>Michael O'Donnell</b>                      Partner, Orrick LLP</p>		<p><b>Patrick Scannon, MD/PhD</b>                      Formerly, Founder &amp; CSO/CMO - XOMA Corporation</p>		
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	<p><b>Eric Schoen - Chief Financial Officer</b>   </p>														
															



# SAB MIA: Old Friends and Conflicted Cronies

**Jeffrey Cummings MD**



Director of Cleveland Clinic Lou Ruvo Center for Brain Health and Professor of Neurotherapeutics and Drug Development, Cleveland Clinic.

**Hoau-Yan Wang PhD**



Tenured Medical Professor at CUNY Medical School; co-lead scientist on discovery & development of simufilam and SavaDx.

**Steven E. Arnold MD**



Translational Neurology Head of the Interdisciplinary Brain Center, Massachusetts General Hospital, Harvard Medical School.

**Patrick Scannon MD, PhD**



Founder and former previous Executive Vice President, Chief Biotechnology Officer of Xoma Corporation.

**Trevor W. Robbins CBE FRS FMedSci**



Professor of Cognitive Neuroscience at the University of Cambridge and Past President of the British Neuroscience Association.

**Barbara J. Sahakian FBA, FMedSci**



Professor of Clinical Neuropsychology at the Department of Psychiatry and Medical Research Council /Wellcome Trust Behavioral and Clinical Neuroscience Institute, University of Cambridge.

**Robert Gussin PhD**



Dr. Gussin worked at Johnson & Johnson for 26 years, most recently as Chief Scientific Officer and Corporate Vice President, Science and Technology from 1986 through his retirement in 2000.

Sounds impressive!  
But, like everything at  
Cassava Sciences,  
things are not what  
they seem..

# Cassava Advisors: Asleep at the Switch, or Selling Out?

Jeffrey Cummings MD



[Aduhelm Cheerleader](#)

SAB member of speculative Alzheimer's stock promotions

[Anavex \\$AVXL](#)

[Annovis \\$ANVS](#)

[Cortexyme \\$CRTX](#)

[Green Valley](#)

Barbara J. Sahakian FBA, FMedSci



Denies working with Cassava, despite still being listed on website and SAVA SEC filings



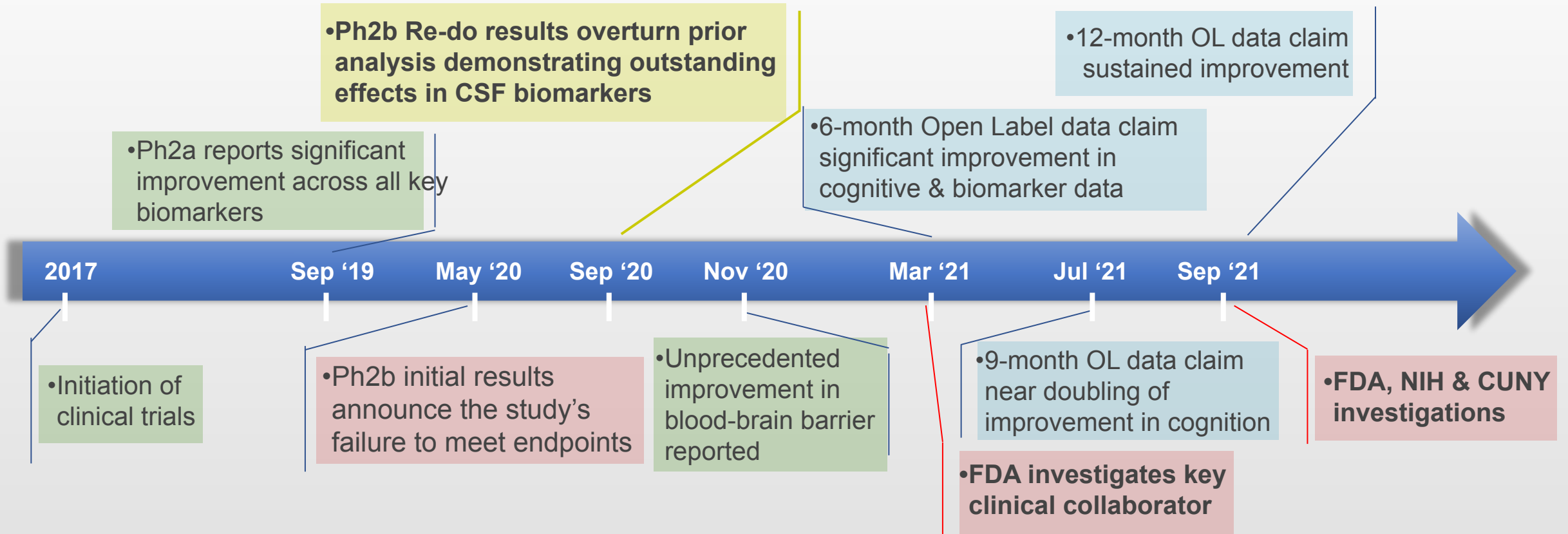
Steven E. Arnold MD



Co-author with Dr. H-Y Wang of [multiple papers with manipulated images](#) flagged on PubPeer

***Are the Cassava Scientific Advisory board members aware of the ongoing misconduct?***

# The Simufilam Saga Timeline



***In a short 2 years Cassava Sciences has announced a series of unprecedented advances in the treatment of Alzheimer's disease***

# Too good to be true?

- Cassava has claimed a series of significant and unprecedented clinical “milestones” in AD
- In nearly every patient and after only 28 days of treatment with Simufilam, Cassava claimed:
  - significant reduction biomarkers of neurodegeneration & neuroinflammation
  - significant increases biomarkers of blood-brain barrier (BBB) integrity
  - significant reduction in biomarkers of Alzheimer’s in the blood
  - improvement in patient’s cognition
- In follow-up, open label studies, Cassava claims the drug showed sustained improvement or stabilization in cognitive function for up to 12 months
- Nearly every reported outcome is a world-first in AD treatment
- To top it all off, Cassava claims to have successfully developed a blood-based diagnostic that detects AD prior to any symptoms with >98% accuracy

***Our report looks at the evidence - from preclinical to the latest reported clinical data - provided by Cassava Sciences to support these claims***



# A Precarious Scientific Hypothesis...

The foundation of Simufilam's action is biologically implausible. According to Cassava:

- a key structural protein Filamin A (FLNA) is found almost entirely in a misfolded state in AD patients' neural AND blood cells - but not in healthy individuals

FLNA has been studied for over 35 years and acts as a key scaffold for a wide range of signaling proteins. Yet Cassava alone have reported its critical role in AD

Filamin A (FLNa), the first non-muscle actin filament crosslinking protein, was identified in 1975. Thirty-five years of FLNa research has revealed its structure in great detail, discovered its isoforms (FLNb and c), and identified over 90 binding partners including channels, receptors, intracellular signaling molecules, and even transcription factors. Due to this diversity, mutations in human FLN genes result in a wide range of anomalies with moderate to lethal consequences. This review focuses on the structure and functions of FLNa in cell migration and adhesion.

From Nakamura, Stossel & Hartwig, 2011

***Why has no other research group confirmed or reported similar findings - especially for such a key discovery?***

***Why do patients not exhibit any other major symptoms, infections or immune-related diseases?***

# ...resting entirely on Wang's Dubious 'Discoveries'

- A claim that Naloxone binds to Filamin-A
- A claim of sub-picomolar affinity of Naloxone and Simufilam for Filamin-A
- A claimed connection between Filamin-A function and Alzheimer's
- A claim of 'altered' Filamin-A in Alzheimer's affecting signaling function
- A claim that Simufilam 'restores' the 'altered' Filamin-A

**All of these dubious claims rely on Dr Wang's work using fabricated scientific data, and have been assembled into a just-so story to justify the Simufilam IND.**

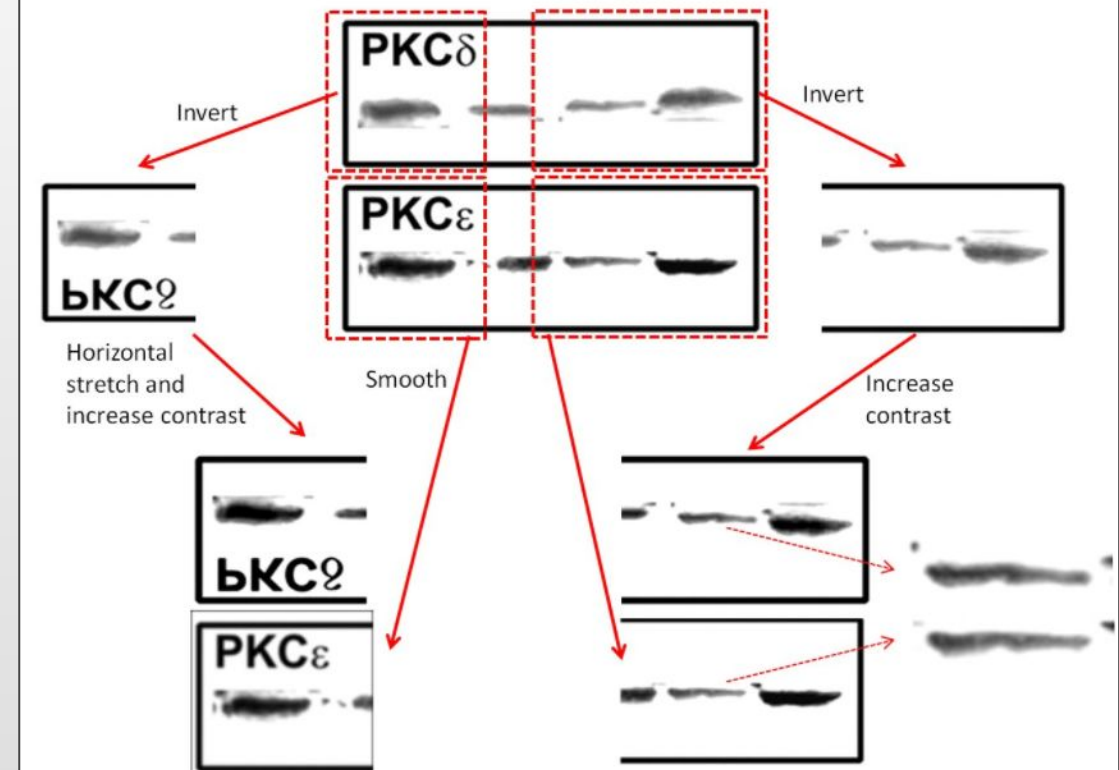
**Dr Wang is also an inventor on Cassava's key Simufilam patents; "inequitable conduct" such as faking data will render those patents invalid.**

# Dr. Hoau-Yan “Photoshop” Wang’s work...

- Dr. Hoau-Yan Wang at the City University of New York is responsible for all of the papers that form the scientific basis for Simufilam
- Dr. Wang named on all key Simufilam patents
- 24 papers by Wang flagged on PubPeer for suspicion of manipulated images  
<https://pubpeer.com/search?q=Hoau-Yan+Wang>
- Wang’s fabrication spans his entire career, including collaborations independent of Cassava
- Wang’s fabrications are **egregious** and **undeniable**, and now under investigation by City University of New York

## Representative Example of the “Magic Wang Western Blot Protocol”

Jing Liu, Andres Stucky, Ekkehart Trenkner, Eitan Friedman, Robert G Nagele, Hoau-Yan Wang. Prenatal phosphorylation of the synaptic anchoring protein GRIP. J Neurosci 2009 May 13;29(19):6308-19. doi:



identified by “Garra Congoensis”

<https://pubpeer.com/publications/CC864761DDB5944F85280C42B86BB6>

# ...has now been flagged publicly by experts

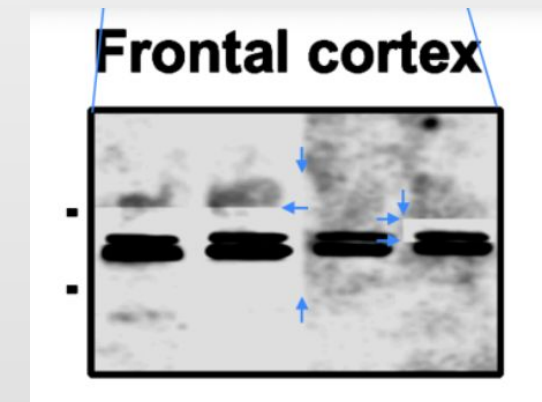
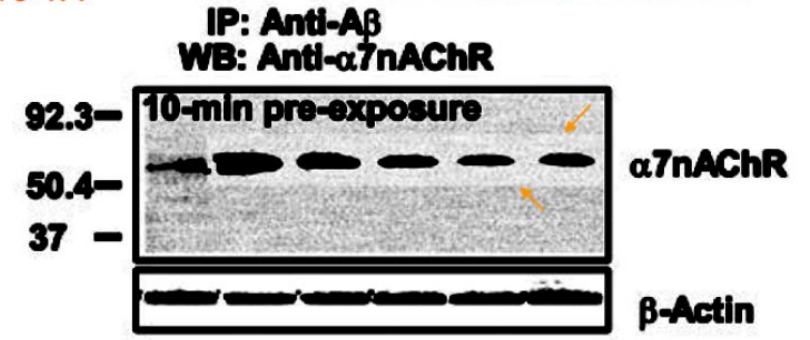
- Publications dating back over 2 decades have been flagged and **reported** publicly
- Amongst those reporting concerns was world expert on scientific fraud Dr Elisabeth Bik
- The pattern of systematic data manipulation and fabrication is consistent with the findings of our report

**There is now no serious question that the majority of Dr. Wang's work - including that with Cassava - contains fabrications**

***Nothing he has touched can be trusted or presumed to be valid***

Figure 1A

Wang et al., *Biological Psychiatry* (2010),  
DOI: 10.1016/j.biopsych.2009.09.031



<https://scienceintegritydigest.com/2021/08/27/cassava-sciences-of-stocks-and-blots/>



# Key Cassava Phase 2 Clinical Site Under FDA Scrutiny

**Dr. Evelyn Lopez-Brignoni**, a clinical investigator for the Simufilam Ph2a & Ph2b studies, received a [Warning Letter](#) (related to a different study) documenting unaddressed FDA inspection concerns about the **validity and integrity of data collected at the site**:

- “Subjects may have taken placebo only instead of the required study drug, or less than the full intended dose of the study drug”
- “The investigator failed to ensure that subjects adhered to the dosing regimen”
- “The investigator failed to conduct the clinical studies in accordance with the investigational plan”

**Neither safety nor efficacy** data from studies supervised Lopez-Brignoni can be trusted!

***Why does Cassava rely on such disreputable investigators to run its trials?***



# Is Simufilam really safe? Probably? Maybe?

- Cassava claims Simulfilam is safe, but data suggests a cavalier attitude towards safety, a calculated avoidance of critical studies, and dependence on unreliable investigators
- Simufilam doses administered are **millions** of times higher than should be required based on the purported mechanism and pharmacokinetics. **Simufilam *might* be safe.. but only because it is inert and does not bind its supposed target.**
- Cassava's Phase 1 study tested only a **single administration** of the drug
- If the Ph2 biomarker studies were manipulated or fabricated, as the data suggests, how can safety results from the same trials be relied upon?
- A key clinical site for the Ph2a study, upon which the presumption of Simufilam safety is based, was the subject of FDA concerns about integrity and reliability, documented in a rare **Warning Letter** to the clinical investigator, Dr. Lopez

# Unreliable and Nonsensical Clinical Data

Dr. Wang and the Miraculous 'Re-Do'  
Phase 2: Impossible Biomarker Data  
Phase 2: Shifting Cognitive Goalposts  
Uncertain Safety

# The same Dr Wang who single-handedly reversed Cassava's fortune, fixed the failed biomarkers

- Cassava moved Ph2b biomarker analysis to Dr Wang after announcing a **failed first analysis** by an “outside lab” ... despite partially relying on the outcomes of the original analysis
- Though never identified; a reference to the analytical method SIMOA indicates the initial lab was Quanterix - an established, respected provider of analytical services
- The ‘re-do’ by Dr Wang miraculously revealed **significant improvements** “never been shown before in patients” - in just 28 days

May  
2020

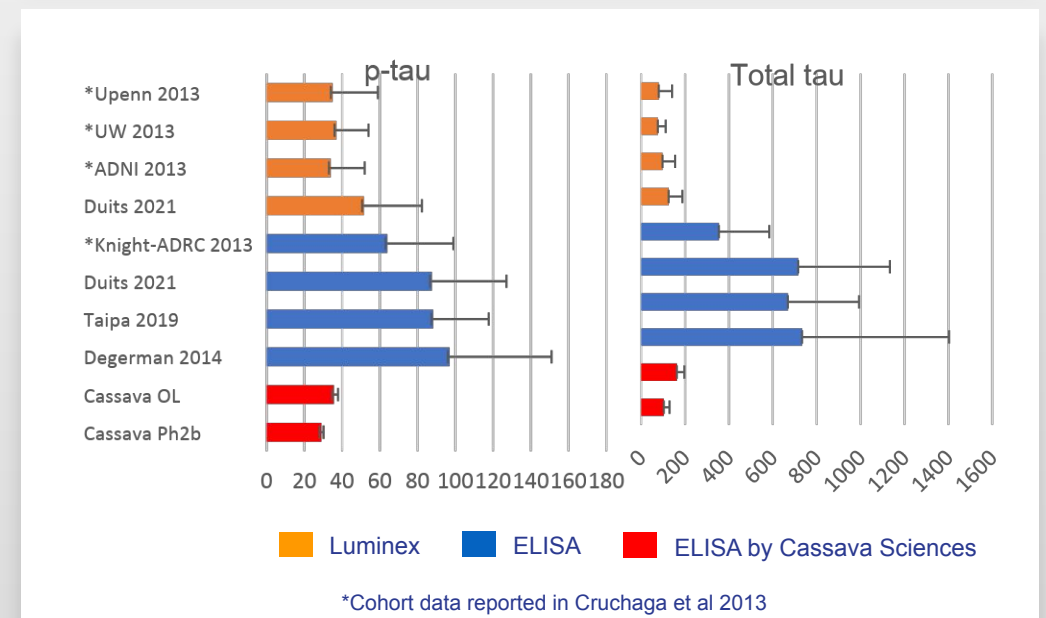
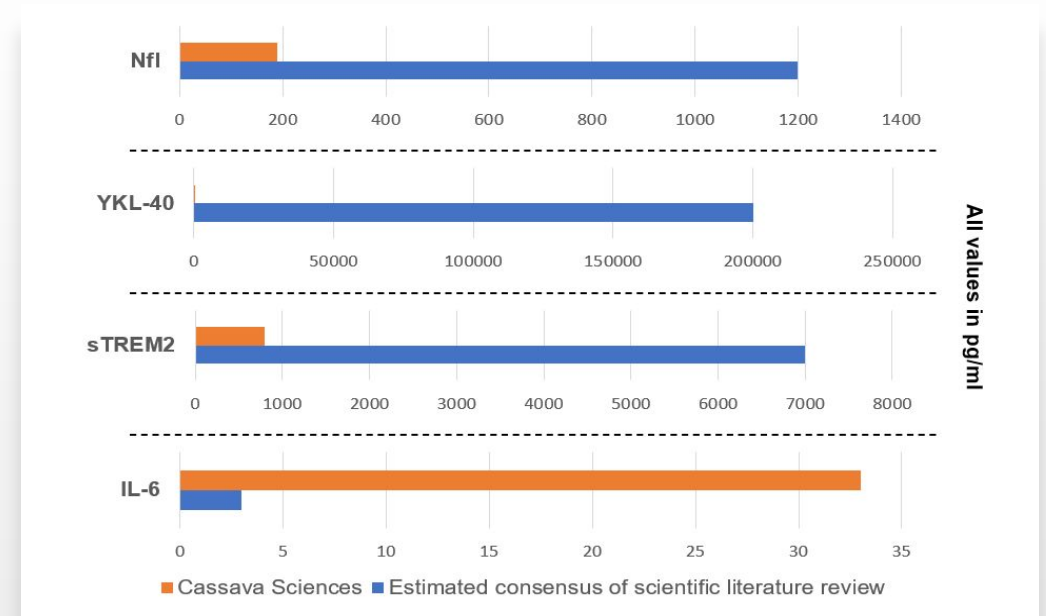
“Today's top-line results disappoint and are not consistent with previous clinical experience for reasons that are unclear at the moment,” said Remi Barbier, President & CEO. “We plan to thoroughly analyze these top-line data, and to re-analyze CSF biomarkers from study participants, to better understand the outcome of this study. Alzheimer's is a disease in dire need of new treatments. It is worth reflecting on what we can learn from this study and how to move forward with drug development plans for PTI-125 in Alzheimer's disease.”

Sep  
2020

AUSTIN, Texas, Sept. 14, 2020 (GLOBE NEWSWIRE) -- Cassava Sciences, Inc. (Nasdaq: SAVA) today announced final results of a Phase 2b study with its lead drug candidate, sumifilam, in Alzheimer's disease. In a clinical study funded by the National Institutes of Health (NIH), sumifilam significantly improved an entire panel of validated biomarkers of disease in patients with Alzheimer's disease. The ability to improve multiple biomarkers from distinct biological pathways with one drug has never been shown before in patients with Alzheimer's disease. Study results are

# Dr Wang's lab alone analysed the biomarker data...

- Dr Wang and his laboratory were ultimately entrusted to analyze nearly ALL the clinical samples of the Simufilam program
- On review of the reported Phase 2b data; 7 of 9 CSF biomarker readings are either:
  - entirely inconsistent with scientific literature
  - in ranges incompatible with human biology
  - compatible only with alternative analytical methods then those reportedly employed
- **Remarkably, values based on ELISA match those of Luminex assays instead of like-to-like (lower panel on right)**





# ...using his questionable methods to produce incomprehensible readings

Amongst the incomprehensible values reported were albumin levels in CSF and plasma

- These are routinely evaluated in clinical setting to provide QAlb - a ratio that informs BBB integrity
- Instead of standard assays, these were analysed by WB to provide inexplicable values AND ultimately QAlb ratio
- The results naturally prompted inquiries as to the methodology applied
- The CSO's response shows total disregard for protocol and good, acceptable practice in clinical studies

***Why are precious clinical CSF samples being analyzed using ad-hoc methods seemingly for the sole purpose of fitting Dr Wang's "expertise"?***

██████████ commented on 11 September, 2021

Thank you for the excellent work Dr. Burns and team. Would you be able to comment in the baseline values of CSF /plasma albumin ratio. Those values seem to be off from the clinical measurement of QAlb. Thanks!

[REPLY](#) Report

View 2 replies

Lindsay replied on 11 September, 2021

As noted, both were measured by Western and quantified by densitometric quantitation (automated). So yes the values and even the ratios could be different from a different technique with a readout in pg/mL. The important thing is that the same technique was used to compare treatment groups at baseline and post-treatment effects between groups.

[REPLY](#)

██████████ replied on 11 September, 2021

Why use WB/densitometry at all, instead of more accurate/precise ELISAs?

[REPLY](#) Report

View 1 reply

Lindsay replied on 11 September, 2021

Agree, ELISA would have been more accurate. I'm not sure why this was done this way probably because antibodies were already in the lab and ELISA kits were not. It was something we thought we should check.

[REPLY](#) Report

<https://www.researchsquare.com/article/rs-249858/v1>

# Cassava's Unrealistic Claims

Study	Cassava Sciences' Claims	Our findings / comments	Report Section
Phase 2a	Improvement in CSF & plasma biomarkers	Reported values are unrealistic	Questionable Biomarker Readings
Phase 2a	Concomitant reduction in CSF & plasma neurogranin	Neurogranin in plasma is not a biomarker of AD	Questionable Biomarker Readings
Phase 2b	Significant improvement in neurodegeneration biomarkers	Values inconsistent with published research	Inexplicable Tau & A $\beta$ Values
Phase 2b	Significant improvement in inflammation biomarkers	Values inconsistent with published research	Questionable Biomarker Readings
Phase 2b	Significant improvement in BBB integrity	Data acquired through unorthodox, DIY method	Non-sensical Albumin Levels
Open Label	Significant improvement in neurodegeneration & neuroinflammation biomarkers	Baseline values inconsistent with previous Ph2b reporting	Inconsistent Baseline Readings

***Refer to our report for the complete investigation of the company's claims and published data on biomarkers***

# The story behind the data

- In our view, the failure of the original analysis was choreographed to justify the analysis of samples by Dr Wang's lab who could produce desirable outcomes
- In signature fashion, the fabrication of results becomes evident upon basic scrutiny by experts
- The attempted simulation of ELISA results based on data from Luminex assays is, like Dr. Wang's photoshopped westerns, comical and grave at the same time
- The choice of WB method to measure albumin ratio is likely an attempt to publish "film evidence" in support of the unprecedented finding of BBB integrity improvement
- Cassava Sciences have inexplicably entrusted one of their own instead of recruiting accredited providers per standard industry practice
- To inquiries on the puzzling data reported, the company's CSO Dr Burns responds with outrageous excuses and no concern for quality control as expected of a study sponsor



# Key Questions on Biomarkers

- Why was a method with known limitations in quantification used to measure high concentration protein (albumin) in CSF and plasma – both from precious clinical samples?
- Why, despite both the range of values and ratio reported being entirely incompatible with scientific literature and clinical references, was Cassava Sciences eager to announce a never-before finding of such major significance without taking steps to validate the results using other assays?
- Why are the A $\beta$ 42 and Tau values published similar to those reported by researchers using the Luminex immunoassay when analysis was conducted by ELISA?
- How can the clinical safety and efficacy of simufilam be assumed based on biomarker data that is – in all cases we investigated – entirely out of line with literature in AD?
- What is the explanation for the wide variation in baseline values for these biomarkers between studies?
- Why did the sponsor discard the original biomarker measurements, and elect to re-do the measurements using non-validated methods in an academic laboratory?

# Simufilam Improving Cognition?

Cassava claims the greatest advance in medicine in 50 years: Reversing Alzheimer's

*“Today's data with simufilam suggests disease modification”, added N. Friedmann, Phd, MD, CMO.  
“It appears the drug's unique mechanism of action has potential to provide transformative treatment benefits following 9 months of dosing”*

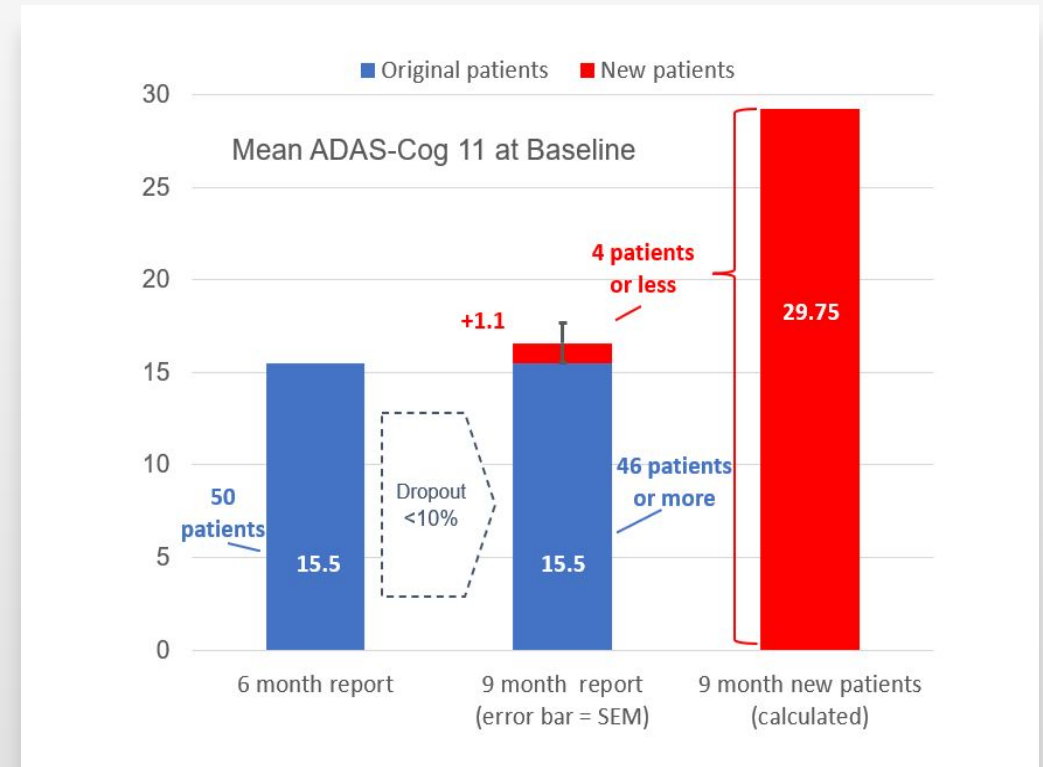
From Cassava Sciences [Press Release](#) Jul 2021

But:

- Ph2b was NOT statistically significant despite data being **heavily massaged**
- Ongoing Open Label study results appear to have been **gamed with Questionable Research Practices**
- Cassava's response to inquiries has been to:
  - **decrease** transparency of OL data reporting
  - **revise** and **erase** previous data without amending the statistical analysis
  - **eliminate** an NIH funded placebo controlled Ph2b confirmation study

# Moving the Starting Line in Open Label study...

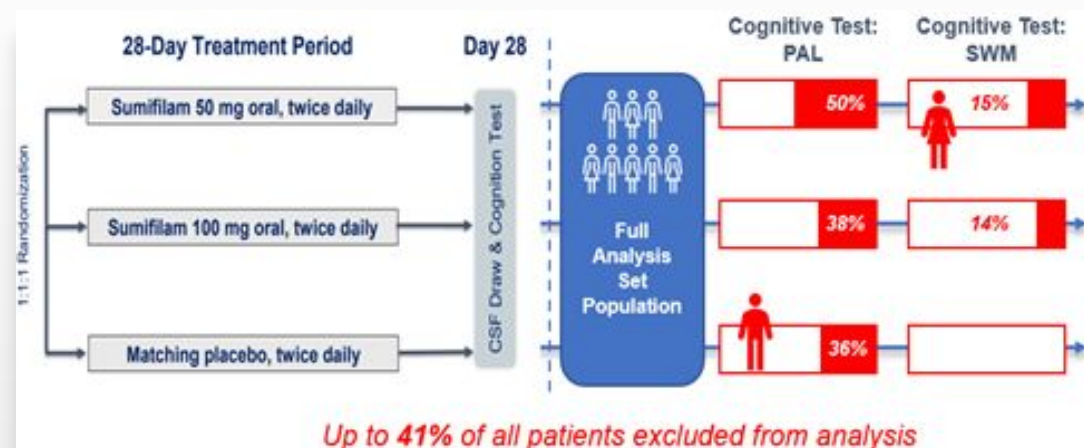
- Cassava reported improvement in cognition of **1.6 points at 6 months** and **3 points at 9 months**
- This “improvement” was caused by 4 patients that were dropped-in with **baseline symptoms twice as severe** as the original cohort\*
- Simple **regression to the mean** completely explains Cassava’s claim of “improvement”
- In fact, the cognition scores **did not change** between 6 months and 9 months - 13.6 vs. 13.9
- After this maneuver was noticed, **Cassava declined to report baseline values** in their 12 month read-out



\*ADAS-Cog values for new patients calculated based on the assumption that the mean score for drop-outs didn't differ from that of other patients

# ...and picking the “right” points

- Cassava created exclusion criteria **AFTER** the data was analyzed
- Each assay had a **customized mix** of exclusion criteria applied
- As much as 40% of data was creatively **removed**
- Ph2b Official Statistical Analysis Plan **specifically prohibited post-hoc exclusion** of patient’s data.



## The Cassava-FDA Protocol Agreement:

### 4.1.1. Full Analysis Set Population (FAS)

The Full Analysis Set population includes all subjects who receive at least one dose of study treatment and have evaluable efficacy records at baseline and post-baseline visits. The Full Analysis Set population will be used for all efficacy analyses. Subjects will be analyzed as treated.

Endpoints	Cognitive		Plasma	
	# 7 PAL Test	# 8 SWM Test	#11 pTau	#12 SavaDx
Score too high or low	⊘	⊗	-	-
Pill count	⊘	⊘	⊗	⊗
Plasma levels	⊘	⊘	⊗	⊘
CVs too high	-	-	⊘	⊗
If(x/y>150% AND x-y>2.5)	-	-	⊘	⊗
<b>Total Patients excluded</b>	<b>41%</b>	<b>10%</b>	<b>17%</b>	<b>8%</b>
Placebo	36%	0%	9%	0%
100mg Tx	38%	14%	19%	10%
50mg Tx	50%	15%	25%	15%

⊘ Protocol violation      ⊗ Criteria not applied

# Or simply removing an entire study

- Cassava Sciences received \$374,500 from the National Institutes of Health to extend the placebo controlled Ph2b trial to 3 months (2018)
- That study never happened, even though it was referenced again in the title of a later grant the company received from NIH (2020)
- Instead, the company pivoted from a 1 month placebo controlled trial immediately to a 2 year open label study.

## Extending clinical trial in AD patients from 1 to 3 months

Project Number	Former Number	Contact PI/Project Leader	Awardee Organization
3R44AG060878-01S1	1R44AG060878-01	BURNS, LINDSAY H	CASSAVA SCIENCES, INC

***Why would Cassava, after reporting “unprecedented” trends in cognitive improvement after 1 month, eschew a preplanned 3 month follow-up?***

# Questions on Cognitive Data

- Were Ph2b post-hoc outlier criteria designed to mislead?
- Is Cassava manipulating drop-out replacements for the Open Label study to obscure true effects?
- Are the patients recruited in the trial confirmed mild-to-moderate AD?
- Why were 12 month baseline values from the Open Label study not reported?
- Why has Cassava silently eliminated a preplanned confirmatory and NIH funded 3 month placebo controlled study of the cognitive effects they claim?

# Connecting the Dots ...

The Final Clue  
Our Version  
FDA Must Act!  
Cassava End-Game Catalysts



# SavaDx: a miraculous diagnostic...

Cassava have been developing a companion diagnostic to Simufilam since 2016, SavaDx

- Claimed to detect Alzheimer's from blood samples before the onset of any symptoms
- Can distinguish vs healthy subjects with  $\geq 98\%$  accuracy...
- ...and AD patients vs those with only mild cognitive impairment with  $\geq 92\%$
- Received nearly \$2M in funding from the NIH in grants between 2017 and 2020

**Yet another phenomenal, unprecedented breakthrough by Cassava... with zero external validation**

## From Cassava Sciences

SavaDx (formerly known as PTI-125Dx) is our blood-based diagnostic to detect Alzheimer's disease.

The goal of SavaDx is to make the detection of Alzheimer's disease as simple as getting a blood test, possibly years before the appearance of any overt clinical symptoms.

We are developing SavaDx as a simple, accurate and quantitative blood-based diagnostic to detect and monitor Alzheimer's disease. If successful, we believe SavaDx has potential to make obsolete many of the current approaches for diagnosing Alzheimer's disease.

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).

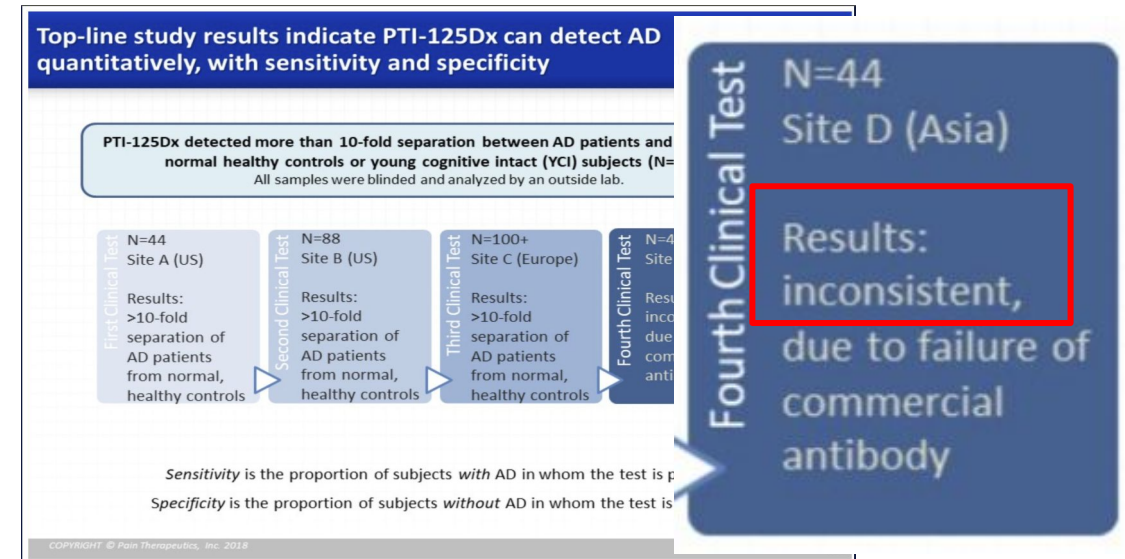
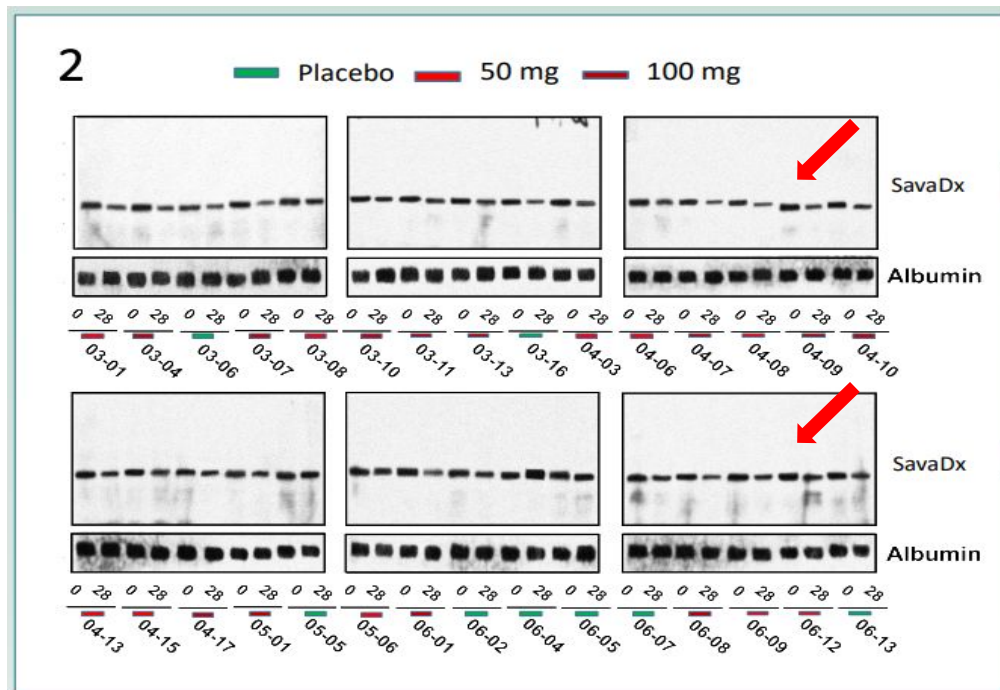


# ...and the final clue

According to Cassava Sciences, SavaDx: “measures the ratio of two protein fragments”  
Yet, **only a single band** appears on film (bottom)

**By what novel mechanism can WB detect the ratio of 2 targets from a single band?**

**And why has the failure of the final trial not been disclosed in grants to NIH or published?**



# Our version of events...

- Cassava Sciences fabricated the failure of sample analysis by an external, accredited lab and avoided the reporting of clinical endpoints (IL-1 $\beta$ ) to main
- Closer inspection of the biomarker data generated by Dr Wang show clear evidence of fabrication in an effort to produce favorable readings
- In an effort to manipulate those Phase 2 study outcomes which were out of Dr Wang's reach (cognition and plasma tests), Cassava Sciences intentionally used Questionable Research practices\* such as patient cherry picking and arbitrary outlier definition in order to obtain favorable results in patients' cognition data
- The planned blinded 3-month extension study was dropped since blinded cognition data would not have been easy to selectively report (compare, e.g., with non-significant findings in cognition data of blinded Ph2b study)

\*for an overview on Questionable Research Practices see: Andrade (2021). <https://doi.org/10.4088/JCP.20f13804>

# FDA Must Act!

Sponsors of clinical studies are held to high standards and have specific responsibilities to ensure the integrity and safety of clinical research. **Cassava Sciences has failed in its responsibilities, and their egregious behavior meets multiple specific criteria that justify imposing a Clinical Hold under 21 CFR 312.**

- The pattern of errors and misconduct in measuring and reporting biomarker and cognitive outcomes, as well as the reliance on clinical investigators whose conduct has been flagged by FDA inspections and Warning Letters, calls into question whether the investigators leading the Simufilam program are qualified to conduct the trial;
- In light of the misleading and erroneous clinical and preclinical results communicated to date, the Investigator Brochures for the Phase 3 trials are necessarily misleading and erroneous and require amendment;
- Given the incongruous and apparently manipulated clinical and preclinical data, the Simufilam IND does not contain sufficient information to properly assess the risks to subjects

Ultimately, only the conduct of a full, thorough investigation of the data, investigators, sponsor, and collaborators can provide reassurance. Furthermore, we believe that the conduct of the company and its program application should be reviewed by the FDA's Application Integrity Policy Committee (AIP-C) and appropriate action taken.

# Cassava Science's Swan Song:

- FDA halt/pause ongoing OL study & Ph3 enrollment pending Ph2 misconduct audit
- Investigation by FDA's Office of Scientific Integrity for Application Integrity Policy
- CUNY concludes Wang misconduct inquiry (est. April 2022)
- Possible SEC investigation (undisclosed nature)
- NIH misappropriation of funds audit and/or investigation
- Journals retract key paper(s)