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The Cult of Cassava Sciences: Fraudulent Data, Impossible Conclusions and a Worthless Drug (NASDAQ: SAVA)

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October 2024

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Part 1: Overview, History, and Pain Therapeutics

"Those who cannot remember the past are condemned to repeat it." – George Santayana

Cassava Sciences Inc ('Cassava') is a clinical-stage biopharmaceutical company that develops drugs for neurodegenerative diseases, with a special focus on Alzheimer's Disease ('AD'). Currently valued at around US$1.35bn, the company is the 272nd largest biotech globally and is by no means financially insignificant. Cassava has one primary therapeutic product candidate dubbed simufilam (PTI-125), an investigational small molecule oral drug that purports to 'restore the normal shape and function of altered filamin A (FLNA), a scaffolding protein in the brain' (Cassava Sciences, 2024). The drug seeks to significantly slow the progression of AD and is promoted by Cassava as a potential breakthrough drug for AD, though this paper will attempt to provide reasonable grounds for suspicion of the company, its drug, and its future.

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To begin, we must first establish that the days of entropy-born drugs (drugs that work by accident or chance) are long gone, with the last major drugs fitting this description being thalidomide, lenalidomide, and pomalidomide (The 'Lides'), and the subsequent development of PROTAC technology. Virtually all modern biopharmaceutical research is done with a cause-and-effect mentality, and entropy (uncertainty, disorder, and unpredictability) plays a now minor role in drug discovery. With innovations like molecular biology and genomics, structural biology, computational chemistry, and most importantly, rational drug design, entropy plays a greatly lessened role in the industry (Mandal, et al., 2009). Despite this, Simufilam is functionally an entropic discovery, arising from chance more so than rational drug design.

Since little foundational knowledge exists about Alzheimer's Disease, with the root cause of the disease being unknown, and 55 million people currently living with the disease globally, it stands to reason that pharmaceutical companies would have a large interest in treating the disease. Since 2003, 98/100 treatment clinical trials for AD have failed, and the disease is still largely ineffectively treated by existing medication (Kim C. K., et al., 2022). Bapineuzumab is possibly the most famous clinical trial failure; a drug developed by Élan and co-owned by Wyeth, some of the largest pharmaceutical companies of the time, showed 'ok' phase 2 data but flunked in phase 3 (Salloway, S., et al., 2014). Pfizer's Dimebon also failed in phase 3 studies, with results published in the Lancet Journal of Medicine (Cassava's results remain unpublished). By establishing this, we see that there is no shortage of interest in Alzheimer's Disease treatment, by companies with significantly more resources than Cassava, which begs the question: How did Cassava, a small, former opioid analgesic drug company, manage to crack the code while the rest of the biopharmaceutical industry failed? The answer is, simple, they didn't.

The Cassava journey begins in 1998 with the incorporation of Pain Therapeutics (PT), by Remi Barbier. The PT drug development catalogue involved 3 key formulations:

1. Remoxy ER (oxycodone), billed as a 'long-acting, abuse-resistant, narcotic analgesic formulation for the treatment of moderate to severe chronic pain'.
2. Oytrex, an oxycontin/naltrexone formulation that tried to minimise the development of physical dependence, making it less prone to abuse.
3. An additional super-low dose naltrexone formulation, for fibromyalgia, Crohn's disease, and acute pain.

All these 3 drugs failed, and none are approved by the FDA. PT also said Naltrexone had a completely different effect at low dose vs high dose, which is false. There is no drug that has the opposite effect at a low dose vs high dose. PT also tries their ultra-low dose naltrexone for IBS, with the trial failing, unable to separate from placebo.

At some point, Pain Therapeutics encountered Dr. Wang, who before the company, was a relatively unknown professor at the City University of New York (CUNY). Dr. Wang is publishing relatively basic neuroscience and biochemistry work; it is important to note that he is not a chemist, and is not experienced in medicinal chemistry, nor does he have prior experience in designing drugs. Dr. Wang's lab is not a drug lab, it is a neuroscience basic research lab. Dr. Wang and Dr. Burns (wife of Remi Barbier) then begin to re-evaluate naltrexone, naloxone, and other opioid binders for PT, which are already very well studied drugs; the RCSB PDB has cocrystal structures of naltrexone and naloxone, with each of the 3 opioid receptors, it is well understood and is one of the most fundamental parts of pharmacology.

During Dr. Wang's studies, Filamin A becomes a topic of interest. Dr Wang starts to examine the protein broadly, and concludes naloxone/naltrexone binds to this protein, specifically a 'pentapeptide region', a 5 amino acid region that is solvent facing. It is unclear what this region does at all, but he suspects this is where naloxone and naltrexone bind to FLNA. Dr Wang and Burns published two (retracted) papers showing their FLNA findings between 2006-2009. Determining what this small region does is crucial, and usually done by structural biology work. Since proteins are just strings of amino acids, after around 40 amino acids (peptides), these peptides start to fold and make complex shapes called proteins; 80-90% of drugs target proteins, and Dr. Wang says naltrexone targets the FLNA protein, that's how the drugs work. This raises more questions than answers: Why would this opioid drug work through a receptor that isn't the opioid receptor? Wang says it's because of FLNA. He was trying to make an analgesic that didn't work through the opioid receptor, instead, through the filamin receptor. After the failure of all 3 Pain Therapeutics pipeline drugs, Dr. Wang abandons his pain reliever drug efforts, and instead focuses more on his specific 5 amino acid region of FLNA. FLNA is in the top 1% of proteins by size and has a variety of functions including maintaining cell structure, signalling, and interacting with various other proteins. Dr. Wang stipulates that this specific region of FLNA (a protein with 2640 amino acids), if blocked, results in an incredible pain reliever, which is already dubious as FLNA is a cytoskeletal protein.

This hypothesis is largely ignored and never makes it to human testing. Wang then files more patents saying if you target this protein in this spot specifically, it can hinder cancer progression, help diabetes, and Alzheimer's. In 2012, Dr. Wang and Dr. Burns formulate their new hypothesis concerning

FLNA binding and Alzheimer's. It is very rare for one protein to do everything, but Dr. Wang has discovered it! Why this specific 5 amino acid section, when there are 2640 other amino acids everywhere in FLNA, you may ask? Dr. Wang has no idea why these 5 specifically work; establishing the cause is *crucial* in rational drug design, though this is not something investigated further. Structural biology is typically necessary to determine the 'why', usually through crystal structures. A clinical stage biotech company would want to be sure their drug is hitting the right protein in the right place, and hundreds of experiments are routinely conducted in drug discovery. Pain Therapeutics did no serious verification of this, and the subsequent drug simufilam is designed without a blueprint.

Dr. Wang's pain reliever drug efforts are abandoned after the fourth FDA rejection of Remoxy, and Simufilam is created in its stead. The exact creator of Simufilam is unclear, as there is no medicinal chemist at Pain Therapeutics; Dr. Wang and Dr. Burns both appear on the patent, and both are not chemists. It is important to note all of Dr. Wang's and Dr. Burns' papers have been retracted, and they are now functionally unpublished scientists. A published *Science* 50-page report from CUNY's 10-month investigation into wang concluded he engaged in 'egregious misconduct', and 20 of his papers (co-authored by Dr. Burns) were 'highly suggestive of deliberate scientific misconduct'. Various preclinical experiments were conducted on Simufilam, that were so bad, Dr. Wang got indicted, which is unfathomably rare in the scientific community (*U.S.A. v. Hoau-Yan Wang).* There is a 99%+ conviction rate in criminal federal court, and it's a functional certainty Wang will be found guilty of scientific fraud.

Before the discovery of massive fraud, Cassava raises hundreds of millions for their Alzheimer's effort and hundreds enrol in clinical trials. Simufilam ends up in the clinic based on Dr. Wang's fabricated preclinical data. Pain Therapeutics don't use a contract research organisation (CRO), and they don't have an in-house lab, so they instead outsource everything to Dr. Wang, who then sends back provably fabricated data. For scientific detail of what data was falsified and how, I refer you to the detailed poster below, by Heilbut, Brodkin, Milioris, and Markey (2022).

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Rigor and Replication in Alzheimer's Therapeutic Development: A Case Study

Adrian Heilbut[1], Jesse Brodkin[2], Enea Milioris[3], Patrick Markey[4]
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Disclosure: The Authors (independently) have or previously had short positions and/or related hedges in Cassava Sciences stock, and have engaged in paid consulting to discuss Cassava Sciences and other companies.

CTAD 2022, San Francisco
www.simuflimflam.com
LP105A

Evaluation of Preclinical & Clinical Simufilam Studies: Strange Observations Raise Scientific Doubts

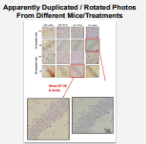
The Simufilam Story

- Simufilam (PTI-125) is an investigational drug in Ph3 trials for AD (NCT04994483, NCT05026177) sponsored by **Cassava Sciences** (Pain Tx)
- First proposed as non-opiod analgesic or modulator of opioid signaling / addictiveness, based on mimicking apocryphal paradoxical effects of "ultra-low-dose Naloxone" **[1, 2]**
- Wang 2008 **[1]** reported Naloxone (**NLX**) bound Filamin-A (**FLNA**) with pM affinity at specific 5mer VAKGL to modulate opioid signaling, and that NLX bound the isolated VAKGL peptide, which competed with FLNA to bind NLX
- Simufilam claimed to have been discovered **[3]** as competitor to NLX binding to VAKGL and FLNA, without opioid antagonism
- Wang 2012 **[4]** claimed Simufilam reduced pathogenesis in a mouse AD model by modulating toxic signaling of Aβ42 via α7nAChR, by binding FLNA & changing protein intx
- Cassava received **>$20M from NIH** for Simufilam development

Reports of Manipulated Images & Data

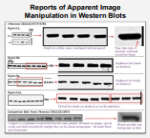
- In 2021, many scientists independently flagged concerns about images & data in **>30** papers authored by **Dr. Hoau-Yan Wang** of City College (CCNY) of **City University of New York** (**CUNY**) [Petitions & Letters to FDA; PubPeer]

Apparently Duplicated / Rotated Photos From Different Mice/Treatments



PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis
Neurobiology of Aging 2017 [PubPeer]

Reports of Apparent Image Manipulation in Western Blots

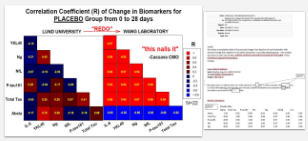


Reducing amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting FLNA
Journal of Neuroscience 2012 [PubPeer; Cliquera Petition]

The "Re-Do" & Puzzling Correlations

- 28-day P2b **failed** when initially reported (**Lund analysis**)
- Back-up CSF samples sent to **Dr. Wang** at for "re-do"
- Wang reported highly significant CSF biomarker effects
- Use of Wang's data was justified based on ***correlations*** between ***changes of different biomarkers in placebo*** (patient-level; 28d)
- No valid statistical rationale for this justification; in short term, uncorrelated random errors are expected in placebo

Correlation Coefficient (R) of Change in Biomarkers for PLASEBO Group from 0 to 28 days

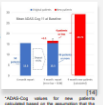


Implausible Phase 2 Biomarker Data

- Wang analyzed **all** P2 CSF samples
  7 of 9 CSF biomarkers appeared:
  - Inconsistent with scientific literature
  - Inconsistent with human biology
  - Inconsistent with assay (Luminex v ELISA)

Open-Label Cognitive Baseline Shifts

- Reported ADAS-Cog **improvement** of **1.6pts at 6mo** and **3pts at 9mo**
- "Improvement" likely due to 4 (est.) patients dropped-in w/ **baseline scores 2x as severe** as the original cohort*
- Absolute scores **did not change** significantly 6mo → 9mo: 13.6 vs.13.9
- After this was noticed, **baseline values** were not reported in 12mo read-out (Δ-1.5pts)



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

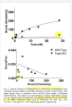
A Foundational Question: Does Simufilam Really Bind Its Purported Molecular Target, VAKGL peptide in Filamin-A?

Claim 1: A New Naloxone Target

Naloxone Binds Filamin-A?

- The only paper **[1]** to report Naloxone binding FLNA is by Wang and Burns and was retracted by PLoS editors

- There is no reported non-opioid specific binding site for Naloxone **[9]**; Naloxone does not distribute to tissues with high FLNA expression **[10]** (50yrs of study)



Autoradiography of opioid and ORL1 ligands in opioid receptor triple knockout mice

Claim 2: A Specific New Naloxone Binding Site

Naloxone Binds VAKGL Peptide?

- No reported analogous small molecule ligands for any other pentapeptides
- No binding pocket near VAKGL in structure of the FLNA dimerization domain [3CNK]
- No model ever proposed for how binding to VAKGL causes conformational change, pI shift, or allosteric modulation of FLNA protein interactions or function
- VAKGL occurs in dozens of other human proteins; if Naloxone bound VAKGL (both as a pentapeptide and in native FLNA), unclear why it would not bind other proteins with VAKGL

Claim 3: A Novel Molecule Mimicking Naloxone

Simufilam Binds VAKGL and Filamin-A?

- Simufilam reportedly discovered with *in vitro* screen against biotinylated VAKGL competing with FITC-tagged NLX **[3]**
- Simufilam claimed to bind AD brain tissue in displacement assay vs [^{3}H]NLX **[5]**
- Simufilam claimed to induce pI shift of FLNA from AD mice and AD patients in ***lymphocytes*** **[5, 6]**
- VAKGL claimed to compete vs FLNA for Simu & block effects on FLNA intx in synaptosome preps

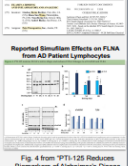


Fig. 4 from "PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients" JPAD **[6]**

Claim 4: High Affinity & Two FLNA Conformations

Simufilam binds altered FLNA; fM IC50?

Reported Radiolabeled Simufilam Binding Assay

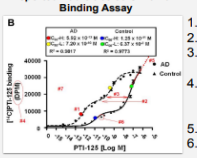


Fig. 1 from "PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis" **[5]**
Neurobiology of Aging 2017
[Expression of Concern@PubPeer]

1. 4 Affinities
2. Wrong Ratio
3. Thermodynamic Paradox
4. Physically Impossible Radiochemistry
5. No Asymptote
6. n=6 but no error bars
7. Time to equilibrium

Experiment & Results: No Evidence for Naloxone or Simufilam Binding VAKGL By Isothermal Titration Calorimetry

What is ITC? How does it work?

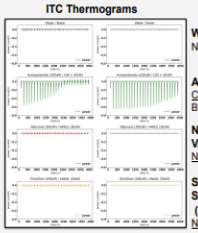
- Molecules interact due to thermodynamic driving forces. Major contributors to non-covalent interactions are hydrogen bonding and van der Waals forces, hydrophobic interactions, & entropy. **ΔG = ΔH − TΔS**
- Isothermal Titration Calorimetry directly measures the heat (enthalpy; ΔH) of a molecular interaction **[11]** as small volumes of a solution containing the ligand are sequentially injected into solution containing target
- As molecules bind (if they bind), heat is released & measured, until all target binding sites are saturated
- Advantages: Easy; automated; does not require labeling molecules; very sensitive; quantitative

Experimental Design & Methods

- Automated calorimetry: MicroCal Auto iTC 200; 25°C
- No +ve control exists for a small mol binding any pentapeptide; high-affinity Carbonic Anhydrase II (CAII) inhibitors eg. Acetazolamide (K_d ~20nM) often used to benchmark detection of binding intx
- VAKGL(target) and VAAGL (-ve control) peptides synthesized (GenScript)
- Simufilam HCl (MedchemExpress), Naloxone (Selleckchem), Acetazolamide (Fisher) ligands were dissolved in DMSO
- Peptides,CAII dissolved in dH_20 (VAKGL) or PBS
- ITC binding assay in PBS;matched [DMSO] <5%
- Integration & baseline correction using NITPIC **[12]**

ITC Results: Does It Bind???

ITC Thermograms



Water + Water
No Signal, as Expected

Acetazolamide + CAII
Clear Signal of Binding
Binding is saturable

Naloxone + VAKGL peptide
No Signal of Binding!

Simufilam + VAKGL
Simufilam + VAAGL (-ve ctrl)
No Signal of Binding!

Interpretation & Limitations

- **Analysis of published claims together with our experiments suggests that Simufilam does not bind its reported target.**
- We believe Simufilam couldn't have been discovered as patents claim, since NLX doesn't seem to bind FLNA
- Proving a negative result is hard; a single experiment is not determinative. ITC & other expts should be repeated by others
- If Simufilam or NLX bound FLNA, it should be easy to determine structure of bound complex by crystallography, cryo-EM, or NMR. No such structures were ever reported.
- Simufilam authors have failed to offer *any* new experimental data to address concerns for over a year.
- **All pre-clinical & clinical claims about Simufilam [3,4,5,6,7,8] are in doubt if they rely biologically or logically upon retracted, invalidated, fabricated, or falsified scientific claims.**

Conclusion: In Our Opinion, a Drug that Doesn't Bind Its Purported Target Has No MoA, Nor Possible Clinical Utility

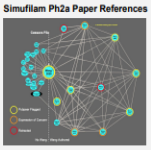
Ethics & Law of Trials in Humans

- Human experimentation must be "justified on the basis of a favorable risk/benefit assessment" **[16]**
- Can informed consent be obtained if veracity of science used to justify clinical trials is in question?
- Is offering hope, denying access to alternative trials, & doing lumbar punctures justified if prospect of any clinical benefit is in question?
- Can clinicians & IRB properly evaluate a trial if Investigator Brochure cites dubious papers & science?
- When should FDA take enforcement action to ensure compliance with 21 CFR 312?

Correcting the Scientific Record & Investigating Possible Misconduct

- 7 retractions to date
- Some journals refused to investigate, take further action, or address errors
- Initial 2021 CUNY inquiry determined that an investigation was required under Research Misconduct Policy, yet CUNY has provided no public updates for over a year
- Multiple ongoing federal investigations have been reported [WSJ; New York Times; Reuters]

Simufilam Ph2a Paper References



PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients **[6]**

Beyond the Simufilam Case Study

- Many other drugs in development deserve scrutiny; peer review is an ongoing process
- Questionable research practices all too common
- **Mechanism of action matters**, especially for drugs from rational, target-directed discovery
- Large unmet needs & long development timelines create perverse incentives to exaggerate claims
- **Potential conflicts of interest must be considered, but are independent of truth & validity of observations and arguments**
- **Institutions of science must encourage debate, investigate concerns, & protect skeptics & whistleblowers – not attack them [15]**

Acknowledgements: We thank everyone speaking up for scientific integrity and participating in open discussion and debate, especially on PubPeer and Twitter. We thank those who provided helpful feedback on our abstract and discussed and analyzed scientific issues with us privately. ITC experiments were done at the Precision Biomolecular Characterization Facility (PBCF) in the Dept of Chemistry at Columbia University. We thank Dr. Jia Ma for training and assistance with ITC.

Disclosures: The Authors (independently) have or previously had short positions and/or related hedges in Cassava Sciences stock, and have engaged in paid consulting to discuss Cassava Sciences and other companies. The Authors are defendants in a federal defamation lawsuit, Cassava Sciences v. Bredt **[13]**

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Part 2: Pain Therapeutics Out, Cassava In

"The definition of insanity is doing the same thing over and over again and expecting different results" – Albert Einstein

After the staggered failure of all its drug candidates, Pain Therapeutics rebrands to Cassava, to pursue Simufilam as a cure to Alzheimer's, despite having no in-house scientific capability and no chemist, instead outsourcing all science to Dr Wang. Cassava begins clinical trials.

The core hypothesis of simufilam is as follows, summarised by the Cure Alzheimer's Fund:

"The company's core hypothesis is that when filamin-A changes its conformation, it triggers amyloid deposition, synaptic dysfunction and tau phosphorylation. The hypothesis is essentially unique to the company and its scientific founders, and the underlying science long has been challenged by the rest of the field as unable to be replicated by other labs and as inconsistent with other scientific data. In recent years, scientific sleuths and financial whistleblowers have accused the early publications supporting Cassava's hypothesis of image manipulation, and Cassava's clinical trials have been assailed for failing to follow generally accepted practices for statistical and scientific integrity. Recently, the lead scientist on the studies that led to the development of simufilam and SavaDx, Dr. Hoau-Yan Wang, was indicted by a federal grand jury for falsifying data to fraudulently obtain NIH grants on his own and on the company's behalf. Although Cassava points out that Dr. Wang had no part in designing the ongoing phase 3 clinical trial of simufilam, the data he allegedly falsified is the foundation of what justified the trial at all".

Toxicology is crucial for clinical trials, as it determines where the drug went in the body. In the investigator's brochure Cassava supplied (a document supplied to doctors willing to do the clinical trial), it says that in animal experiments, the brain was one of the organs with the LEAST amount of drug exposure, while other crucial organs (lungs, liver, etc) all had the highest trace amounts of Simufilam, while the brain had very little. For a disease like Alzheimer's, one would typically expect the drug would need to go to the brain. A possible explanation for this lack of travel, is that the brain is a very hard place for drugs to go, due to endothelial tight junctions (TJs), which stop any old molecule from entering the brain; they functionally act as bouncers for the brain. To get past the TJs, you need the following (not an exhaustive list):

1. Active transport through a receptor, or passive transport if the drug is small enough.
2. Lipophilicity, can't be too hydrophilic or polar, must be relatively non-polar.
3. Not be a PGP substrate.

Or the TJs will kick your drug out. Simufilam does not end up in the brain much, which is very odd, as Alzheimer's disease is a known to be caused by changes in the brain. Pharmacokinetic (PK) analysis from Cassava's own publications indicates Cmax at 1020ng/mL, CSF/plasma at 0.61, and simu MW 259 at 2.4 nmol/mL; after 3 half-lives, it reaches 0.3pmol/mL trough concentration. An estimated $4.5*10^{16}$ filamin molecules are in the brain, meaning simufilam would bind to less than 1% of filamin in the brain.

Table 2. Mean PK parameters of PTI-125 100 mg b.i.d. in AD patients (± SD)

Day	Cmax (ng/mL)	Tmax (h)	Clast (ng/mL)	Tlast (h)	λz (1/h)	AUClast (h*ng/mL)	T1/2 (h)	CSF/plasma ratio
Day 1	1020 ± 442	2.00 (1.00-3.00)	176 ± 112	12 ± 0.015	0.176 ± 0.496	5320 ± 2230	4.51 ± 2.43	---
Day 28	1100 ± 417	2.06 (1.00-5.93)	238 ± 168	12 ± 0.029	0.174 ± 0.051	6700 ± 3240	4.35 ± 1.39	0.61 ± 0.41

Note: Tmax is reported as median (min-max)

Cassava's Mean PK parameters table

Concerns of the mechanisms of simufilam include:

1. The bioavailability of simufilam is unknown due to it being undisclosed by Cassava.
2. The simufilam half-life is 4 hours, which is as low as it gets for small molecules, making it borderline useless as steady state concentration cannot be effectively built.
3. Simufilam has 30% plasma binding and has roughly 70% free fraction, meaning only 70% of the drug can hit the target region.
4. AlphaFold analysis shows the 5-peptide binding region is very flat, and probably isn't even an active site of FLNA. It is not a place of

importance, why would binding there help or hurt, even if you could bind there. A flat, inactive region lacks the structural features necessary to propagate conformational changes throughout the protein (Dobson, C. M. 2003).

5. Simufilam does not have many places to form bonds. It can only form one hydrogen bond at 2kilocal per mole affinity. The benzine portion of the molecule does not have a place to stack.
6. It is not clear why Cassava has the dose it does, why it isn't getting into the brain, or why the drug is ultimately useful.

The underlying scientific claims of Dr. Wang and Dr. Burns are also implausible, including:

1. The high-affinity binding of naloxone to FLNA.
2. The high-affinity binding of simufilam to FLNA.
3. The patented claim simufilam is an opioid agonist, and the subsequent contradictory claim simufilam is not an opioid agonist.
4. The claim FLNA has a misfolded conformation associated with AD.
5. The claim simufilam reverts the allegedly misfolded conformation of FLNA to its natural shape.

None of these claims have ever been corroborated by any independent scientist, nor deployed by any other commercial or academic venture. Cassava knows its foundational simufilam claims are entirely unique to the company, based on unverified, contested research by Dr. Wang and Dr. Burns.

Much of the missing, or non-existent data is related to a research method known as Western blot analysis. Western blotting is an important technique as researchers can separate and identify the number of proteins in a sample and quantify them by molecular weight or charge. The result of this method is a film/scan of a membrane (a sheet of paper) on which the presence of targeted protein is shown by dark areas where the film has been exposed to a signal detected by antibodies bound to the protein. The number of proteins in a sample can be established by densitometry.

Dr. Wang did not save or retain these crucial Western blot experiments, nor did he retain his crucial ELISA tests, including those that underpin the decades of research behind Cassava's claims about simufilam. The necessary research required to defend simufilam's patent is missing, including research that would supposedly show simufilam's improvement of biomarkers during clinical trials. The only evidence that FLNA is misfolded in AD patients are Western blots reported by Dr. Wang and Dr. Burns in a 2017 paper, though the DOJ has found these images to be fabricated.

The idea that predicates simufilam, a drug not designed to be a protein-protein interaction inhibitor (PPI) but made one after the fact, can stop protein-protein binding is far-fetched, to say the least; these two proteins have 2700 and 2000 amino acids respectively, while simufilam uses 1 (one) amino acid. This is beyond belief, as one would have to stop the points of contact on these two large proteins totalling 4700 amino acids, with a singular amino acid, or you won't have affinity. This is analogous to trying to stop an oil tanker docking in port with an inflatable mattress. Cassava has made a theoretical protein-protein inhibitor, despite not knowing where Alpha7 (A7) binds, and assuming it is their specific designated region. Why is stopping this protein from working even going to be useful? Alpha7 has been tried in ADHD, AD, and depression, and mainly functions as a nicotinic inhibitor. Alpha7 is very well studied in AD, and it didn't work. Why would simufilam be any different? The drug works by stopping Alpha7 from binding to the filamin, but what is Alpha7 doing that is so bad in the first place? These are questions unanswerable by Dr. Wang. Alpha7 is fundamentally irrelevant to Alzheimer's, as it is an amyloid beta disease. Genes related to amyloid beta are involved in AD, if Alpha7 is involved, why not just make a drug specifically for Alpha7?

The very scientific underpinning of simufilam relies on the assumption that Filamin A is misfolded in AD patients, though current scientific consensus is that filamin A is not prone to misfolding in any way that contributes significantly to human diseases. Misfolding is not a recognised mechanism, and the conditions that result in misfolding are from Ph conditions or genetic mutations; it also cannot be refolded. There have been no studies into FLNA being 'folded incorrectly' as Cassava alleges (Heyningen, V. van, 2005). If the protein was misfolded, you could take a photo of it with x-ray crystallography. If the protein is misfolded, how is simufilam refolding it by binding to a peptide region? Does it seem plausible that by binding to a 5-peptide region, it refolds an entire 2700 amino acid protein? Anfinsen's Dogma demonstrated the native structure of a protein is determined by its amino acid sequence, implying correcting a misfolded protein involves addressing interactions throughout the entire protein, not just a small region (Anfinsen, C. B., 1973). The efficacy of small molecule pharmacological chaperones is limited to proteins with minor folding defects, not large scale misfolding (Uyeda, C., et al., 2016). Further, why would this small molecule refold this protein, especially with a 4-hour half-life? There is nothing stopping the protein from refolding once the drug is gone, the underpinning of simufilam is entropy. There is no fundamental reason for simufilam to work, *it just does*.

Despite these fundamental scientific queries being publicly unanswerable, Cassava proceeds with their studies and observe a half-life of four hours. A novel drug with a 4-hour half-life is unheard of, and drug developers do not make novel drugs in most fields with such a low half-life. Cassava goes to phase 2 anyway, despite the fact a drug with a 4-hour half-life being functionally useless; the typical biotech would see this, and not continue study. This is the key takeaway from phase 1.

A phase 2 trial was then conducted, beginning in 2019, wherein Cassava conducted a randomised, double-blinded study to assess biomarker changes over 28 days of Simufilam treatment. This is a crucial step to generate evidence that supports simufilam as a treatment for AD and justify larger studies required for FDA approval. Cassava hired a laboratory at Lund University in Sweden, which is one of the best-regarded labs in the world, to measure the biomarkers. On May 15, 2020, Cassava issued a release reporting the phase 2 data showed the drug failed to improve biomarkers in the disease, and the stock dropped 75%. Dr. Burns, former senior vice president of Cassava, sees the data has been terrible, and, knowing simufilam is the only drug Cassava has, chooses to fudge the data by ejecting patients who declined in cognition significantly, until the data shows simufilam is more effective than placebo. They attempted to justify this by suggesting Lund University improperly analysed patient samples, and sought to re-do the biomarker analysis in a different laboratory. This laboratory was Dr. Wang's, which is obviously not independent, and has a vested interest in the success of the drug. In September 2020, Cassava reported the 're-done' results, and simufilam dramatically improved biomarkers (45%), doubling Cassava's stock. These results have now been completely discredited: "Dr. Burns failed to disclose the full set of patient data, which showed no measurable cognitive improvement in the patients' episodic memory" – SEC.

Further study was then conducted, which is the largest point of contention amongst Cassava's supporters, despite the data being even worse than the preceding data. In phase 2b, a controlled withdrawal study, patients received a year of open label simufilam, meaning they knew they were taking simufilam. In the 2-year open label study, patients got worse, as one would expect AD patients to do. Cassava, recognising this failure to show decline in the whole population, spliced the data in half; Cassava separated the groups, post-hoc, into 'mild', and 'moderate', with the mild group showing significantly better results than the moderate group. It's a tautology; they ordered the patients based on how well they did, then recognised the top half did better than the bottom half, labelling the top as mild and bottom as moderate.

Importantly, if you combine the groups and find their average, the patient declines exactly as one would expect; significantly. $SAVA bulls point to the mild group, in this uncontrolled, open label study, with unpublished results, and say patients did very well. While it is true patients did well in this half, it is quite literally just the better half of a dataset. One cannot simply negate the bottom half of the dataset, and the average of both shows significant decline vs placebo; proof simufilam does not work. The phase 2 data is being fooled by division. Anyone can make more subgroups, and eventually one group will outperform the others. The problem is that it is not a priori; Cassava did not decide mild would perform better before the data but did post-hoc analysis instead. These subgroups never replicate; they are after the fact, not before the fact.

The 6-month controlled experiment was conducted after 1 year of open label, then patients were reverted to open label for the final 6 months. The control group of the test failed, and had a P value more than 0.05, suggesting there is not enough evidence to reject the null hypothesis; the data proved to be statistically insignificant. The T-test failed. The phase 2b withdrawal study also failed; at the 1 year open-label mark, half of the patients were withdrawn to placebo, the other half remained on simufilam. At the end of the 6 months, both groups had similar changes in outcome, both mild and moderate, with mild only being marginally better. Cassava's working theory is that the drug is so good that it keeps working throughout the 6 months even though you're not taking the drug. When you stop taking a medicine, it stops working. Cassava says there is a 6-month carryon effect.

Researchers cannot simply look at the clinical trial data post-hoc and decide why the post-hoc observation is good, the drug and the placebo had the same effect, with Cassava themselves acknowledging the P value was not statistically significant. Cassava further released that simufilam has a 0.5-point benefit in ADAS-COG values (a measure of cognition, with scores ranging from 0-85), despite ADAS-COG values typically having a standard deviation of 6-7. A 0.5-point difference is superfluous and irrelevant.

Hence, to believe in Cassava, you must:

1. Accept the drug is well designed, despite not having any chemists work on it, and its formulator (Dr. Wang) was arrested.
2. Accept there is a large, statistically significant difference between mild and moderate patients, and that simufilam works in mild but fails entirely in moderate.
3. Accept the drug works as a protein-protein interaction inhibitor despite there being roughly 2 (two) FDA approved protein-protein interaction inhibitors.
4. Accept simufilam can effectively treat Alzheimer's despite minimal brain penetration.
5. Believe a drug with a 4-hour half-life can maintain therapeutic levels necessary for chronic treatment.
6. Believe binding to a flat, inactive 5-amino acid region on FLNA can refold a misfolded protein with 2700 amino acids.
7. Believe that a small molecule can effectively disrupt protein-protein interactions involving large proteins (1 amino acid vs a binding of 2000 and 2700).
8. Rely on post-hoc subgroup analyses as evidence of efficacy, despite raw clinical trial data showing no separation from placebo.
9. Consider minimal improvements on ADAS-COG as clinically meaningful (a 0.5-point increase).
10. Accept simufilam's purported refolding of FLNA is plausible with little to no 3rd party support from the scientific community.
11. Believe simufilam continues to exert therapeutic effects even after 6 months of discontinuation.
12. Trust efficacy claims despite massive concerns over data integrity, and a complete lack of published results.
13. Assume that targeting the Alpha7 nicotinic receptors is effective in Alzheimer's despite previous failures.

It borders on the impossible that all these conditions are collectively true, keeping in mind that none are individually sufficient to create a marketable drug.

Part 3: Conditional Probability, Cassava Stock, and Conclusion

"The best trades are the ones in which you have all the factors in your favor" – Stanley Druckenmiller

To accurately determine the probability of simufilam working, one must first understand basic conditional probability. It is a measure of the probability of event *A* occurring, given that another event *B* is already known to have occurred. When working with statistics, independence of variables must also be assumed, which is why some probabilities may seem 'high' (PPI). Below is a *generous* table of probabilities that Cassava must meet to make an effective drug.

Probability of Event Occurring	Event
2.00%	An Alzheimer's drug beating phase 3 trials, 2/100 drugs meet phase 3 primary endpoint.
90.00%	Simufilam works as a protein-protein interaction inhibitor.
90.00%	Pharmacokinetics make sense, despite the brain having the least amount of simufilam.
50.00%	Mild vs. moderate in pharmacology is a result of accurate data
25.00%	Simufilam has a "disease modifying effect"/follow-on effect (6-month effect range)
Sum: 0.18%	There is ultimately a 0.18% chance of all these conditions being true.

Curiously, the investors on the other side of the short trade are overwhelmingly average retail investors; roughly 70% of the stock is owned by retail investors, compared to the typical 13-15% ownership in any other public company. Cassava stock also has a Discord server, which is an instant messaging platform where users can participate in community discussion. Asides from the oddity of a stock having a dedicated community server, members of this community conducted a self-reported poll, titled "Have you made a significant bet on biotech before?". 71% of Cassava investors reported 'no, Sava is my first', while 14% reported 'Yes, was burned at readout'. The typical Cassava investor has this as their first biotech stock pick and are functionally gambling; 'the most I can lose is the money I put in, but the most I can make is, potentially, 50x of my money!'. When examining the probabilistic reality of this bet, this is analogous to betting you can pick the right number on a roulette table not once, but twice consecutively; it is a functional impossibility.

When a speculator can bet against an event with a probability of occurrence of less than 1%, even 0.5% in this case, with a potential return being greater than 90%, they should be seizing the moment with both hands; such asymmetric bets are one of the greatest speculative successes possible. By recognising that the market implies a probability of simufilam succeeding above 1% , a trade can be formed.

Currently, $SAVA trades at around US$27/share, with a book value of around $4 per share. With simufilam constituting roughly 85% of the stock's current valuation, it stands to reason that if the drug is proven ineffective in phase 3, the stock will plummet by 80%+ as the single largest asset of the company is now functionally worthless. As the phase 3 readout is expected by year end 2024, the borrow cost of 47% p.a. is negligible. Half of the stock's float is currently short, so finding large quantities of shares to short may prove challenging.

Overall, the author of this paper is short Cassava Sciences (NASDAQ: SAVA) due to their extremely implausible drug candidate simufilam, which should never have been allowed to reach phase 3 in the first place. Cassava and its collaborators have shown a history of persistent fraud and misrepresentation in and of simufilam, an entropy-born drug with no coherent scientific rationale.

The author anticipates Cassava sciences will print negative phase 3 results, and its days of a 1.3-billion-dollar market capitalisation are numbered.

Legal Disclaimer

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