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November 17, 2021

VIA ONLINE & FEDEX

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Third Supplement to Citizen's Petition Associated with Cassava Sciences, Inc. (FDA-2021-P-0930)

Dear Commissioner Woodcock:

Things aren't always as they appear. Things that aren't right can be made to look right. And, tragically, my clients' worst fears about Cassava Sciences appear to have been true.

Increasingly, evidence suggests that Cassava has doctored its research and clinical trial results, duped peer-reviewed journals, used the tainted science to trick the NIH and FDA into approving grants and clinical trials, misled investors by touting their grants and clinical trials without disclosing their troubling research practices, and withheld material information about the true nature of its drug from vulnerable Alzheimer's Disease patients. To confirm the existence and scope of these problems, the FDA has a duty to immediately halt the simufilam (PTI-125) clinical trials, conduct a rigorous audit of all the company's research and clinical trial results, and report the agency's findings to interested law enforcement and regulatory authorities.

As detailed in our original Citizen's Petition and in subsequent filings, including this one, the major concerns of my clients relate to the apparent manipulation of clinical data by Cassava. Since our last supplemental submission, select potentially relevant developments and discoveries include:

Wall Street Journal Exposé

As you may have been briefed, investigative journalists at the Wall Street Journal have been working on an article about Cassava Sciences. Attached please find the award-winning publication's recent story.

With these significant concerns, my clients remain skeptical about the entirety of Cassava's clinical data, including the safety data, which may also have been manipulated. From the first filing of the

Citizen's Petition, my clients have simply asked the FDA to pause the clinical trials until these concerns have been investigated and to continue clinical trials only when the public can be assured that there are no safety issues and that there is a reasonable efficacy signal.

There is considerable urgency, as Cassava's SEC 10-Q filed November 15, 2021 states: "We commenced patient screening for RETHINK-ALZ [a Phase 3 clinical trial, NCT04994483] in October 2021, followed by patient dosing in November 2021." While it is unclear if dosing has already begun or if is scheduled to commence before the end of November 2021, my clients feel that an immediate halt of patient exposure to simufilam is pressing.

Due to their serious concerns about simufilam and related research by Cassava, and at great personal and professional risk, my whistleblower clients, along with other prominent doctors and scientists, have voluntarily gone on the record.

- **Dr. David S. Bredt** is an authority on the neuropharmacology and molecular pathways implicated in the mechanism of action of simufilam. Since graduating *summa cum laude* in Chemistry from Princeton University in 1986 and obtaining M.D. and Ph.D. degrees from Johns Hopkins University School of Medicine in 1993, Dr. Bredt has had a varied and distinguished career in neuroscience both in academia and in industry. Most recently (March 2011 through March 2021), he was the Global Head of Neuroscience Discovery for Janssen Pharmaceuticals, with responsibility for neuroscience biology, biomarkers, and external innovation. From 2017 to 2021, he also served as Site Head for Janssen's La Jolla, California, site, which focused on Research and Development for Neuroscience, Immunology, and Biotechnology. From 2004 to 2011, he worked for Eli Lilly and Company, first as Vice President of Integrative Biology and later as Vice President of Neuroscience Discovery and Early Development. At Janssen and Lilly, he oversaw research focused in part on Alzheimer's Disease discovery. Bredt obtained post-doctoral training in the laboratory of Solomon H. Snyder in the Department of Neuroscience at Johns Hopkins School of Medicine in 1993-1994. From 1994 to 2004, he served on the faculty of the University of California at San Francisco Medical School, attaining tenure as a Professor of Physiology. His research has yielded more than 225 papers that have been cited approximately 75,000 times in the scientific literature. His awards and honors include, among numerous others, the Society for Neuroscience Young Investigator Award, the Daniel H. Efron Award from the American College of Neuropsychopharmacology, the EJLB Neuroscience Research Fellowship Award, and the Klingenstein Fellowship Award in the Neurosciences. During his distinguished academic career, he was awarded at least ten NIH grants.

- **Dr. Geoffrey S. Pitt** is an authority on translational science and ion channels similar to those implicated in the mechanism of action of simufilam. He is the Ida and Theo Rossi Distinguished Professor of Medicine and Director of the Cardiovascular Research Institute at Weill Cornell Medicine. He is a physician-scientist caring for patients with cardiovascular disorders and running a NIH-funded research laboratory studying the role of cellular electricity in the heart and brain. He has authored over 100 research papers in scientific journals including Nature and Cell, and he has received numerous honors and awards. Pitt graduated from Yale College in 1984, obtained an Sc.M. degree from Johns Hopkins School of Public Health in 1987, and obtained M.D. and Ph.D. degrees from Johns Hopkins School of Medicine in 1993. He performed clinical training at Stanford University Hospital and obtained post-doctoral training at the Stanford University School of Medicine in the laboratory of Richard W. Tsien in the Department of Molecular and Cellular Physiology. He previously held academic positions at Columbia University Medical School and Duke University Medical School before being recruited to Weill Cornell Medicine as the inaugural director of the Cardiovascular Research Institute. He has been a member of the Society for Neuroscience since 2001. He is an elected member of the American Society of Clinical Investigation and the Association of American Physicians. During his distinguished career, he has personally been awarded funding for more than ten NIH grants and served on committees that review allegations of scientific misconduct at academic institutions and journals.

Quintessential Capital and Coalition Reports

On November 3, 2021, Quintessential Capital released a public report that raises new and serious questions about Cassava Sciences and its drug candidate simufilam [https://assets.empirefinancialresearch.com/uploads/2021/11/Cassava-Sciences-SAVA_-Game-Over.pdf]. Following an in-depth investigation, among other things, the firm found that Cassava's clinical trials were administered by several controversial and questionable characters, that there were irregularities in the manner that the simufilam trials were conducted, and that the reported results of Cassava's clinical trials appear to have been manipulated—in various ways. The report included links to an authoritative opinion by a pharmaceutical industry expert, Dr. Diane K. Jorkasky, as well as an opinion from an expert on clinical trials and medical affairs, Dr. Andrew Jacobson. My clients were unaware of and did not contribute to Quintessential's report.

On the same date, a coalition of four scientists released a public presentation [https://www.cassavafraud.com/docs/SAVAReport_Deck_2021_11_03.pdf] and report [https://www.cassavafraud.com/docs/SAVAReport_Nov2_Final_links.pdf] that both mirrored and expanded upon the numerous serious concerns about the accuracy and integrity of clinical and

preclinical data outlined in our Citizen's Petition. Specifically, among other significant things, the authors [Dr. Enea Milioris, Dr. Adrian Heilbut, Dr. Jesse Brodkin, and Dr. Patrick Markey] reported that Cassava Sciences and Dr. Hoau-Yan Wang appear to have fabricated pre-clinical and clinical evidence across the entire simufilam program, provided inadequate and unreliable safety studies for simufilam, and engaged in serious misconduct in the analysis of and reporting of clinical trial data—particularly the drug's much touted cognitive outcomes. My clients were unaware of and did not contribute to this report.

Cassava Scientists Repeatedly Claim to Have Conducted Seemingly Undoable Experiments

As your staff certainly knows, the alpha7 version of the nicotinic acetylcholine receptor (nAChR) is central to simufilam's proposed mechanism in Alzheimer's disease. In their 2017 review (Neuroimmunology and Neuroinflammation **4**: 263), Drs. Burns and Wang state that "PTI-125 binds and reverses the altered FLNA conformation to prevent Aβ's signaling via α7nAChR and aberrant activation of TLR4, thus reducing multiple AD-related neuropathologies." Like most of their claims, this research is unique to Drs. Wang/Burns/Cassava and relies heavily on Western blotting. These results are elaborated in Cassava's 2012 Journal of Neuroscience paper and their 2017 Neurobiology of Aging paper.

A major problem with this is that international leaders in the nAChR field agree that there are no antibodies suitable for Western blotting of alpha7 nAChR in the brain (see: Moser et al. Evaluating the suitability of nicotinic acetylcholine receptor antibodies for standard immunodetection procedures Journal of Neurochemistry, 2007, 102, 479–492). Therefore, the alpha7 nAChR data that form a mechanistic foundation for simufilam seem scientifically undoable.

This fundamental limitation for alpha7 nAChR Western blotting raises serious questions regarding the validity of Fig. 1A, Fig. 2A, Fig. 9A, Fig. 10A, and Fig. 12A in Cassava's 2012 Journal of Neuroscience paper—the very same paper that Cassava heavily touted in a recent press release as having only one "human error." The alpha7 nAChR Western blot in Figure 9A was also flagged by Dr. Elizabeth Bik for image manipulation on PubPeer (https://pubpeer.com/publications/F91E0D22B887598445BB1F908393EE) .

On Twitter (https://twitter.com/adrian_h/status/1458330292578660353?s=27) and PubPeer (https://pubpeer.com/publications/F91E0D22B887598445BB1F908393EE, comment 17), Dr. Adrian Heilbut noted bigger problems for Cassava's alpha7 nAChR Western blots. Dr. Heilbut found that for the 2012 Journal of Neuroscience and 2017 Neurobiology of Aging papers, Drs. Wang and Burns used an antibody specific for the alpha1 subunit of the nAChR yet reported that they were able to detect the alpha7 nAChR in brain tissue. Western blots rely on antibodies that recognize specific proteins. Thus, an antibody to the alpha1 nAChR does not recognize the alpha7

nAChR. The alpha1 nAChR is primarily found in muscle tissue and not in brain. Using an alpha1 nAChR antibody to detect alpha7 nAChR in brain is senseless. It would be like checking for Covid-19 infection with a pregnancy test kit.

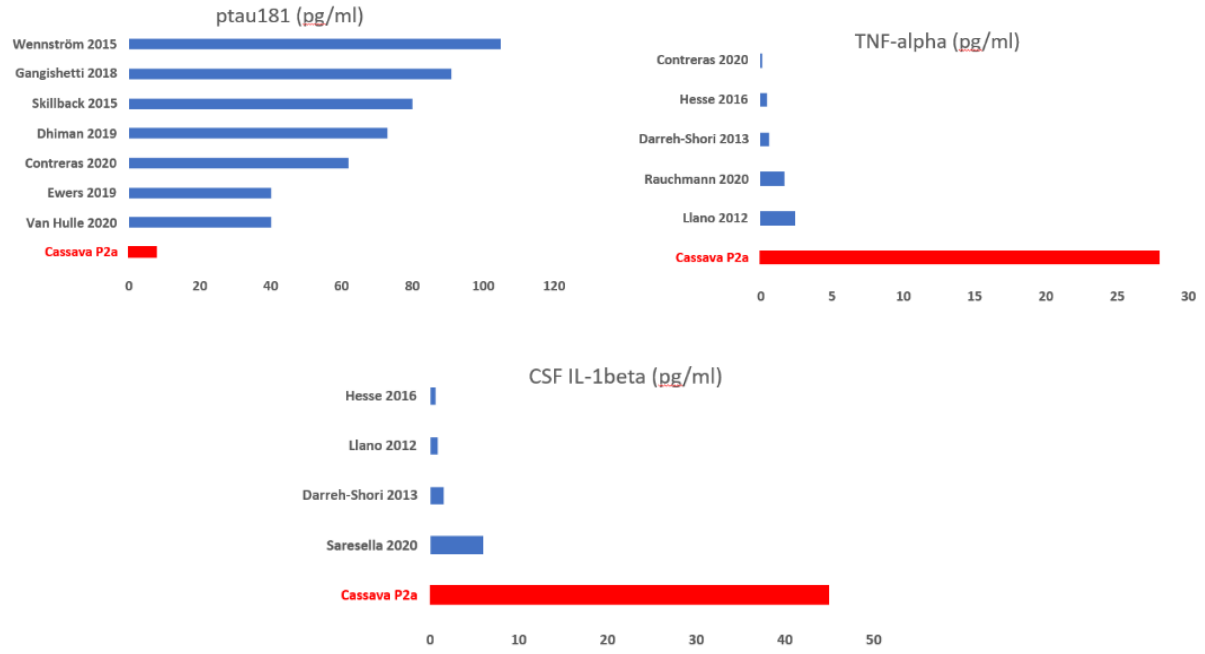
For the 2012 Journal of Neuroscience paper, Drs. Wang and Burns claim to use two antibodies from Santa Cruz Biotechnology. One is catalog # SC-5544, which does not work for Western blotting at all. This limitation is stated explicitly in a 2017 paper (J Histochem Cytochem. **65**: 499–512), which states "Figure 2 shows four antibodies that fail to recognize rat α7 nAChRs on western blots: Santa Cruz sc-5544 (H-302)…" Undeterred, their 2012 Journal of Neuroscience paper shows several Western blots claiming to detect alpha7 nAChR by Western blotting.

Even worse, Drs. Wang and Burns also mention antibody catalog # SC-65844 in their 2012 Journal of Neuroscience paper. However, Santa Cruz Biotechnology sells this to detect the alpha1 nAChR, not the alpha7 nAChR. For the Neurobiology of Aging, they only mention using SC-65844, which detects alpha1 and not alpha7 nAChR.

In the end, all their purported alpha7 nAChR Western blotting research in the brain is seemingly undoable. Furthermore, they didn't even use an alpha7 nAChR antibody in one of their most important foundational studies.

Cassava Scientists Report Highly Improbable Clinical Trial Results

In our September 9th supplement, we noted that three of the ten the biomarkers analyzed by Dr. Wang and presented by Cassava in the phase 2b study of simufilam in Alzheimer's disease had baseline values so far outside expectations that they suggest lab errors or manipulation. On September 11th, William Hu, M.D., Ph.D., a prominent neurologist at University of Rutgers posted on Twitter (https://twitter.com/williamhu43/status/1436651705530204161) that he agreed with our concerns. Subsequently, we found that at least three of the nine biomarkers analyzed by Dr. Wang and published by Cassava for the phase 2a study of simufilam in Alzheimer's disease also appear to have wildly anomalous baseline measures. As shown below, CSF levels of pTau-181 are far lower, whereas CSF levels of TNF-α and IL-1β are far higher, than in other biomarker studies of Alzheimer's disease patients. All references will be provided upon request.



These apparent biomarker discrepancies are so extreme that they suggest lab errors or manipulation. It is worth noting that Cassava's publication of these suspicious phase 2a biomarker data occurred in a paper (JPAD 2020 **4**:256) that was accepted just 6 days after submission, which calls into question the credibility and rigor of that journal's peer review process.

Simufilam's Reported Effects on Cognition in Alzheimer's Patients Show Signs of "Cherry Picking"

In their phase 2b open label study of simufilam in Alzheimer's disease, Cassava claims improvement in patient's cognition. Careful evaluation of patient baseline cognition scores shows peculiarities that raise significant concerns about their interpretation of the data. Critical analyses of these results are posted on Twitter (e.g., https://twitter.com/PatricioMarceso/status/1439616367372685313), and we incorporate aspects of those analyses below.

In Cassava's phase 2b study, patients are assessed with ADAS-Cog 11 repeatedly: at baseline, after six months, after nine months, and after 12 months. Although the study aims to enroll 200 patients, ADAS-Cog 11 scores for only "the first 50 patients" have been reported for each of the time points. The following paragraphs all refer to these data for "the first 50 patients":

On February 2, 2021, the company issued a press release announcing that at 6 months ADAS-Cog 11 scores had improved 10%, dropping on average 1.6 points from a reported mean baseline score of 15.5. Thus, the actual observed mean score at 6 months was 13.9. See: https://www.cassavasciences.com/news-releases/news-release-details/cassava-sciences-simufilam-improves-cognition-and-behavior

On July 29, 2021, the company presented the 9-month interim results at the Alzheimer's Association International Conference 2021. Here, the reported ADAS-Cog 11 mean baseline in the "first 50 patients" was 16.6, with an observed mean improvement of 18% or 3.0 points, so the actual observed mean score at 9 months was 13.6. In this same presentation the company stated that the dropout rate was *less than* 10%. See: https://www.cassavasciences.com/static-files/13794384-53b3-452c-ae6c-7a09828ad389

There are two red flags with these reported data. First, the observed mean ADAS-Cog 11 scores after 6 and 9 months are virtually the same (13.9 vs. 13.6, respectively), so the data do not appear to demonstrate a continued improvement. Second, the baseline data between the 6-month and 9-month analyses change substantially, and to a degree that seems inconsistent with other information provided by the company, suggesting possible manipulation. Specifically, Cassava reported 9-month baseline of 16.6 compared to the reported 6-month baseline of 15.5. However, since the company reported that *less than* 10% of patients dropped out, a maximum of 4 patients should have dropped out between 6 months and 9 months and replaced by 4 new patients in the 9-month analysis of the "first 50 patients." If this is true, those 4 new patients would have had an average baseline score that was 13.75 points *higher* than that of those patients who dropped out, as can easily be calculated: ((50x16.6)-(50x15.5))/4=13.75. Compared to the reported baseline standard deviation of 7.7 points (representing the average deviation of each individual score from the overall mean), and the observed improvement of 3 points, a 13.75 differential in the baseline score is unexpectedly large. Thus, the 4 added patients would have had an average baseline score of 15.5+13.75=29.25. Since the ADAS-Cog shows differential sensitivity for patients with mild vs. moderate AD, this baseline issue becomes even more problematical.

Considering these baseline changes and the uncertainty regarding the process of determining dropout subjects, the presented results become inconclusive, as they could easily be explained by regression to the mean (patients who by chance exhibit "extreme" scores the first time tend to have more "normal" scores the second time) or similar mechanisms.

Additional Red Flags Discovered by the Scientific Community

Since the filing of the Citizen's Petition, publicly and privately, the scientific community has validated many of my clients' concerns and identified countless new errors and anomalies that are consistent with scientific misconduct in Cassava Sciences' reports about both preclinical and clinical data. Less than 90 days ago, when our initial Citizen's Petition filing first identified potential image manipulation in papers authored by Dr. Wang, the scientific community began a comprehensive review of Dr. Wang's research and 29 papers have already been red flagged on Pubpeer.com. Nine of these flagged papers are co-authored by Dr. Lindsay Burns, Cassava's SVP of Neuroscience (and Cassava CEO's wife), and three are co-authored by Dr. Steven E. Arnold, a member of Cassava's Scientific Advisory Board. Many of these papers were questioned by Dr. Elisabeth Bik, a renowned expert in scientific integrity and image forensics, who my clients do not personally know, who my clients have not engaged with, and who has not contributed to any of their Citizen's Petitions.

What follows are some of the challenged papers not discussed in our previous FDA filings. They are noteworthy for their number, similarity of issues, and consistency over more than 20 years**.** The nature and extent of these anomalies strongly suggest systematic data manipulation and misrepresentation because they frequently favor the authors' hypotheses and are outside of the scientific norm.

Cassava/PTI Related:

1. PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients.

   Wang HY, Pei Z, Lee KC, Lopez-Brignoni E, Nikolov B, Crowley CA, Marsman MR, Barbier R, Friedmann N, Burns LH. J Prev Alzheimers Dis. 2020;7(4):256-264. doi: 10.14283/jpad.2020.6. PMID: 32920628
   https://pubpeer.com/publications/A8DD7059A8A7F13D4899049A83F61E

   Concerns about image manipulation of western blots and clinical biomarker values.

2. Naloxone's pentapeptide binding site on filamin A blocks Mu opioid receptor-Gs coupling and CREB activation of acute morphine.

   Wang HY, Burns LH. PLoS One. 2009;4(1):e4282. doi: 10.1371/journal.pone.0004282. Epub 2009 Jan 27. PMID: 19172190
   https://pubpeer.com/publications/FFE5E8F7E73D0ECA931EEF424B9E70

   Concerns about image manipulation of western blots.

3. Oxycodone plus ultra-low-dose naltrexone attenuates neuropathic pain and associated mu-opioid receptor-Gs coupling.

   Largent-Milnes TM, Guo W, Wang HY, Burns LH, Vanderah TW. J Pain. 2008 Aug;9(8):700-13. doi: 10.1016/j.jpain.2008.03.005. Epub 2008 May 12. PMID: 18468954
   https://pubpeer.com/publications/F4F044BFB08C2F509B7FAD79D66D96

   Concerns about image manipulation of western blots.

Wang Related:

1. Prenatal cocaine reduces AMPA receptor synaptic expression through hyperphosphorylation of the synaptic anchoring protein GRIP.

   Kalindi Bakshi, Serena Gennaro, Christopher Y Chan, Mary Kosciuk, Jingjing Liu, Andres Stucky, Ekkehart Trenkner, Eitan Friedman, Robert G Nagele, Hoau-Yan Wang. J Neurosci. 2009 May 13;29(19):6308-19. doi: 10.1523/JNEUROSCI.5485-08.2009. PMID: 19439608
   https://pubpeer.com/publications/CC864761DDB5944F85280C42B86BB6

   Concerns about image manipulation of western blots.

2. Repetitive transcranial magnetic stimulation enhances BDNF-TrkB signaling in both brain and lymphocyte.

   Hoau-Yan Wang, Domenica Crupi, Jingjing Liu, Andres Stucky, Giuseppe Cruciata, Alessandro Di Rocco, Eitan Friedman, Angelo Quartarone, M Felice Ghilardi. The J Neurosci. 2011 Jul 27;31(30):11044-54. doi: 10.1523/JNEUROSCI.2125-11.2011.
   https://pubpeer.com/publications/80954A76304E165873FDC462B6F64B

   Concerns about image manipulation of western blots.

3. Oxycodone Plus Ultra-Low-Dose Naltrexone Attenuates Neuropathic Pain and Associated μ-Opioid Receptor–Gs Coupling

   Tally M. Largent-Milnes, Wenhong Guo, Hoau-Yan Wang, Lindsay H. Burns, Todd W. Vanderah. J Pain. 2008 Aug;9(8):700-13. doi: 10.1016/j.jpain.2008.03.005. Epub 2008 May 12
   https://pubpeer.com/publications/F4F044BFB08C2F509B7FAD79D66D96

Concerns about image manipulation of western blots.

4. Dissociating beta-amyloid from alpha 7 nicotinic acetylcholine receptor by a novel therapeutic agent, S 24795, normalizes alpha 7 nicotinic acetylcholine and NMDA receptor function in Alzheimer's disease brain

   Hoau-Yan Wang, Andres Stucky, JingJing Liu, Changpeng Shen, Caryn Trocme-Thibierge, Philippe Morain. J Neurosci. 2009 Sep 2;29(35):10961-73. doi: 10.1523/JNEUROSCI.6088-08.2009.
   https://pubpeer.com/publications/F30562EB414EB792A9474E55318F0B

   Concerns about image manipulation of western blots.

5. Stress Diminishes BDNF-stimulated TrkB Signaling, TrkB-NMDA Receptor Linkage and Neuronal Activity in the Rat Brain

   Siobhan Robinson, Allison S. Mogul, Elisa M. Taylor-Yeremeeva, Amber Khan, Anthony D. Tirabassi, Hoau-Yan Wang. Neuroscience. 2021 Oct 1;473:142-158. doi: 10.1016/j.neuroscience.2021.07.011. Epub 2021 Jul 21.
   https://pubpeer.com/publications/C40B664B5CE4DB0328C38182C8B73C

   Concerns about image manipulation of western blots.

6. In utero cocaine-induced dysfunction of dopamine D1 receptor signaling and abnormal differentiation of cerebral cortical neurons

   Liesl B. Jones, Gregg D. Stanwood, Blesilda S. Reinoso, Ricardo A. Washington, Hoau-Yan Wang, Eitan Friedman, Pat Levitt. J Neurosci. 2000 Jun 15;20(12):4606-14. doi: 10.1523/JNEUROSCI.20-12-04606.2000.
   https://pubpeer.com/publications/75D810A0EF29F6E90CEF804E49ADA0

   Concerns about image manipulation of western blots.

7. Stimulated D(1) dopamine receptors couple to multiple Galpha proteins in different brain regions

   Li-Qing Jin, Hoau-Yan Wang, Eitan Friedman. J Neurochem. 2001 Sep;78(5):981-90. doi: 10.1046/j.1471-4159.2001.00470.x.

https://pubpeer.com/publications/DEB3D9A0EEB3F623BBB70F28831319

Concerns about image manipulation of western blots.

8. BDNF-trkB signaling in late life cognitive decline and Alzheimer's disease

   Hoau-Yan Wang, Andres Stucky, Chang-Gyu Hahn, Robert Wilson, David Bennett, Steven Arnold. Translational Neuroscience (2011).
   doi: 10.2478/s13380-011-0015-4 issn: 2081-6936 issn: 2081-3856
   https://pubpeer.com/publications/6B61CC848B6177E3A1A957F063AEA6

   Concerns about image manipulation of western blots.

9. Gbetagamma that interacts with adenylyl cyclase in opioid tolerance originates from a Gs protein

   Hoau-Yan Wang, Lindsay H. Burns. J Neurobiol. 2006 Oct;66(12):1302-10. doi: 10.1002/neu.20286.
   https://pubpeer.com/publications/0E9795FA0A219C48F2E432F31A7DB9

   Concerns about image manipulation of western blots.

10. mGluR5 hypofunction is integral to glutamatergic dysregulation in schizophrenia

    Hoau-Yan Wang, Mathew L. MacDonald, Karin E. Borgmann-Winter, Anamika Banerjee, Patrick Sleiman, Andrew Tom, Amber Khan, Kuo-Chieh Lee, Panos Roussos, Steven J. Siegel, Scott E. Hemby, Warren B. Bilker, Raquel E. Gur, Chang-Gyu Hahn. Mol Psychiatry. 2020 Apr;25(4):750-760. doi: 10.1038/s41380-018-0234-y. Epub 2018 Sep 13.
    https://pubpeer.com/publications/17ADBE932E6F89CD4A4017FD154DC3

    Concerns about image manipulation of western blots.

11. Increased Aβ42-α7-like nicotinic acetylcholine receptor complex level in lymphocytes is associated with apolipoprotein E4-driven Alzheimer's disease pathogenesis

    Hoau-Yan Wang, Caryn Trocmé-Thibierge, Andres Stucky, Sanket M. Shah, Jessica Kvasic, Amber Khan, Philippe Morain, Isabelle Guignot, Eva Bouguen, Karine Deschet, Maria Pueyo, Elisabeth Mocaer, Pierre-Jean Ousset, Bruno Vellas, Vera Kiyasova. Alzheimers Res Ther . 2017 Jul 27;9(1):54. doi: 10.1186/s13195-017-0280-8.

https://pubpeer.com/publications/B8A32AD7E71A128B6897D4315AC065

Concerns about image manipulation of western blots.

12. Altered neuregulin 1–erbB4 signaling contributes to NMDA> receptor hypofunction in schizophrenia

    Chang-Gyu Hahn, Hoau-Yan Wang, Dan-Sung Cho, Konrad Talbot, Raquel E Gur, Wade H Berrettini, Kalindi Bakshi, Joshua Kamins, Karin E Borgmann-Winter, Steven J Siegel, Robert J Gallop, Steven E Arnold. Nat Med. 2006 Jul;12(7):824-8. doi: 10.1038/nm1418. Epub 2006 Jun 11.
    https://pubpeer.com/publications/0F12807ED2839C13DB8234B913B0D0

    Concerns about image manipulation of western blots.

13. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline

    Konrad Talbot, Hoau-Yan Wang, Hala Kazi, Li-Ying Han, Kalindi P. Bakshi, Andres Stucky, Robert L. Fuino, Krista R. Kawaguchi, Andrew J. Samoyedny, Robert S. Wilson, Zoe Arvanitakis, Julie A. Schneider, Bryan A. Wolf, David A. Bennett, John Q. Trojanowski, Steven E. Arnold. J Clin Invest. 2012 Apr;122(4):1316-38. doi: 10.1172/JCI59903.
    https://pubpeer.com/publications/603286311C3DC6766716B01565CA72

    Concerns about image manipulation of western blots.

14. Alpha 7 nicotinic acetylcholine receptors mediate beta-amyloid peptide-induced tau protein phosphorylation

    Hoau-Yan Wang, Weiwei Li, Nancy J. Benedetti, Daniel H.S. Lee. J Biol Chem. 2003 Aug 22;278(34):31547-53. doi: 10.1074/jbc.M212532200. Epub 2003 Jun 11.
    https://pubpeer.com/publications/C8AF3ABCCD9DDD8AE61C7D0F18A648

    Concerns about image manipulation of western blots.

15. Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling

    Andres Stucky, Kalindi P. Bakshi, Eitan Friedman, Hoau-Yan Wang. PLoS One . 2016 Aug 5;11(8):e0160585. doi: 10.1371/journal.pone.0160585. eCollection 2016.

https://pubpeer.com/publications/6440159132C1DBC81AFA2DD7584526

Concerns about image manipulation of western blots.

16. Calcium-dependent cytosolic phospholipase A activation is implicated in neuroinflammation and oxidative stress associated with ApoE4

    Shaowei Wang, Boyang Li, Victoria Solomon, Alfred Fonteh, Stanley I. Rapoport, David A. Bennett, Zoe Arvanitakis, Helena C. Chui, Carol Miller, Patrick M. Sullivan, Hoau-Yan Wang, Hussein N. Yassine. Mol Neurodegener. 2021 Apr 16;16(1):26. doi: 10.1186/s13024-021-00438-3.
    https://pubpeer.com/publications/7F7FDCB04BEF64E1AF1695586A2CCB

    Concerns about image manipulation of western blots.

17. Insulin and adipokine signaling and their cross-regulation in postmortem human brain

    Hoau-Yan Wang, Ana W. Capuano, Amber Khan, Zhe Pei, Kuo-Chieh Lee, David A. Bennett, Rexford S. Ahima, Steven E. Arnold, Zoe Arvanitakis. Neurobiol Aging. 2019 Dec;84:119-130. doi: 10.1016/j.neurobiolaging.2019.08.012. Epub 2019 Aug 20
    https://pubpeer.com/publications/5A1F84E296C09EDB963B81808B6651

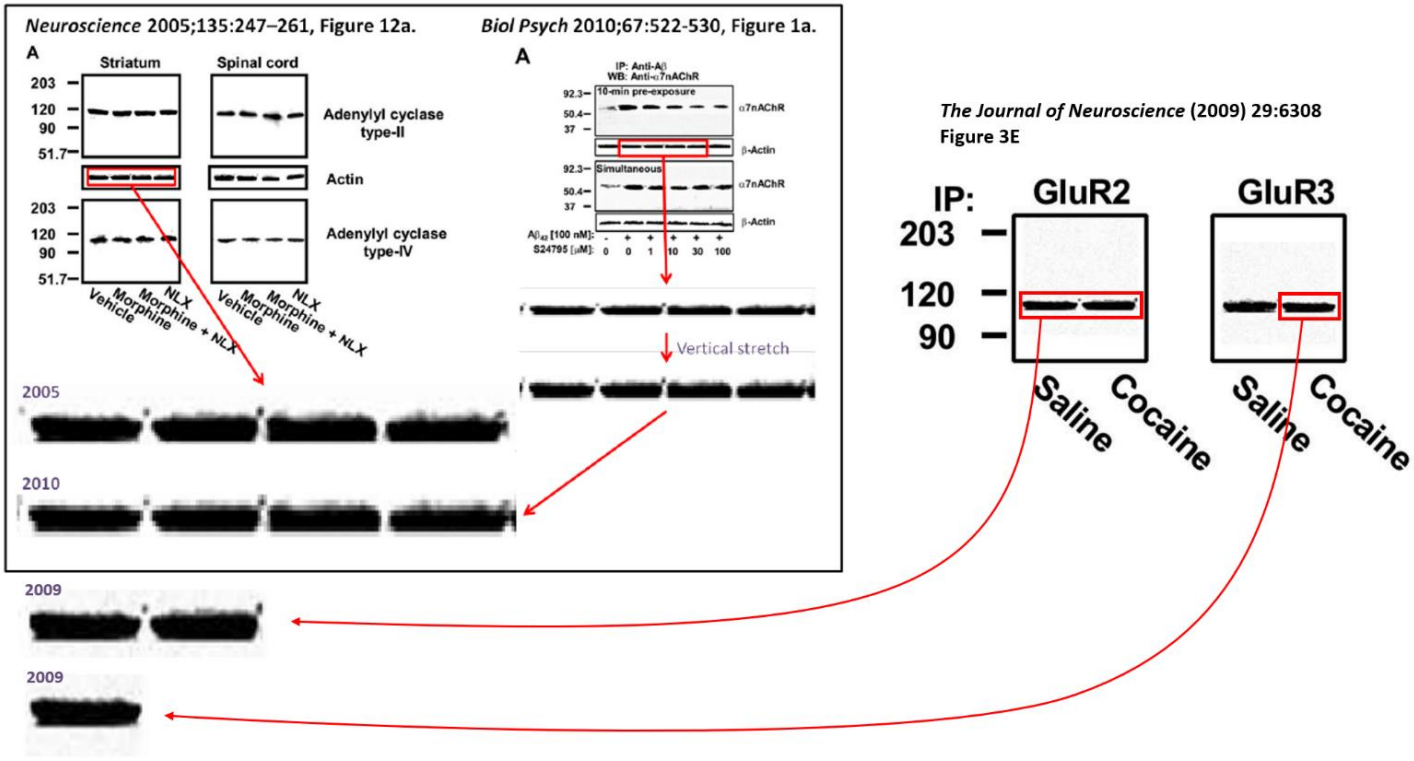
    Concerns about image manipulation of western blots.

Recent Expression of Editorial Concern

Following the many red flags raised about data in papers authored by Drs. Wang and Burns, a recent and highly notable development is the editorial expression of concern issued by the Editor in Chief of Neuroscience, the IBRO Journal, concerning a 2005 Wang/Burns/Cassava paper, *Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbeta-gamma signaling*, H.-Y. Wang, E. Friedman, M.C. Olmstead, L.H. Burns Neuroscience (2005). The editor's note (first published: https://twitter.com/ClicksAndHisses/status/1460680955702562818), explains that the Expression of Concern arises from "…the apparent duplication and insertion of spurious bands in Western Blots that raise suspicions that some data have been fabricated. Upon request to the authors, no evidence has so far been submitted to the journal to ensure that these bands are authentic, instead the author informed us that this and other issues are currently under investigation by the academic authorities at the City University of New York (CUNY). The Editor in Chief and Publisher await the outcome of that investigation before taking further action."

As shown in the Figure below, this article contains images that were apparently duplicated and "reused" to represent three entirely different proteins, in three entirely different experiments, in three entirely different publications, including the 2005 Neuroscience, 2009 Journal of Neuroscience, and 2010 Biological Psychiatry papers. These concerns have been documented on PubPeer, at the following links:

https://pubpeer.com/publications/CD34FCE900CAA9CC35B5E4190DCBE5
https://pubpeer.com/publications/CC864761DDB5944F85280C42B86BB6
https://pubpeer.com/publications/CD34FCE900CAA9CC35B5E4190DCBE5



This seemingly irrefutable data manipulation is important both because it implies a pattern of reckless scientific misconduct and because it undercuts foundational science related to simufilam mechanism of action in Alzheimer's disease. The 2005 Neuroscience paper describes a molecular signaling pathway associated with ultra-low dose naloxone that Drs. Wang and Burns later allege involves a high affinity binding site on filamin A that also binds to simufilam. The 2010 paper

describes a cascade of Abeta42 binding to the alpha7 nAChR that somehow leads to tau phosphorylation, which is the pathway that they have touted is interrupted by simufilam. If data in Cassava Sciences' foundational papers are fabricated (a concern expressly raised by the Neuroscience Editor in Chief), the scientific rationale for simufilam and the credibility of red-flagged research from Drs. Wang and Burns are lost.

Whereas, Cassava has misleadingly suggested that a recent audit by the Journal of Neuroscience exonerated the company, this new editorial expression of concern is yet another reason that the Journal of Neuroscience editors will likely reevaluate their assessment and correct their previous statement. Moreover, this expression of concern by the Neuroscience Editor in Chief is likely the first domino in a long line to fall. Elsevier is a leading scientific publishing company, owning 2650 different journals. As listed below, in addition to the 2005 Neurobiology paper already subject to this expression of concern, Dr. Wang has seven additional Elsevier published papers that have been flagged on PubPeer, including two others associated with Cassava Sciences research that were co-authored with Dr. Burns (most notably the 2017 Neurobiology of Aging article that claimed to support the effectiveness of simufilam):

1. S 24795 limits beta-amyloid-alpha7 nicotinic receptor interaction and reduces Alzheimer's disease-like pathologies

   Hoau-Yan Wang, Kalindi Bakshi, Changpeng Shen, Maya Frankfurt, Caryn Trocmé-Thibierge, Philippe Morain. Biol Psychiatry. 2010 Mar 15;67(6):522-30. doi: 10.1016/j.biopsych.2009.09.031
   https://pubpeer.com/publications/CD34FCE900CAA9CC35B5E4190DCBE5#5

2. Oxycodone plus ultra-low-dose naltrexone attenuates neuropathic pain and associated mu-opioid receptor-Gs coupling.

   Largent-Milnes TM, Guo W, Wang HY, Burns LH, Vanderah TW. J Pain. 2008 Aug;9(8):700-13. doi: 10.1016/j.jpain.2008.03.005. Epub 2008 May 12. PMID: 18468954
   https://pubpeer.com/publications/F4F044BFB08C2F509B7FAD79D66D96

3. Stress Diminishes BDNF-stimulated TrkB Signaling, TrkB-NMDA Receptor Linkage and Neuronal Activity in the Rat Brain

   Siobhan Robinson, Allison S. Mogul, Elisa M. Taylor-Yeremeeva, Amber Khan, Anthony D. Tirabassi, Hoau-Yan Wang. Neuroscience. 2021 Oct 1;473:142-158. doi: 10.1016/j.neuroscience.2021.07.011. Epub 2021 Jul 21.
   https://pubpeer.com/publications/C40B664B5CE4DB0328C38182C8B73C

4. A model of negative emotional contagion between male-female rat dyads: Effects of voluntary exercise on stress-induced behavior and BDNF-TrkB signaling

   Gavin M. Meade, Lily S. Charron, Lantz W. Kilburn, Zhe Pei, Hoau-Yan Wang, Siobhan Robinson. Physiol Behav. 2021 May 15;234:113286. doi: 10.1016/j.physbeh.2020.113286. https://pubpeer.com/publications/DBE94DCFD3B1DFA8DA0D3337C4AD35#2

5. PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis

   Hoau-Yan Wang, Kuo-Chieh Lee, Zhe Pei, Amber Khan, Kalindi Bakshi, Lindsay H. Burns. Neurobiol Aging. 2017 Jul;55:99-114. doi: 10.1016/j.neurobiolaging.2017.03.016. https://pubpeer.com/publications/80DD10169D3C375C5828BC2711A49B#8

6. Insulin and adipokine signaling and their cross-regulation in postmortem human brain

   Hoau-Yan Wang, Ana W. Capuano, Amber Khan, Zhe Pei, Kuo-Chieh Lee, David A. Bennett, Rexford S. Ahima, Steven E. Arnold, Zoe Arvanitakis. Neurobiol Aging. 2019 Dec;84:119-130. doi: 10.1016/j.neurobiolaging.2019.08.012. https://pubpeer.com/publications/5A1F84E296C09EDB963B81808B6651

7. Astrocytes accumulate A beta 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains

   Robert G. Nagele, Michael R. D'Andrea, H. Lee, Venkateswar Venkataraman, Hoau-Yan Wang. Brain Res. 2003 May 9;971(2):197-209. doi: 10.1016/s0006-8993(03)02361-8. https://pubpeer.com/publications/8D6FD5A8BE34C38AAC2BB7CA035675#1

In conclusion, if contacted by law enforcement or regulatory authorities, we are confident that Elsevier Publishing will confirm that its editors have other open investigations or referrals to CUNY about Cassava Sciences and Drs. Wang and Burns' research. And, this is very likely to be just the first of many journals that issue expressions of concern and later retract papers from Wang/Burns/Cassava.

False and/or Misleading Press Release

Like Tesla and Elon Musk's use of Twitter, Cassava Sciences and Remi Barbier regularly get into trouble with their press releases. As illustrated by their 9/14/20 press release that falsely claimed

that a different academic lab conducted the redo (and increased the company's share price by 133.4%), or the misleading 8/26/21 press release in which the company tried to use Quanterix as an alibi for its alleged misconduct, they tend to make misleading statements in an effort to exonerate themselves or boost the company's flagging share price. Another recent and powerful example of this is Cassava's 11/4/21 press release.

In a sensational move worthy of PT Barnum, Cassava Science halted its stock during early trading on 11/4/21. As you may know, trading halts are temporary suspensions for a particular security at one or more exchanges. They are unusual events, typically used in advance of highly significant news about a company or to correct an order imbalance in the market [https://www.investopedia.com/terms/t/tradinghalt.asp]. Due to dark clouds over the company since the Citizen's Petition was filed, market participants anticipated a regulatory development.

Having fully captured the attention of the market and business media outlets, Cassava released a press release entitled "Review by Journal of Neuroscience Shows No Evidence of Data Manipulation in Technical Paper Foundational to Cassava Sciences' Lead Drug Candidate" [https://www.cassavasciences.com/news-releases/news-release-details/review-journal-neuroscience-shows-no-evidence-data-manipulation]. The release references an article co-authored by Dr. Wang and Dr. Burns in the July 2012 issue of the Journal of Neuroscience. The company touted the article as being foundational to simufilam. It also included an authorized statement from the Journal of Neuroscience which purportedly notes that "…there was one duplicated panel in Figure 8 and a Corrigendum was requested and will be printed. No evidence of data manipulation was found for Western blot data." Seizing on this, Cassava's CEO, Remi Barbier, suggested that the company and its scientists (i.e., Drs. Wang and Burns) have been exonerated and Mr. Barbier is quoted as saying "I never doubted the integrity of our people or science" and "notwithstanding pundits who may be louder than they are learned. We will stay the course until our job is done." Further, the release states "One human error that does not impact data conclusions was identified [sic] (a duplicated panel in Figure 8B of the article), and the publisher is expected to print a correction." In response to these statements, the company's stock price increased by almost 100% [https://www.google.com/search?q=cassava+sciences+stock+price&oq=&aqs=chrome.0.35i39i362l8...8.267288510j0j15&sourceid=chrome&ie=UTF-8].

Based on a closer review of Cassava's press release, we suggest that it contains material misrepresentations or omissions. As a preliminary matter, if contacted by law enforcement or regulatory authorities, we are confident that the editors of the Journal of Neuroscience will state that the authorized statement did not constitute an endorsement or exoneration of any kind. As for the journal's purported statement "no evidence of data manipulation was found for Western blot data," we suspect that the editors will acknowledge that they only conducted a limited review, and that the statement means that they were unable to decide because the original data were not available or

there was insufficient evidence to make that damning charge. Furthermore, and more significantly, we also believe that the editors will confirm that the Journal of Neuroscience has other open investigations or referrals to CUNY about Cassava Sciences and Drs. Wang and Burns' research—including the July 2012 article heavily touted by the company in its press release.

Nevertheless, Cassava dramatically suggested to the market that they had been exonerated—without qualification. The company failed to disclose to the market the limited scope of the Journal of Neuroscience's review. Furthermore, at the time of the press release, Cassava knew that more than 25 papers written by Dr. Wang (several of which were co-authored with Dr. Burns, a Cassava employee) had been identified by the scientific community as having possible scientific misconduct, including image manipulation, and that the relevant journals are currently investigating many of these allegations. Since Cassava Sciences and those associated with it have received requests from multiple journals and Mr. Barbier is married to the corresponding author, Dr. Burns, who is believed to have responded to some of those requests, the company knew about these problems. But it failed to even mention this avalanche of ongoing reviews, including those in which the company or the journal appear to have found irregularities. The failure to disclose these other material matters, at the same time the company was dramatically suggesting exoneration from claims of data manipulation by the Journal of Neuroscience based on a single incomplete review, was highly misleading to investors and to regulators.

Use of Doctored Images to Secure Journal of Neuroscience's Exculpatory Statement

On November 10, 2021, the Journal of Neuroscience issued an erratum (https://www.jneurosci.org/content/early/2021/11/10/JNEUROSCI.2154-21.2021) to the 2012 publication authored by Drs. Wang, Burns, et al. Because the erratum seemed so obviously inadequate and suggestive of foul play, Dr. Elisabeth Bik and others raised public concerns within hours of issuance.

The red flags included, but were not limited to:

- The erratum addresses concerns with images in Figures 6A, 6B, and 9A. The erratum does not address other Figures (e.g., Fig 1, Fig 2, Fig 5, Fig 10, and Fig 11) that have also been noted for apparent data manipulation.

- The erratum does not address other concerns about the publication that we raised in our first petition, such as the methodology for the brain tissue "re-animation" experiments.

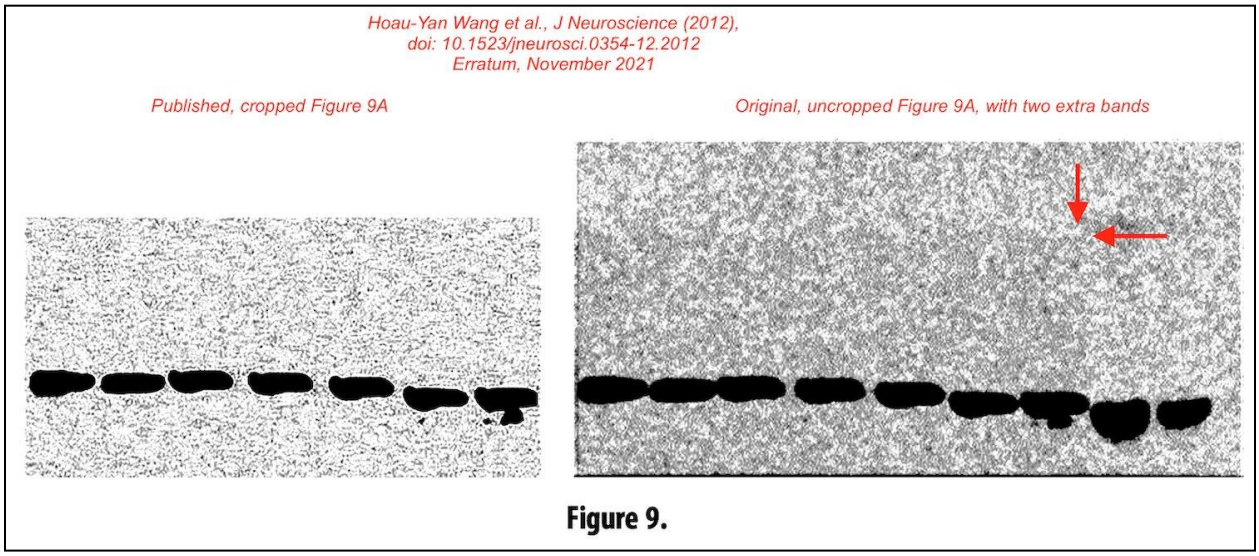
- The images supplied as "originals" do not show the edges of the x-ray film from which they were said to have been obtained. Thus, they are not the "complete" original images, if originals at all.

- The images supplied as "originals" do not show molecular weight markers. Molecular weight markers are standard proteins that are always run in one lane of the gel so that the relative position of the bands-of-interest can be sized. Since no molecular weight markers were shown, the images supplied as "originals" appear to be, at best, cropped versions.

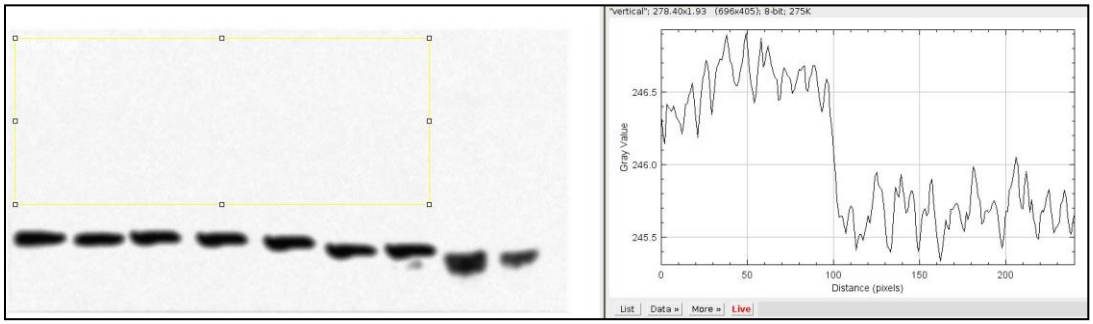
- The published erratum reports that for Fig. 9A, "The left image is the higher-resolution image with the additional bands cropped out, as seen in the full image on the right." The supplied "original" images are of lower resolution than the images published in the 2012 paper. Resolution of the original should be higher, not lower, than subsequent ones.

- Several forensic analyses suggest that the suppled "original" images are composites of cropped images, and thus not original.

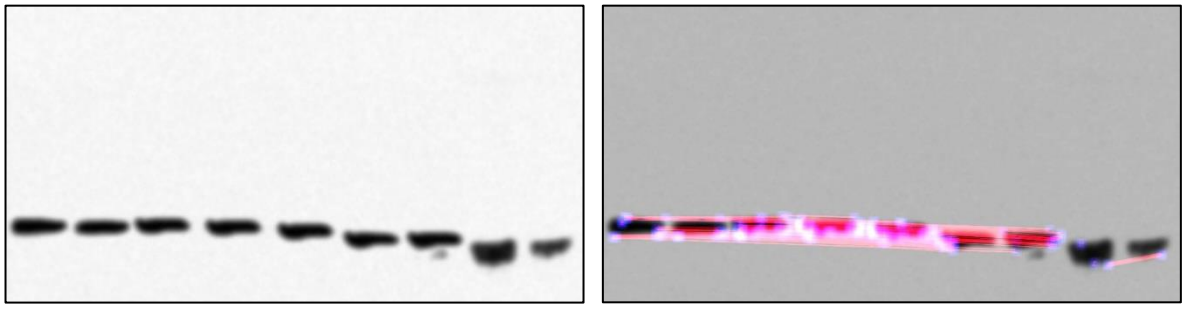
    1. Dr. Bik simply adjusted the contrast on the "original" image, which reveals an alteration in the background (see below). She states "There is a potential big concern in the provided original β-actin blot for Figure 9A. The authors/journal say the blot on the right shows the original blot with two additional lanes on the right. But I see a box around those lanes that matches the published blot's size." (https://twitter.com/MicrobiomDigest/status/1458570137670328322). She also posted these concerns on PubPeer (see comment #16 on https://pubpeer.com/publications/F91E0D22B887598445BB1F908393EE).



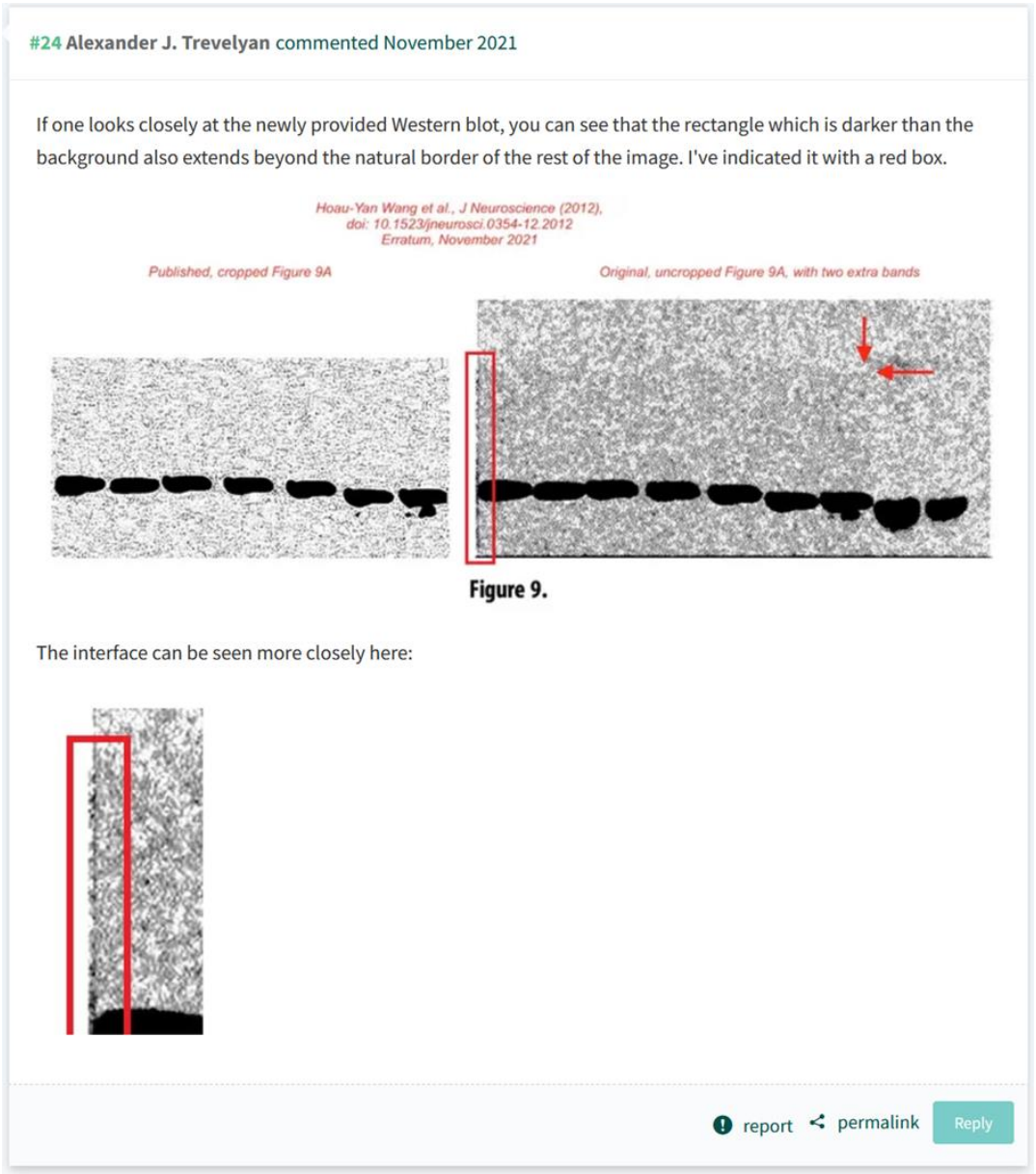
2. Dr. Adrian Helibut states: "Similar sharp difference in the mean background level with a "vertical profile" going from top down into the "original" image. 100% faked." He shows this additional analysis:



3. Adam Tywonia on Twitter (https://twitter.com/AdamTywoniak/status/1458524826428182544) used an image forensic program (Clone Detection in Forensically) to analyze the image. Areas of pink identified in the program suggest band duplication. The resulting image, and the "original," are shown below:



4. Alexander Trevelyan supplemented Dr. Bik's analysis on PubPeer https://pubpeer.com/publications/F91E0D22B887598445BB1F908393EE, showing an unexpected partial "edge" on the left side of the figure:



#24 **Alexander J. Trevelyan** commented November 2021

If one looks closely at the newly provided Western blot, you can see that the rectangle which is darker than the background also extends beyond the natural border of the rest of the image. I've indicated it with a red box.

Hoau-Yan Wang et al., J Neuroscience (2012), doi: 10.1523/jneurosci.0354-12.2012 Erratum, November 2021

Published, cropped Figure 9A *Original, uncropped Figure 9A, with two extra bands*

Figure 9.

The interface can be seen more closely here:

report permalink Reply

The bottom line is Cassava Sciences does not appear to have provided the Journal of Neuroscience "original, uncropped Western blots" as represented in its 11/4/2021 press release, so the journal could not have exonerated them, as they so dramatically suggested. Making matters far worse, the company appears to have knowingly taken the published image (the one on the left above), blurred it a bit, and then photoshopped it onto a slightly different canvas to "create" the image on the right. Undoubtedly, these apparently deceptive acts were not disclosed to the Journal of Neuroscience, and countless investors were misled, as is evidenced by the market capitalization of Cassava Sciences almost doubling on this press release. For the foregoing reasons, we expect that the Journal of Neuroscience will conduct a second more comprehensive review of all the questioned Western blots in the 2012 paper and at least two other Dr. Wang Journal of Neuroscience papers flagged on PubPeer.

In conclusion, while you have 150 days to adjudicate the Citizen's Petition, the need for the FDA to take emergency action couldn't be more urgent. Despite countless red flags associated with the company's foundational research, Cassava Sciences has recently announced that it has commenced recruiting for a Phase 3 clinical trials of simufilam (NCT0499483), with as many as 750 vulnerable Alzheimer's Disease patients; and plans an additional Phase 3 clinical trial (NCT05026177) with as many as 1,083 vulnerable Alzheimer's Disease patients. Again, the Citizen's Petition simply requests that the agency pause any related clinical trials, until a rigorous audit of all related Cassava Sciences research and clinical trial results can be conducted. Of course, if Cassava Sciences has truly found a groundbreaking drug, after it explains the many irregularities in its research and clinical trial results, it will still have a groundbreaking drug and public confidence in the company will be restored.

As always, my clients are standing by to answer questions and assist your teams with their important work.

Respectfully submitted,

Jordan A. Thomas

Enclosure

HEALTH

SEC Investigating Cassava Sciences, Developer of Experimental Alzheimer's Drug

Cassava Sciences, one of best-performing U.S. stocks this year, denies claims that it manipulated research results

By Dave Michaels and Joseph Walker
Nov. 17, 2021 9:00 am ET

The Securities and Exchange Commission is investigating claims that Cassava Sciences Inc., SAVA 1.95% ▲ the sixth-best performing U.S. stock this year, manipulated research results of its experimental Alzheimer's drug, according to people familiar with the matter.

Cassava disclosed Monday in a securities filing that it is cooperating with government investigations, without naming any agency. Cassava said an investigation isn't a sign that wrongdoing occurred.

An SEC spokeswoman declined to comment.

The National Institutes of Health, which awarded $20 million in grants to Cassava and its academic collaborators since 2015 for drug development, is also examining the claims, according to the company's chief executive officer.

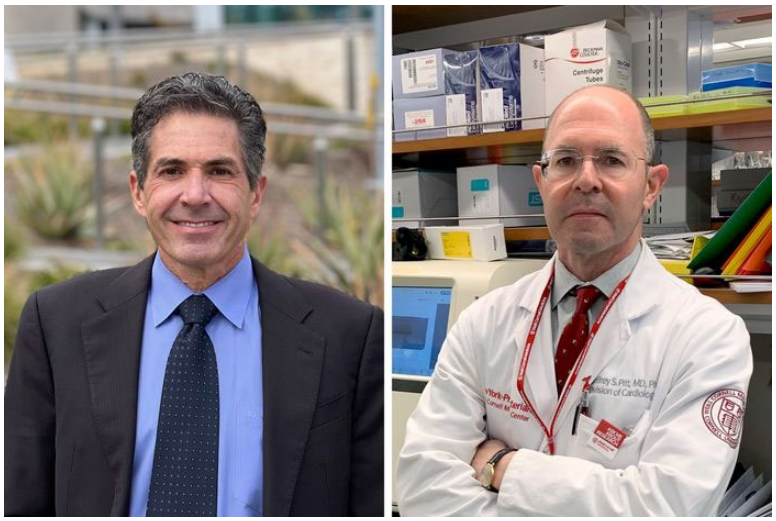
SHARE YOUR THOUGHTS

What hopes and concerns do you have about the medications to treat Alzheimer's? Join the conversation below.

The accusations appeared in a public petition filed in August to the Food and Drug Administration asking it to suspend Cassava's clinical trials. The petition's authors are two physicians who said they came to doubt Cassava's research and have shorted its stock, betting the share price would fall once investors recognized the problems they found, they said. David Bredt, a biotech entrepreneur and former neuroscience research chief at Johnson & Johnson and Eli Lilly & Co., and Geoffrey Pitt, a cardiologist and professor at Weill Cornell Medicine, wrote that Cassava's research, published in several different scientific journals, include images of experiments that appear to have been manipulated using software such as Photoshop.

Cassava Chief Executive Remi Barbier denied the doctors' claims. He said short sellers have abused the FDA's petition process, which allows people to raise public-health concerns with the government.

"There is zero evidence, zero credible evidence, zero proof that I've ever engaged in, nor anyone I know, has ever engaged in funny business," Mr. Barbier said last month. Short sellers have lodged "outlandish accusations" against his company, he wrote this week in an email response to questions. "Under these conditions you would hope that someone in a position of authority is looking into the legitimacy of the allegations," Mr. Barbier wrote.



Physicians David Bredt, at left, and Geoffrey Pitt, both of whom have short positions in Cassava's stock, co-wrote a petition alleging manipulation in three published papers on the company's Simufilam drug and asking the FDA to halt trials.

PHOTO: DAVID BREDT; GEOFFREY PITT

Cassava's experimental drug, called Simufilam, aims to restore a protein, filamin A, that its scientists say is misshaped in the brains and blood of Alzheimer's patients. In its contorted state, according to Cassava, the protein triggers a toxic process that leads to the buildup in the brain of another protein called amyloid, which is a hallmark of Alzheimer's disease.

Cassava's journal articles, all co-authored with a professor at the City University of New York School of Medicine, include pictures of experiments that support Cassava's theory for what causes Alzheimer's and how its drug addresses the culprit.

An Austin-based biotech company with 25 employees, Cassava shot from obscurity to become a favored stock among individual investors drawn by the prospects for its treatment for Alzheimer's, a form of dementia that affects six million Americans.

Its stock surged over the summer to as high as $126, when the company's market value eclipsed $5 billion, on the prospects of its drug becoming a new Alzheimer's treatment. It has no commercial drugs and hasn't reported any product revenue since 2013.

The shares fell to as low as $42 after the public petition was filed to the FDA, which posted it on a website in late August. The stock rose again in recent weeks after Cassava said that the Journal of Neuroscience, which published one of its papers, had reviewed the images and found no evidence of data manipulation. It closed at $61.69 on Tuesday.

Marina R. Picciotto, editor in chief of the Journal of Neuroscience and a professor at the Yale School of Medicine, confirmed in an email that the journal had found no proof of data manipulation in the papers after requesting the original source data from the authors. The journal did find an instance of duplicate images in the paper, Dr. Picciotto said. A correction was issued on Nov. 10, which said the error didn't affect the article's conclusions.

Several other scientists interviewed by The Wall Street Journal said some images in the articles depicting experimental results appear to have been copied and pasted from other sources. The images show western blots, a common laboratory technique for detecting proteins in samples of tissue or blood. Samples are run through gel and then transferred to a film that displays "bands" of proteins separated by their molecular weights.

Microbiologist and image-manipulation consultant Elisabeth Bik. Ms. Bik says some of the western blot images supporting the company's experimental Alzheimer's drug appeared to be photoshopped.

PHOTO: CLARA MOKRI FOR THE WALL STREET JOURNAL

Elisabeth Bik, a microbiologist and image-manipulation consultant who has identified inappropriately duplicated images in hundreds of other scientific papers, said she concurred with many of the claims in the petition. Dr. Bik said she found other potentially manipulated images in papers describing how Simufilam works. She doesn't have a position in Cassava's stock, she said.

Mike Rossner, a former managing editor of the Journal of Cell Biology and president of Image Data Integrity Inc., a consulting firm that works with universities and other institutions to evaluate claims of image manipulation, said many of the accusations merited further investigation. He also said he had no stake in Cassava.

Mr. Barbier said the way critics have examined his company's research isn't proper. "In order to make allegations on the scale that they have, in order for those allegations to be credible, you've got to look at the originals," he said. "Blowing up western blots and, you know, looking for funny faces or funny shapes or whatever… it doesn't have legitimacy."

It is possible that Simufilam is effective against Alzheimer's disease even if the accusations of data manipulation are correct, according to Dr. Bik and other scientists. "The drug might work great," Dr. Bik said.

The doctors' petition refers to articles co-authored by Hoau-Yan Wang, a Cassava adviser and CUNY associate medical professor, and Cassava Senior Vice President Lindsay Burns. Drs. Burns and Wang, who sits on Cassava's scientific advisory board, didn't respond to calls and emails requesting comment.

The accusations have prompted inquiries by the NIH and CUNY, according to Mr. Barbier.

A CUNY spokeswoman said, "The College takes accusations of research misconduct very seriously," and would follow university rules for looking into such allegations. An NIH spokeswoman declined to comment.

An FDA spokeswoman said the agency was reviewing the doctors' petition and would respond directly to them.

The Securities and Exchange Commission is investigating claims that Cassava Sciences Inc. manipulated research results of its experimental Alzheimer's drug.

PHOTO: ARIEL ZAMBELICH/THE WALL STREET JOURNAL

Aside from any gains made from shorting the stock, Drs. Bredt and Pitt could profit from a whistleblower tip they filed with the SEC, according to their lawyer, Jordan Thomas of Labaton Sucharow LLP. The SEC enforces laws that require public companies to speak truthfully to the market and can reward people who provide credible information leading to an enforcement action.

Cassava pays Dr. Wang as a consultant, and he is eligible to receive cash bonuses tied to the growth of Cassava's market value, said Mr. Barbier. Under the bonus plan, which also applies to Cassava's officers, Mr. Barbier could receive as much as $108 million if all valuation milestones are met, according to securities filings.

Last year, Cassava said its drug had failed in a mid-stage study, causing its shares to plummet nearly 75%. Months later, the company backtracked and said the data was reanalyzed by an outside lab that found the trial had succeeded. That news caused the stock price to more than double.

Mr. Barbier said the outside lab work was done by Dr. Wang, whose role wasn't disclosed in Cassava's filings to investors. Drs. Bredt and Pitt, in their petition, said it was misleading to refer to Dr. Wang as running an "outside lab" because he is a longtime paid consultant to the company.

Mr. Barbier said he considered Dr. Wang's lab to be separate from the company because he isn't an employee.

Drs. Bredt and Pitt said they continue to hold short positions in Cassava's stock. They said they intervened because they worry that patients enrolled in Cassava's clinical trials are taking a drug whose scientific rationale is unsound.

Write to Dave Michaels at dave.michaels@wsj.com and Joseph Walker at joseph.walker@wsj.com