

From: Hoau-yan Wang
Subject: Fw: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

From: Peter Rapp <peter@nbaging.com>
Sent: Monday, November 22, 2021 7:07 PM
To: Hoau-yan Wang
Cc: Beidel, Jennifer L.
Subject: Re: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

Dear Dr. Wang:

Thank you very much for this quick reply. I look forward to resolving the issues raised.

Sincerely,
Peter R. Rapp
[Peter R. Rapp, PhD](#)
Editor-in-Chief
[Neurobiology of Aging](#)

On Mon, Nov 22, 2021 at 10:20 AM Hoau-yan Wang <hywang@med.cuny.edu> wrote:

Dear Dr. Rapp,

We will provide a full response to your inquiries as soon as possible. The primary antibody from Santa Cruz against nicotinic alpha7 receptor should be **SC-65607** as indicated below. My laboratory has never worked on alpha1 nicotinic receptors so that we do not possess and use SC-65844. We will also include this correction in our full response.

**Anti-Nicotinic Acetylcholine Receptor alpha 7/CHRNA7
Antibody (319): sc-58607**

Thank you.

Best regards,

Hoau-Yan Wang

From: Peter Rapp <peter@nbaging.com>
Sent: Sunday, November 21, 2021 5:17 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

Dr. Wang:

One additional issue needing attention in your report, the primary antibody from Santa Cruz listed in your Methods against nicotinic alpha7 receptor (i.e., SC-65844) appears to bind a different subunit, not the alpha7 subunit reportedly examined.

Again, I appreciate your attention to these matters.

Sincerely,
Peter R. Rapp
[Peter R. Rapp, PhD](#)
Editor-in-Chief
[Neurobiology of Aging](#)

On Sat, Nov 20, 2021 at 10:59 AM Peter Rapp <peter@nbaging.com> wrote:

Dear Dr. Wang:

I write regarding your article, Wang et al., (2017) PTI-125 binds and reverses an altered confirmation of filamin A to reduce Alzheimer's disease pathogenesis. *Neurobiol. Aging*, 55, 99-114, for which you serve as corresponding author. A reader has brought to our attention credible concerns that, as Editor-in-Chief of the journal, I must take seriously.

The specific substance of the concerns is copied below:

1. Figure 12:

- **All blots in this figure contain 13 bands, corresponding to the 13 different conditions indicated at the bottom. However, the NR1 normalization blot shown at the top contains only 12 bands.**
- **The right-most four bands of the NR1 blot appear to show a different background than the left lanes of that blot**
- **The right-most three bands of the PLCgamma1 blot (and other blots) appear to show a different background than the left lanes of that blot**

Editor's Note: Consistent with this description, each of the 7 blots in Fig. 12 in your originally submitted manuscript (NBA 16-1080) includes two separately selectable items, one of 3 or 4 lanes on the right, and a second panel with the remaining lanes.

2. Figure 3:

- **One of the bands representing a 10-month sample, in the right blot, appears to be surrounded by a rectangle of a different background than the rest of the blot.**

3. Figure 6:

- **the same area appears to be visible both in the 6 month old HP panel as well as the 10 month old HP panel, albeit rotated and perhaps distorted.**

Please provide a full response to these complaints of figure manipulation, ideally including uncropped copies of the blots or photomicrographs used to configure Figs 3, 6, and 12. I would appreciate a response at your earliest convenience, within 30 days. Consistent with COPE guidelines, we anticipate informing the complainant regarding the response.

Please note that, in the absence of a satisfactory timely response, the journal may be obligated to pursue other corrective action.

Thank you for your attention to this important issue, and for supporting the accuracy and integrity of data published at *Neurobiology of Aging*.

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Peter R. Rapp, PhD

From: Hoau-yan Wang
To: Ana Carrillo
Subject: Re: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

From: Ana Carrillo
Sent: Wednesday, December 22, 2021 6:14 AM
To: Hoau-yan Wang
Cc: Marc Scullin
Subject: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

Dear Prof. Wang,

Good morning. I hope this email finds you in good health. This is a reminder to please certify the academic effort for the following semesters:

Fall 2020

Kindly be reminded to complete the other categories (Instruction, Departmental Administration, Other instructional activities etc..) as you see fit. Please use the link provided and be reminded to log in first for the link to work: <https://www.rfcuny.org/effortreporting/certification/>.

Emp Name	Semester Code	Project	Project Department	Project Name	Start Date	End Date	Certification Status	Grant Effort %	PI Name
Wang, Hoau-yan	FALL2020	72762-00 02	Molecular, Cellular Sciences	HYPOACTIVITY IS INTEGRAL TO GLUTAMATERGI	12/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan
Wang, Hoau-yan	FALL2020	72587-00 02	Molecular, Cellular Sciences	OPEN-LABEL EXTENSION STUDY OF PTI-125	09/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan

Happy Holidays,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

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Happy Holidays,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 11/15/2021 01:33:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Congratulations Hoau-Yan, you achieved top stats last week

ResearchGate



Your publication has a new achievement:
**Effects of simufilam on cerebrospinal fluid
biomarkers in Alzheimer's disease: A randomized
clinical trial**

[View achievement](#)

This message was sent to hywang@sci.ccny.cuny.edu by ResearchGate. To make sure you receive our updates, add ResearchGate to your address book or safe list. [See instructions](#)

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From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent time: 11/15/2021 10:51:42 AM
To: Lindsay Burns <lburns@cassavasciences.com>; Hoau-yan Wang
Cc: Weerd-Wilson, Donna (ELS-AMS) <D.Weerd-Wilson@elsevier.com>
Subject: [EXTERNAL] Suspicious figures in your Neuroscience 2005 paper

Dear Drs. Wang and Burns,

Thanks very much for your responses, Please be advised that we have requested information from Professor Wesson on the research that CUNY appears to be conducting. In the mean time, we decided to publish an expression of concern until a conclusion arises from this investigation. This is the text of the note:

Expression of concern

Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor–G protein coupling and Gβγ signaling

[H.-Y.Wang](#), [E.Friedman](#), [M.C. Olmstead](#), [L.H.Burns](#)

Neuroscience [Volume 135, Issue 1](#), 2005, Pages 247-261. <https://doi.org/10.1016/j.neuroscience.2005.06.003>

The Editor in Chief would like to note an expression of concern related to the above-mentioned publication, arising from the apparent duplication and insertion of spurious bands in Western Blots that raise concerns about the data in the article. Upon request to the authors, no evidence has so far been submitted to the journal to confirm 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.

I hope you understand that we must keep our readers informed of any vicissitudes that may arise from the data published in the Journal.

Best regards,

Juan

Prof. Juan Lerma
Editor-in-Chief of Neuroscience, the IBRO Journal.
[EMBO Member](#)

Instituto de Neurociencias CSIC-UMH
San Juan de Alicante, Spain

P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39



[Brain Imaging Special Issue](#)

On 30 Sep 2021, at 15:35, Lindsay Burns <lburns@cassavasciences.com> wrote:

Dear Dr. Gomez,

It is not appropriate to call these figures fraudulent before any investigation. This has been guilty until proven innocent. We have already responded to JNS with original blots (exonerating claims of fraud) and a corrected IHC figure that was human error. We are having trouble accessing files for this 16-year-old paper. Hopefully Dr. Wesson can be helpful to you.

Thank you,
Lindsay

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, September 30, 2021 8:09 AM
To: Juan Lerma Gomez <jlerma.nsc@umh.es>
Cc: Lindsay Burns <lburns@cassavasciences.com>
Subject: Re: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. Gomez,

Sorry for my late reply. Please contact Dr. Rosemarie Wesson.

Rosemarie D. Wesson, Ph.D., P.E.
Interim Associate Provost for Research
Professor of Chemical Engineering
The Grove School of Engineering
The City College of New York

Steinman Hall, Suite 152
160 Convent Avenue
New York, NY 10031

Phone: 212-650-6902
Fax: 212-650-5768
Email: rwesson@ccny.cuny.edu

Thank you.

Sincerely,

Hoau-Yan Wang

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Monday, September 27, 2021 9:01 AM
To: Lindsay Burns
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

Dear Dr Burns,

Thanks very much for your email. Before making any further movement, I wonder whether you could please

provide the name of the CUNY committee and a contact person.

Thanks very much.

Best regards,

Juan

Prof. Juan Lerma

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<image001.jpg>

[Brain Imaging Special Issue](#)

On 20 Sep 2021, at 21:34, Lindsay Burns <lburns@cassavasciences.com> wrote:

Dear Dr. Gomez,

Dr. Wang has handed over all electronic files for an investigation. CUNY has committed to making their findings of this investigation public. I do not have any files from this paper that is 16 years old.

Thank you,
Lindsay Burns

Lindsay H. Burns, PhD

SVP, Neuroscience

Cassava Sciences, Inc.

O: 512-501-2484 C: 512-574-4238

www.cassavasciences.com

<image001.png>

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Monday, September 20, 2021 1:30 PM

To: Lindsay Burns <lburns@cassavasciences.com>

Subject: Fw: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

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I don't have access to anything at the moment. Can you please help with dealing with this.

Thanks.

Best,

Hoau

From: Juan Lerma Gomez <jlerma.nsc@umh.es>

Sent: Wednesday, September 15, 2021 7:35 AM

To: Hoau-yan Wang

Cc: Weerd-Wilson, Donna (ELS-AMS)

Subject: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

Dear Dr Wang,

It has been brought to our attention that several figures from your 2005 Neuroscience paper (<https://doi.org/10.1016/j.neuroscience.2005.06.003>) have problems that make some figures

fraudulent. Please see <https://pubpeer.com/publications/5E71DFFFC843817787A90968A16765> for understanding what the problems are. I have personally checked these issues and I find them reasonable source of concern so I am requesting your collaboration to clarify the situation, as the Ctte of Publication Ethics (COPE) requires.

We will wait to a maximum of 30 days for your response. I case we don't have a reasonable explanation, we will proceed to retract your paper from our Journal.

Best regards,

Juan

Prof. Juan Lerma
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Tel: +34 965919238/39

[The Neurobiology of Social and Affective Touch](#)

<PastedGraphic-5.tiff>

From: Walker, Joseph <joseph.walker@wsj.com>
Sent time: 11/16/2021 03:19:47 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

Hi, Dr. Wang,

This is Joe Walker from the Wall Street Journal. I just wanted to check back with you to see if you wanted to comment on any of the allegations made pertaining to your work. I know you haven't responded to my emails or calls in the past, but please know that I'm following up now to ensure that you know you still have an opportunity to get across your side in the story. But it will likely have to be tonight as the story could really run any time now.

In addition, we had understood that CUNY was reviewing these allegations -- do you know if that is still the case? Has the matter been resolved?

You can also reach me at 917-689-9598 if you'd like to discuss further.

Joe

On Sun, Oct 17, 2021 at 6:06 PM Walker, Joseph <joseph.walker@wsj.com> wrote:

Professor Wang,

I'm a reporter at the Wall Street Journal and I'm working on a story with my colleague Dave Michaels about the recent allegations of data manipulation and scientific misconduct made against Cassava Sciences and collaborators including yourself regarding work related to Simufilam.

The allegations were filed in a Citizen Petition in August that is posted online here <https://www.regulations.gov/docket/FDA-2021-P-0930/document>

Many of the allegations pertain to western blot images published in papers of yours.

Can you speak with us by phone to discuss the allegations? We're hoping to talk sometime this week.

Absent that, can you comment on the matter by email?

How do you respond to the allegations of cutting and pasting images in the western blots?

Are you aware of whether any institutions, such as the FDA, NIH or CUNY are investigating the allegations?

We understand that your lab has shared the raw data from the experiments with some of the journals where the papers were published? Is that accurate?

We heard from the Journal of Neuroscience that it is preparing a correction after reviewing the raw data shared by yourself and the co-authors for the 2012 paper "Reducing Amyloid-Related Alzheimer's Disease Pathogenesis by a Small Molecule Targeting Filamin A." Is this accurate? Are you aware of what the correction will say?

Are you aware of any other forthcoming corrections or retractions to your work on Simufilam or Filamin A?

Thank you for considering our request. You may reach me anytime at the number below.

Regards,

Joe

--

Joseph Walker
917-689-9598
1211 Avenue of the Americas, 5th Fl, NY, NY 10036
THE WALL STREET JOURNAL.
*IAPF Local 1096: **We Power Dow Jones.***

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To: Juan Lerma Gomez <jlerma.nsc@umh.es>; Hoau-yan Wang
Cc: Weerd-Wilson, Donna (ELS-AMS) <D.Weerd-Wilson@elsevier.com>
Subject: [EXTERNAL] RE: Suspicious figures in your Neuroscience 2005 paper
Attachments: Guidelines since 2014.docx Acta Pharmacologica Sinica.pdf JBC.pdf

Dear Juan,

Thanks for speaking with me again today. We are still looking for the original blots in backup drives, since the original hard drive melted years ago. In the meantime, attached are the guidelines that we could find about WB images in publications. These guidelines were not implemented until 2014, in response to a meeting of NIH and Science and Nature.

Here are two commentaries by another Western blot expert who does ~1000 blots per year, refuting these allegations:

<https://ad-science.org/2021/10/21/notes-from-a-molecular-biologist/>

<https://ad-science.org/2021/10/21/of-shorts-and-blots/>

This is the author, who wishes to keep his identity anonymous online, although he has said he is happy to speak with editors:

<https://www.sbpdiscovery.org/our-scientists/charles-spruck-phd>

Thanks again, and we will see if we can find and return any original blot images for you.

Lindsay

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Monday, November 15, 2021 9:52 AM
To: Lindsay Burns <lburns@cassavasciences.com>; Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Weerd-Wilson, Donna (ELS-AMS) <D.Weerd-Wilson@elsevier.com>
Subject: Suspicious figures in your Neuroscience 2005 paper

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Dear Dr. Gomez,

Sorry for my late reply. Please contact Dr. Rosemarie Wesson.

Rosemarie D. Wesson, Ph.D., P.E.
Interim Associate Provost for Research
Professor of Chemical Engineering
The Grove School of Engineering
The City College of New York

Steinman Hall, Suite 152
160 Convent Avenue
New York, NY 10031

Phone: 212-650-6902
Fax: 212-650-5768
Email: rwesson@ccny.cuny.edu

Thank you.

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<image001.jpg>
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P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39

[The Neurobiology of Social and Affective Touch](#)

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Transparency Is the Key to Quality

Amanda J. Fosang and Roger J. Colbran

A workshop held last June by the National Institutes of Health (NIH) Director's Office, Nature Publishing Group, and *Science* focused on the role that journals play in supporting scientific research that is reproducible, robust, and transparent. The "Principles and Guidelines for Reporting Preclinical Research" (<http://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research>) that emerged from the workshop have since been endorsed by nearly 80 societies, journals, and associations.

Rigorous, objective peer review was widely acknowledged as the key to publication of high quality science. The expert, dedicated members of the JBC Editorial Board provide an invaluable service to the community of JBC authors and readers by ensuring the rigor, reproducibility, and transparency of research reported in the Journal. Over the past year, the JBC Associate Editors have been working to make sure that JBC reviewing editors, and ultimately our readers, have the information they need from authors for rigorous evaluation of the scientific content of JBC manuscripts. This effort has led to extensive revisions of our Instructions for Authors (<http://www.jbc.org/site/misc/ifora.xhtml>) for reporting experimental uncertainty, animal studies, biological materials, immunoblot data, and imaging results.

The JBC has identified three major gaps in overall data reporting. We expect that filling these gaps will have an immediate impact on improving transparency in our journal. These gaps, which will be readily recognized by much of the bioscience community, include the need for (i) more complete disclosure of experimental design and reporting of experimental uncertainty and reproducibility, (ii) improved statistical and graphical presentation of quantitative data, and (iii) revised guidelines for the presentation and quantitation of immuno ("Western") blots.

Experimental Design and Reporting of Experimental Uncertainty and Reproducibility

Editors, reviewers, and the general JBC readership want to know about the reproducibility and also the variation in the observations among multiple experiments. To this end it is critically important that the number of independent biological replicates, the number of technical replicates, and the number of repeated experiments are clearly separated and specified. Surprisingly, this simple rule is often broken or misrepresented. Sometimes, the value of N is, and can only be, one. An example of this is an experiment to compare drug treatments in a line of patient-derived stem cells. Although there may be numerous technical replicates for such an experiment, and the experiment could be repeated several times, the patient is one *independent biological sample*. As another example, if six metatarsals were harvested from the front paws of a single mouse and cultured as six individual explant cultures, the number of biological replicates (again, the value of N) is equal to one, but with six technical replicates. The JBC now requires authors to include explicit information describing N and its value in the figure legends and to distinguish between the biological (independent) and technical replicates for each experiment. More uncertainty is generally seen in the former.

Statistical and Graphical Presentation of Quantitative Data

Many experiments published in the JBC yield qualitative data that are not amenable to statistical analyses, *e.g.* electrophoresis, histology, chromatography, electron microscopy. In these cases authors need to clearly indicate the number of independent replicates that the figure represents. However, when quantitative data are presented, appropriate statistical analyses to portray experimental reproducibility and support an interpretation that experimental manipulations yield significant differences are needed. The JBC encourages the use of the 95% confidence interval (CI) as error bars because they are easier to interpret; the 95% CI is defined as the interval that encompasses 95 out of 100 independent samples from a population. Use of standard deviation (S.D.) or standard error of the mean (S.E.) is also permitted. Both S.E. and CI are inferential statistics, which are used to make inferences about the data; when $N = 3$, the 95% CI is $\sim \text{mean} \pm 4 \text{ S.E.}$, but when $N \geq 10$, the 95% CI is $\sim \text{mean} \pm 2 \text{ S.E.}$

As a complementary measure to graphically improve transparency, the JBC now strongly encourages the use of scatter plots for small data sets (<30 independent samples) or box and whisker plots to compare large data sets. These plots, inclusive of appropriate error bars, provide more transparent information about the variability within the data than the ubiquitous dynamite plunger plots (bar graphs) that historically dominate scientific publications, including JBC (1). Statistical analyses of variation and precision for establishing differences between experimental groups can be reported in the same plot, preferably using the S.D. or 95% CI. The JBC now requires authors to include specific information describing experimental uncertainty and reproducibility of each data set in the figure legends.

Presentation and Quantitation of Western Blots

Western blots have become a standard technology in the tool kit of most biology or biochemistry laboratories, particularly because commercial antibodies are now available for many proteins, even those that have barely appeared in the literature. The JBC requires users of Western blot technologies to define the species of origin and source of all antibodies used, including catalogue/lot numbers, in the "Experimental Procedures" section of their manuscripts. A description of the data supporting the specificity of all antibodies is required. In cases where novel antibodies are used, we are asking authors to describe how the antibody was made, including preparation and purification of the epitope/antigen, and also to provide data validating the specificity of the antibody. As far as possible, data showing loss of immunoreactivity in samples following genetic or other molecular modifications to the antigen are a welcome addition to confirm monospecificity of the antibodies. The specificity of antibodies designed to specifically detect post-translational modifications, *e.g.* methylation, oxidation, phosphorylation, glycosylation, or neoepitopes (2), should also be validated as appropriate and be reported.

An increasing number of journals, including the JBC, do *not* allow surreptitious splicing of Western blots. If it is essential to remove lanes from an original blot for presentation purposes, then the splice positions must be clearly marked and explained in the figure legend. Of course, splicing together lanes from more than one blot is not allowed under any circumstances.

Authors should also be careful to avoid "overcropping" sections of Western blots for presentation in figures. Sufficient surrounding background regions should be retained including the positions of at least one, but preferably more, molecular weight markers above and below the band of interest.

Quantitation of Western blots is not always required but it can be fraught with traps for the unwary investigator and often sparks lively debate among scientists. It is not uncommon to "correct" Western blot signals for protein loading by normalizing to a second Western blot for a housekeeper protein, *e.g.* β -actin, α -tubulin, transferrin, GAPDH, HPRT1. The problem with this approach is that a linear relationship between signal intensity and the mass or volume of sample loaded must be confirmed for every antigen. This is further complicated by the fact that some detection methods, in particular enhanced chemiluminescence using x-ray film, have a very restricted linear range, and careful attention to the experimental conditions is necessary to ensure linearity. It is typically better to normalize Western blots using total protein loading as the denominator (3–11). To avoid potential pitfalls and with a focus on improving transparency, the JBC strongly recommends that authors describe their methods used to quantify signal intensity, how the linearity of signal intensity with antigen loading was established, and how protein loading was normalized between lanes. We prefer that signal intensities are normalized to total protein by staining membranes with Coomassie Blue, Ponceau S, or other protein stains, and we strongly caution against the use of housekeeping proteins for normalization, unless there is a clear demonstration that expression of the housekeeping protein is unaffected by the experimental treatments.

Authors should be prepared to submit raw data showing original Western blots or validating their reagents and quantitative analyses during the review of a manuscript upon request from the reviewers or an Associate Editor. JBC also reserves the right to digitally analyze all figures for undisclosed splicing of gels or other inappropriate image manipulation (<http://www.jbc.org/site/misc/ifora.xhtml#manipulation>).

It is worth reiterating a point made by other transparency advocates (12–15) that while statistics is a necessary mainstay for data interpretation by clinical researchers, psychologists, and epidemiologists, whose conclusions depend wholly on statistics, the interpretation of data in papers published in the biological sciences, including the JBC, do not always require sophisticated statistical analyses. JBC papers are selected because they provide novel and important mechanistic insights into cellular or biological processes at the molecular level. To this end, the JBC requires diligent data reporting and transparency so that readers, reviewers, and journal editors can identify sound papers with reliable data.

Acknowledgments—We acknowledge Prof. Susan Donath, University of Melbourne, Australia, and Prof. David Vaux, Walter & Eliza Hall Institute, Melbourne, Australia, for their advice and helpful discussions.

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EDITORIAL

A brief guide to good practices in pharmacological experiments: Western blotting

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Western blotting (WB) is an antibody-based experimental technique used to detect and quantify target proteins, which are often within a complex mixture extracted from cells or tissue. Although there are many new alternative technologies, such as enzyme-linked immunosorbent assay (ELISA), immunofluorescence, and mass spectrometry (MS), they all have their own limitations to some extent. ELISA lacks loading controls, immunofluorescence is an in situ technique and is semiquantitative, while MS is expensive and depends on the experimental technique and conditions. Therefore, WB remains the most commonly used methodology in the lab for protein detection. However, concerns about WB have been voiced by many scientific journals in an effort to reduce potential mistakes and increase reproducibility [1]. Here, we will focus on some essential caveats during the WB experiment. This guide, therefore, aims to provide an updated and more concise and useable reference for future experiments and paper writing.

WB includes the following steps. First, proteins are separated from the mixture by sodium dodecyl sulfate–polyacrylamide gel electrophoresis according to their molecular weights. Next, the separated proteins are transferred and bound to a solid membrane. Then, the target protein on the membrane is detected by the immunological method. The identification of a specific protein is based on two parameters: molecular weight and signal intensity. Molecular weight could be estimated by prestained molecular weight markers. The signal is determined by a secondary antibody following the addition of primary antibodies to detect the protein blotted onto the membrane.

Since WB involves multiple steps for detection of different proteins, there is no one particular set of optimal conditions suitable for all proteins. Researchers usually spend considerable time optimizing the conditions to obtain the best signal-to-noise ratios, yet difficulties persist in obtaining consistent and high-quality results. Many specific techniques used in the experiment influence the result of WB, among which the experimental controls, the characterization of antibodies, the choice of loading controls, and the image processing and presentation are the most noticeable challenges. Next, we will discuss those important aspects of WB.

Sample preparation will directly affect the quality of the results, so the choice of correct lysis buffer is a critical step. In general, lysis buffers containing nonionic detergents such as NP-40 or Triton X-100 are sufficient to release proteins from cells, while ionic detergents such as SDS and sodium deoxycholate can be considered for harsh extraction conditions. Thus, the most commonly used commercial lysis buffers are radioimmunoprecipitation assay buffer containing SDS and NP-40 buffer without SDS. In special cases, guanidine-HCl, a chaotropic agent, can be added into lysis buffer to denature oligomerized proteins into their native conformations. Moreover, proteolysis could be inhibited by protease inhibitors, such as PMSF, pepstatin, and

EDTA; and protein dephosphorylation could be prevented by phosphatase inhibitors, such as NaF and Na_3VO_4 . Thus, the appropriate commercial protease inhibitor cocktail could be used according to specific needs.

After sample lysis, the protein concentration is measured before the next procedure. Various methods for protein concentration detection can be applied, including the Bradford assay, Lowry assay, and bicinchoninic assay (BCA). The Bradford assay is based on the absorption of the dye Coomassie Blue G-250 by proteins. The principles of the Lowry assay and BCA assay are similar and rely on color development from the Biuret reaction based on the concentrations of the proteins dissolved in samples. The advantages of the Bradford assay are that it is easy and quick to perform with one reagent, while the advantages of the Lowry assay and BCA assay are their extreme sensitivity and improved compatibility with a wide range of detergents (SDS, Triton X-100, Tween 20, etc.).

It is important to set both positive and negative controls for the detected proteins to validate the WB results. Genetically modified animal tissue or cells are suggested as choices for controls. We can verify the correct molecular weight by comparing the wild-type sample with the knockout or knockdown animal or cell sample. Controls lacking the primary antibody or the blocking peptide of the antibody can verify the specificity of the antibody used in WB. Although the above-mentioned controls may not always be available for all proteins, positive and negative controls need to be included as much as possible.

The selectivity of antibodies directly affects WB results, and poor selectivity may lead to the misinterpretation of the results. There are currently databases that can be used for choosing characterized antibodies with high selectivities, such as Antibodypedia (<https://www.antibodypedia.com/>), the Human Protein Atlas (<http://www.proteinatlas.org/>), and the Antibody Registry (<https://antibodyregistry.org/>). For unvalidated antibodies, there are suggested methodologies to validate the selectivity of the antibodies [2]. These methods include detection of whether the signal is eliminated or significantly reduced after genetic knockout or knockdown of the target gene; analysis of the correlation between WB signals and signals of other detection methods (e.g., MS) in a set of different samples with variable expression of the target protein; analysis of the correlation of protein levels by using two or more independent antibodies targeting different epitopes of the same protein; expression of the target protein with a tag, and analysis of the correlation between antibody labeling and the detection of the tag. If the results are highly correlated, then the antibody is validated for WB analysis.

Usually, there are multiple secondary antibodies suitable for the subsequent detection of the target protein, and the selection can be optimized in specific experiments. When selecting a secondary antibody, both the type of primary antibody and the requirements of subsequent detection schemes should be considered comprehensively:

- (1) Species source of the primary antibody: the reactivity of the secondary antibody should be consistent with the species

source of the primary antibody used. For example, if the primary antibody is a mouse-derived monoclonal antibody, an anti-mouse secondary antibody (goat anti-mouse or rabbit anti-mouse) should be selected.

- (2) Type of primary antibody: the secondary antibody must match the class or subclass of the primary antibody. This is usually applicable for monoclonal antibodies. Polyclonal antibodies are mainly IgG immunoglobulins, so the corresponding secondary antibodies are anti-IgG antibodies. If the primary antibody is mouse IgM, then the corresponding secondary antibody should be anti-mouse IgM. If the primary monoclonal antibody is of a certain subclass of mouse IgG (IgG1, IgG2a, IgG2b, or IgG3), then almost all anti-mouse IgG can bind to it, or the secondary antibody can be selected to specifically target this subclass. If the type of the primary antibody is not clear, IgG against the corresponding species can be used.
- (3) Species source of the secondary antibody: there is usually no predictable connection between species source and the quality of the secondary antibody. However, the use of secondary antibodies from the same species as the primary antibodies should be avoided, especially in double-labeling experiments. If one of the primary antibodies is derived from goat, whereas the other is derived from mice, the corresponding secondary antibodies must be anti-goat and anti-mouse secondary antibodies, respectively. The secondary antibody cannot be derived from goat or mice.
- (4) Coupling of probes to the secondary antibody: probes coupled to secondary antibodies mainly include enzymes (such as horseradish peroxidase and alkaline phosphatase), fluorescent molecules (FITC, rhodamine, Texas Red, PE, Dylight, etc.), biotin, and gold particles. The probes can be selected according to the detection system used for WB. For WB and ELISA, the most commonly used secondary antibody is an enzyme-labeled secondary antibody, while cell or tissue labeling experiments (cellular immunocytochemistry, histoimmunocytochemistry, and flow cytometry) usually use fluorescent molecule-labeled secondary antibodies.

Another critical issue is the selection of the loading control, which has been widely used in the normalization of WB results to adjust for systematic differences between samples or even between experiments. Housekeeping proteins, such as β -actin and GAPDH, have been commonly used as loading controls. However, the expression of these proteins can change under certain conditions [3, 4]. The selected housekeeping proteins need to be proven stable under the experimental conditions. An alternative to the use of a specific protein as the loading control is the staining of total protein. Some methods used for staining of total protein on the membrane, such as Ponceau S [5] and Fast Green [6], have been found to be reliable as loading controls. Ponceau S is the most commonly used removable stain and can be conveniently used before immunodetection, but it is relatively insensitive. Fast Green is a more permanent dye used for staining in histology and electrophoresis. It cannot be easily removed and may inhibit subsequent immunodetection. Alternatively, staining with Fast Green after immunodetection has been used in some recent publications. Moreover, some housekeeping proteins are also used as markers for subcellular compartments according to their intracellular distribution [7] (Table 1).

Therefore, to achieve reproducible WB results, the following information should be provided in "Materials and Methods" of a paper:

- (1) The primary antibody species (for monoclonal or polyclonal antibodies), isotype (IgG, IgY, etc.), and epitopes generated.
- (2) Secondary antibody species, isotype, and labeling.
- (3) Source of the primary and secondary antibodies; catalog

Table 1. Markers for subcellular compartments.

Compartments	Markers
Nucleus	Histone H4, Lamin B1, TCF4, RanBP3
Cytosol	GAPDH
Cytoskeleton	Actin, Tubulin, Vimentin, α actinin
Plasma membrane	Caveolin, Cadherins, LRP6, Flotillin
Lysosome, Late endosome	Lamp1
Early endosome	EEA1
Golgi	Golgin97
Mitochondria	Tom20, COX IV, VDAC1
Endoplasmic reticulum	Calreticulin, Calnexin

and lot numbers are needed if they were obtained from a commercial company.

- (4) Dilution and incubation conditions of the primary and secondary antibodies.
- (5) Type of blotting membrane (nitrocellulose, polyvinylidene fluoride, etc.).
- (6) Blocking agents (bovine serum albumin (0.2%–5.0%), nonfat milk, casein, gelatin, etc.).

The most critical rule for image processing and presentation is to maximally preserve the integrity of the original immunoblots. Full scans or images of uncropped blots should be provided (as supplementary files) to reviewers and editors during the submission of papers. If pre-cut blots are used for the antibody treatment, this must be clearly stated and justified by the authors in the Methods section or figure legends. In addition, the number of repetitions performed for the same WB experiment (usually more than two) should also be stated, especially when representative images from only one experiment are shown.

Oversaturated exposure of blots should be avoided to maintain the band signal intensity (expressed either as optical density or fluorescence units) in the linear range for quantitation. Trial experiments aiming to generate a standard curve are recommended, especially when new antibodies or methods are employed. Fig. 1a shows an example of oversaturated bands, which may have masked or at least reduced the differences among samples.

Comparisons (whether statistical or not) between bands and normalization to loading controls should only be conducted on the same blot. In case the number of samples exceeds the capacity of one single gel, the same control sample in the exact same amount can be included on separate gels. However, comparison with this control sample should still be limited to samples within the same blot.

Separate blots should never be merged into one image. If multiple blots are organized side by side in one figure panel, there should be clearly visible space between them (as shown in Fig. 1b). If certain lanes contain data not relevant to the topic, they can be cut out from the blot, but the full blot should still be provided to editors or reviewers according to the journals' requirements (Fig. 1c, d). However, if these irrelevant lanes were located in the middle of a blot, they should not be simply removed. In this case, the gel should be rerun with reorganized samples. The positions of molecular weight markers should be shown or marked on all the blot images. If the blots have been cropped horizontally, at least two neighboring marker positions (i.e., above and below the bands) should be indicated, as shown in Fig. 1c.

Any image adjustments (e.g., brightness, contrast, rotation, and resizing) should be applied to the whole blot (not just a certain portion of it) to ensure that no specific feature of the original data

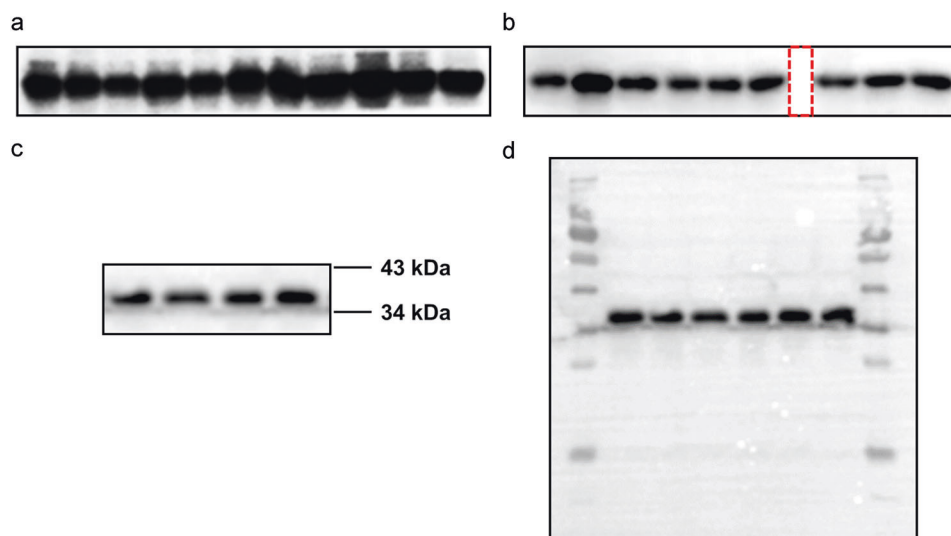


Fig. 1 Representative WB bands. **a** Oversaturated bands in the WB panel. **b** The space (red dotted line) indicates blot splicing. **c** The cut blot. **d** The full blot.

is eliminated or misrepresented. Figures in TIFF format are preferred. For WB images, a minimum resolution of 300 dpi is required.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Lu Tie¹, Han Xiao², Da-lei Wu³, Ye Yang⁴ and Pei Wang^{5,6}

¹Department of Pharmacology, School of Basic Medical Sciences, Peking University and Beijing Key Laboratory of Tumor Systems Biology, Peking University, Beijing 100191, China; ²Department of Cardiology and Institute of Vascular Medicine, Peking University Third Hospital, NHC Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides, Key Laboratory of Molecular Cardiovascular Science, Ministry of Education, Beijing Key Laboratory of Cardiovascular Receptors Research, Beijing 100191, China; ³Helmholtz International Lab, State Key Laboratory of Microbial Technology, Shandong University, Qingdao 266237, China; ⁴School of Medicine & Holistic Integrative Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, China; ⁵Department of Pharmacology, Second Military Medical University, Shanghai 200433, China and ⁶Department of Pharmacy, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China

Correspondence: Lu Tie (tielu@bjmu.edu.cn) or Han Xiao (xiaohan@bjmu.edu.cn) or Da-lei Wu (dlwu@sdu.edu.cn)

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Publications have developed more stringent review guidelines for western blot data, based on recommendations arising from a 2014 meeting organized by the National Institutes of Health (NIH), and the journals Science and Nature.

<https://www.sciencedirect.com/science/article/pii/S0021925820394801?via%3Dihub>

Nature:

<https://www.nature.com/nature-portfolio/editorial-policies/image-integrity#electrophoretic-gels-and-blots>

Electrophoretic gels and blots

- Quantitative comparisons between samples on different gels/blots are strongly discouraged; if this is unavoidable, the figure legend must state that the samples derive from the same experiment or parallel experiments and that gels/blots were processed in parallel.
- Re-arranged lanes that are non-adjacent in the gel must be clearly indicated in a manner that delineates the boundary between the lanes. Re-arrangement of lanes should be stated as such in the figure legend.
- Loading controls (e.g. GAPDH, actin) must be run on the same blot. When sample processing controls are run on different gels, they must be identified as such in the figure legend. Cropped gels in the paper must retain all important bands.
- High-contrast gels and blots are discouraged, as overexposure may mask additional bands.
- Authors should take care to check their manuscripts for the following (1) check figures for duplications (2) check blots and gels for splicing of lanes (3) indicate whether panels are sample processing or loading controls (4) ensure that the unprocessed scans provided match the figures.

J Mol Med (springer) :

<https://www.springer.com/journal/109/submission-guidelines>

Western blots and protein quantification

For manuscripts that contain cropped gels/blots, J Mol Med requests the additional submission of a file* containing whole uncropped/unedited images of the original blots (for example Western blots) from which figures have been derived.

For studies reporting semi-quantitative analyses of immunoblots, authors should clearly explain how quantitative data were obtained, and how protein loading was normalized among lanes.

Housekeeping proteins should not be used for normalization without evidence that experimental manipulations do not affect their expression.

Authors must state the number of independent samples (biological replicates) and the number of replicate samples (technical replicates) and report how many times each experiment was repeated.

Key statements about increases, decreases, or lack of changes in protein abundance, phosphorylation, posttranslational modification, association, and activation must be supported by quantification of data amalgamated from at least 3 Western blots (that represent independent biological replicates) and statistical analysis where appropriate. Showing the densitometry from a single Western blot is not acceptable. When quantifying signals from lysates, the signal for the protein of interest must be normalized to that of a loading control. The signal for a phosphorylated form of a protein must be normalized to that for the total abundance of that protein, a requirement that also applies to other posttranslational modifications. When quantifying changes in protein-protein interactions, the signal for the immunoprecipitated protein must be normalized to that in the total lysate.

*Please submit as Supplementary Figure(s). Each gel should be annotated as “full unedited gel for Figure X,” and the authors should highlight which lanes of the unedited gel correspond to those shown in the cropped images within the manuscript.

neuropharmacology

<https://www.elsevier.com/journals/neuropharmacology/0028-3908/guide-for-authors#txt5002>

Electrophoretic blots and gels

Whilst *Neuropharmacology* appreciates the value of concise representation of electrophoretic blots or gels in the main figures of a manuscript, authors should provide the full, untruncated image of the gel or blot as a supplemental figure (DOC, PDF or PPT), not as a compressed file.

From: P Moss <[REDACTED]@yahoo.com>
Sent time: 11/17/2021 11:56:23 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] SAVA

Dr Wang,

Could you give me some acknowledgement that the simufilam studies weren't manipulated? All fingers are pointing to you as the independent research lab that reinterpreted that study results that allowed SAVA to move on in the drug trials. My family and I are in jeopardy of losing our lives savings because I wanted to support Cassava Sciences efforts in finding a treatment for AD that my mother is suffering from. I would appreciate that.

From: Hoau-yan Wang
Sent time: 11/17/2021 12:34:34 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] SAVA

From: P Moss <[REDACTED]@yahoo.com>
Sent: Wednesday, November 17, 2021 11:56 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] SAVA

Dr Wang,

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From: Hoau-yan Wang
Sent time: 11/17/2021 12:39:11 PM
To: [REDACTED]@gmail.com
Subject: Fw: Suspicious figures in your Neuroscience 2005 paper
Attachments: Guidelines since 2014.docx Acta Pharmacologica Sinica.pdf JBC.pdf

From: Lindsay Burns <lburns@cassavasciences.com>
Sent: Tuesday, November 16, 2021 3:54 PM
To: Juan Lerma Gomez; Hoau-yan Wang
Cc: Weerd-Wilson, Donna (ELS-AMS)
Subject: [EXTERNAL] RE: Suspicious figures in your Neuroscience 2005 paper

Dear Juan,

Thanks for speaking with me again today. We are still looking for the original blots in backup drives, since the original hard drive melted years ago. In the meantime, attached are the guidelines that we could find about WB images in publications. These guidelines were not implemented until 2014, in response to a meeting of NIH and Science and Nature.

Here are two commentaries by another Western blot expert who does ~1000 blots per year, refuting these allegations:
<https://ad-science.org/2021/10/21/notes-from-a-molecular-biologist/>
<https://ad-science.org/2021/10/21/of-shorts-and-blots/>

This is the author, who wishes to keep his identity anonymous online, although he has said he is happy to speak with editors:

<https://www.sbpdiscovery.org/our-scientists/charles-spruck-phd>

Thanks again, and we will see if we can find and return any original blot images for you.

Lindsay

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Monday, November 15, 2021 9:52 AM
To: Lindsay Burns <lburns@cassavasciences.com>; Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Weerd-Wilson, Donna (ELS-AMS) <D.Weerd-Wilson@elsevier.com>
Subject: Suspicious figures in your Neuroscience 2005 paper

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Thanks very much for your responses, Please be advised that we have requested information from Professor Wesson on the research that CUNY appears to be conducting. In the mean time, we decided to publish an expression of concern until a conclusion arises from this investigation. This is the text of the note:

Expression of concern

Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and G β y signaling

[H.-Y.Wang](#), [E.Friedman](#), [M.C. Olmstead](#), [L.H.Burns](#)

Neuroscience [Volume 135, Issue 1](#), 2005, Pages 247-261. <https://doi.org/10.1016/j.neuroscience.2005.06.003>

The Editor in Chief would like to note an expression of concern related to the above-mentioned publication, arising from the apparent duplication and insertion of spurious bands in Western Blots that raise concerns about the data in the article. Upon request to the authors, no evidence has so far been submitted to the journal to confirm 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.

I hope you understand that we must keep our readers informed of any vicissitudes that may arise from the data published in the Journal.

Best regards,

Juan

Prof. Juan Lerma
Editor-in-Chief of Neuroscience, the IBRO Journal.
EMBO Member

Instituto de Neurociencias CSIC-UMH
San Juan de Alicante, Spain

P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39



[Brain Imaging Special Issue](#)

On 30 Sep 2021, at 15:35, Lindsay Burns <lburns@cassavasciences.com> wrote:

Dear Dr. Gomez,

It is not appropriate to call these figures fraudulent before any investigation. This has been guilty until proven innocent. We have already responded to JNS with original blots (exonerating claims of fraud) and a corrected IHC figure that was human error. We are having trouble accessing files for this 16-year-old paper. Hopefully Dr. Wesson can be helpful to you.

Thank you,
Lindsay

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, September 30, 2021 8:09 AM
To: Juan Lerma Gomez <jlerma.nsc@umh.es>
Cc: Lindsay Burns <lburns@cassavasciences.com>
Subject: Re: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. Gomez,

Sorry for my late reply. Please contact Dr. Rosemarie Wesson.

Rosemarie D. Wesson, Ph.D., P.E.
Interim Associate Provost for Research
Professor of Chemical Engineering
The Grove School of Engineering
The City College of New York

Steinman Hall, Suite 152
160 Convent Avenue
New York, NY 10031

Phone: 212-650-6902
Fax: 212-650-5768
Email: rwesson@ccny.cuny.edu

Thank you.

Sincerely,

Hoau-Yan Wang

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Monday, September 27, 2021 9:01 AM
To: Lindsay Burns
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

Dear Dr Burns,

Thanks very much for your email. Before making any further movement, I wonder whether you could please provide the name of the CUNY committee and a contact person.

Thanks very much.

Best regards,

Juan

Prof. Juan Lerma
Editor-in-Chief of Neuroscience, the IBRO Journal.
EMBO Member

Instituto de Neurociencias CSIC-UMH
San Juan de Alicante, Spain

P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39

<image001.jpg>
[Brain Imaging Special Issue](#)

On 20 Sep 2021, at 21:34, Lindsay Burns <lburns@cassavasciences.com> wrote:

Dear Dr. Gomez,

Dr. Wang has handed over all electronic files for an investigation. CUNY has committed to making their findings of this investigation public. I do not have any files from this paper that is 16 years old.

Thank you,
Lindsay Burns

Lindsay H. Burns, PhD
SVP, Neuroscience
Cassava Sciences, Inc.
O: 512-501-2484 C: 512-574-4238
www.cassavasciences.com

<image001.png>

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, September 20, 2021 1:30 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: Fw: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

I don't have access to anything at the moment. Can you please help with dealing with this.

Thanks.

Best,

Hoau

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Wednesday, September 15, 2021 7:35 AM
To: Hoau-yan Wang
Cc: Weerd-Wilson, Donna (ELS-AMS)
Subject: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

Dear Dr Wang,

It has been brought to our attention that several figures from your 2005 Neuroscience paper (<https://doi.org/10.1016/j.neuroscience.2005.06.003>) have problems that make some figures fraudulent. Please see <https://pubpeer.com/publications/5E71DFFFC843817787A90968A16765> for understanding what the problems are. I have personally checked these issues and I find them reasonable source of concern so I am requesting your collaboration to clarify the situation, as the Ctte of Publication Ethics (COPE) requires.

We will wait to a maximum of 30 days for your response. In case we don't have a reasonable explanation, we will proceed to retract your paper from our Journal.

Best regards,

Juan

Prof. Juan Lerma
Editor-in-Chief of Neuroscience, the IBRO Journal.
EMBO Member

Instituto de Neurociencias CSIC-UMH
San Juan de Alicante, Spain

P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39

[The Neurobiology of Social and Affective Touch](#)

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EDITORIAL

A brief guide to good practices in pharmacological experiments: Western blotting

Acta Pharmacologica Sinica (2021) 42:1015–1017; <https://doi.org/10.1038/s41401-020-00539-7>

Western blotting (WB) is an antibody-based experimental technique used to detect and quantify target proteins, which are often within a complex mixture extracted from cells or tissue. Although there are many new alternative technologies, such as enzyme-linked immunosorbent assay (ELISA), immunofluorescence, and mass spectrometry (MS), they all have their own limitations to some extent. ELISA lacks loading controls, immunofluorescence is an in situ technique and is semiquantitative, while MS is expensive and depends on the experimental technique and conditions. Therefore, WB remains the most commonly used methodology in the lab for protein detection. However, concerns about WB have been voiced by many scientific journals in an effort to reduce potential mistakes and increase reproducibility [1]. Here, we will focus on some essential caveats during the WB experiment. This guide, therefore, aims to provide an updated and more concise and useable reference for future experiments and paper writing.

WB includes the following steps. First, proteins are separated from the mixture by sodium dodecyl sulfate–polyacrylamide gel electrophoresis according to their molecular weights. Next, the separated proteins are transferred and bound to a solid membrane. Then, the target protein on the membrane is detected by the immunological method. The identification of a specific protein is based on two parameters: molecular weight and signal intensity. Molecular weight could be estimated by prestained molecular weight markers. The signal is determined by a secondary antibody following the addition of primary antibodies to detect the protein blotted onto the membrane.

Since WB involves multiple steps for detection of different proteins, there is no one particular set of optimal conditions suitable for all proteins. Researchers usually spend considerable time optimizing the conditions to obtain the best signal-to-noise ratios, yet difficulties persist in obtaining consistent and high-quality results. Many specific techniques used in the experiment influence the result of WB, among which the experimental controls, the characterization of antibodies, the choice of loading controls, and the image processing and presentation are the most noticeable challenges. Next, we will discuss those important aspects of WB.

Sample preparation will directly affect the quality of the results, so the choice of correct lysis buffer is a critical step. In general, lysis buffers containing nonionic detergents such as NP-40 or Triton X-100 are sufficient to release proteins from cells, while ionic detergents such as SDS and sodium deoxycholate can be considered for harsh extraction conditions. Thus, the most commonly used commercial lysis buffers are radioimmunoprecipitation assay buffer containing SDS and NP-40 buffer without SDS. In special cases, guanidine-HCl, a chaotropic agent, can be added into lysis buffer to denature oligomerized proteins into their native conformations. Moreover, proteolysis could be inhibited by protease inhibitors, such as PMSF, pepstatin, and

EDTA; and protein dephosphorylation could be prevented by phosphatase inhibitors, such as NaF and Na_3VO_4 . Thus, the appropriate commercial protease inhibitor cocktail could be used according to specific needs.

After sample lysis, the protein concentration is measured before the next procedure. Various methods for protein concentration detection can be applied, including the Bradford assay, Lowry assay, and bicinchoninic assay (BCA). The Bradford assay is based on the absorption of the dye Coomassie Blue G-250 by proteins. The principles of the Lowry assay and BCA assay are similar and rely on color development from the Biuret reaction based on the concentrations of the proteins dissolved in samples. The advantages of the Bradford assay are that it is easy and quick to perform with one reagent, while the advantages of the Lowry assay and BCA assay are their extreme sensitivity and improved compatibility with a wide range of detergents (SDS, Triton X-100, Tween 20, etc.).

It is important to set both positive and negative controls for the detected proteins to validate the WB results. Genetically modified animal tissue or cells are suggested as choices for controls. We can verify the correct molecular weight by comparing the wild-type sample with the knockout or knockdown animal or cell sample. Controls lacking the primary antibody or the blocking peptide of the antibody can verify the specificity of the antibody used in WB. Although the above-mentioned controls may not always be available for all proteins, positive and negative controls need to be included as much as possible.

The selectivity of antibodies directly affects WB results, and poor selectivity may lead to the misinterpretation of the results. There are currently databases that can be used for choosing characterized antibodies with high selectivities, such as Antibodypedia (<https://www.antibodypedia.com/>), the Human Protein Atlas (<http://www.proteinatlas.org/>), and the Antibody Registry (<https://antibodyregistry.org/>). For unvalidated antibodies, there are suggested methodologies to validate the selectivity of the antibodies [2]. These methods include detection of whether the signal is eliminated or significantly reduced after genetic knockout or knockdown of the target gene; analysis of the correlation between WB signals and signals of other detection methods (e.g., MS) in a set of different samples with variable expression of the target protein; analysis of the correlation of protein levels by using two or more independent antibodies targeting different epitopes of the same protein; expression of the target protein with a tag, and analysis of the correlation between antibody labeling and the detection of the tag. If the results are highly correlated, then the antibody is validated for WB analysis.

Usually, there are multiple secondary antibodies suitable for the subsequent detection of the target protein, and the selection can be optimized in specific experiments. When selecting a secondary antibody, both the type of primary antibody and the requirements of subsequent detection schemes should be considered comprehensively:

- (1) Species source of the primary antibody: the reactivity of the secondary antibody should be consistent with the species

source of the primary antibody used. For example, if the primary antibody is a mouse-derived monoclonal antibody, an anti-mouse secondary antibody (goat anti-mouse or rabbit anti-mouse) should be selected.

- (2) Type of primary antibody: the secondary antibody must match the class or subclass of the primary antibody. This is usually applicable for monoclonal antibodies. Polyclonal antibodies are mainly IgG immunoglobulins, so the corresponding secondary antibodies are anti-IgG antibodies. If the primary antibody is mouse IgM, then the corresponding secondary antibody should be anti-mouse IgM. If the primary monoclonal antibody is of a certain subclass of mouse IgG (IgG1, IgG2a, IgG2b, or IgG3), then almost all anti-mouse IgG can bind to it, or the secondary antibody can be selected to specifically target this subclass. If the type of the primary antibody is not clear, IgG against the corresponding species can be used.
- (3) Species source of the secondary antibody: there is usually no predictable connection between species source and the quality of the secondary antibody. However, the use of secondary antibodies from the same species as the primary antibodies should be avoided, especially in double-labeling experiments. If one of the primary antibodies is derived from goat, whereas the other is derived from mice, the corresponding secondary antibodies must be anti-goat and anti-mouse secondary antibodies, respectively. The secondary antibody cannot be derived from goat or mice.
- (4) Coupling of probes to the secondary antibody: probes coupled to secondary antibodies mainly include enzymes (such as horseradish peroxidase and alkaline phosphatase), fluorescent molecules (FITC, rhodamine, Texas Red, PE, Dylight, etc.), biotin, and gold particles. The probes can be selected according to the detection system used for WB. For WB and ELISA, the most commonly used secondary antibody is an enzyme-labeled secondary antibody, while cell or tissue labeling experiments (cellular immunocytochemistry, histoimmunocytochemistry, and flow cytometry) usually use fluorescent molecule-labeled secondary antibodies.

Another critical issue is the selection of the loading control, which has been widely used in the normalization of WB results to adjust for systematic differences between samples or even between experiments. Housekeeping proteins, such as β -actin and GAPDH, have been commonly used as loading controls. However, the expression of these proteins can change under certain conditions [3, 4]. The selected housekeeping proteins need to be proven stable under the experimental conditions. An alternative to the use of a specific protein as the loading control is the staining of total protein. Some methods used for staining of total protein on the membrane, such as Ponceau S [5] and Fast Green [6], have been found to be reliable as loading controls. Ponceau S is the most commonly used removable stain and can be conveniently used before immunodetection, but it is relatively insensitive. Fast Green is a more permanent dye used for staining in histology and electrophoresis. It cannot be easily removed and may inhibit subsequent immunodetection. Alternatively, staining with Fast Green after immunodetection has been used in some recent publications. Moreover, some housekeeping proteins are also used as markers for subcellular compartments according to their intracellular distribution [7] (Table 1).

Therefore, to achieve reproducible WB results, the following information should be provided in "Materials and Methods" of a paper:

- (1) The primary antibody species (for monoclonal or polyclonal antibodies), isotype (IgG, IgY, etc.), and epitopes generated.
- (2) Secondary antibody species, isotype, and labeling.
- (3) Source of the primary and secondary antibodies; catalog

Table 1. Markers for subcellular compartments.

Compartments	Markers
Nucleus	Histone H4, Lamin B1, TCF4, RanBP3
Cytosol	GAPDH
Cytoskeleton	Actin, Tubulin, Vimentin, α actinin
Plasma membrane	Caveolin, Cadherins, LRP6, Flotillin
Lysosome, Late endosome	Lamp1
Early endosome	EEA1
Golgi	Golgin97
Mitochondria	Tom20, COX IV, VDAC1
Endoplasmic reticulum	Calreticulin, Calnexin

and lot numbers are needed if they were obtained from a commercial company.

- (4) Dilution and incubation conditions of the primary and secondary antibodies.
- (5) Type of blotting membrane (nitrocellulose, polyvinylidene fluoride, etc.).
- (6) Blocking agents (bovine serum albumin (0.2%–5.0%), nonfat milk, casein, gelatin, etc.).

The most critical rule for image processing and presentation is to maximally preserve the integrity of the original immunoblots. Full scans or images of uncropped blots should be provided (as supplementary files) to reviewers and editors during the submission of papers. If pre-cut blots are used for the antibody treatment, this must be clearly stated and justified by the authors in the Methods section or figure legends. In addition, the number of repetitions performed for the same WB experiment (usually more than two) should also be stated, especially when representative images from only one experiment are shown.

Oversaturated exposure of blots should be avoided to maintain the band signal intensity (expressed either as optical density or fluorescence units) in the linear range for quantitation. Trial experiments aiming to generate a standard curve are recommended, especially when new antibodies or methods are employed. Fig. 1a shows an example of oversaturated bands, which may have masked or at least reduced the differences among samples.

Comparisons (whether statistical or not) between bands and normalization to loading controls should only be conducted on the same blot. In case the number of samples exceeds the capacity of one single gel, the same control sample in the exact same amount can be included on separate gels. However, comparison with this control sample should still be limited to samples within the same blot.

Separate blots should never be merged into one image. If multiple blots are organized side by side in one figure panel, there should be clearly visible space between them (as shown in Fig. 1b). If certain lanes contain data not relevant to the topic, they can be cut out from the blot, but the full blot should still be provided to editors or reviewers according to the journals' requirements (Fig. 1c, d). However, if these irrelevant lanes were located in the middle of a blot, they should not be simply removed. In this case, the gel should be rerun with reorganized samples. The positions of molecular weight markers should be shown or marked on all the blot images. If the blots have been cropped horizontally, at least two neighboring marker positions (i.e., above and below the bands) should be indicated, as shown in Fig. 1c.

Any image adjustments (e.g., brightness, contrast, rotation, and resizing) should be applied to the whole blot (not just a certain portion of it) to ensure that no specific feature of the original data

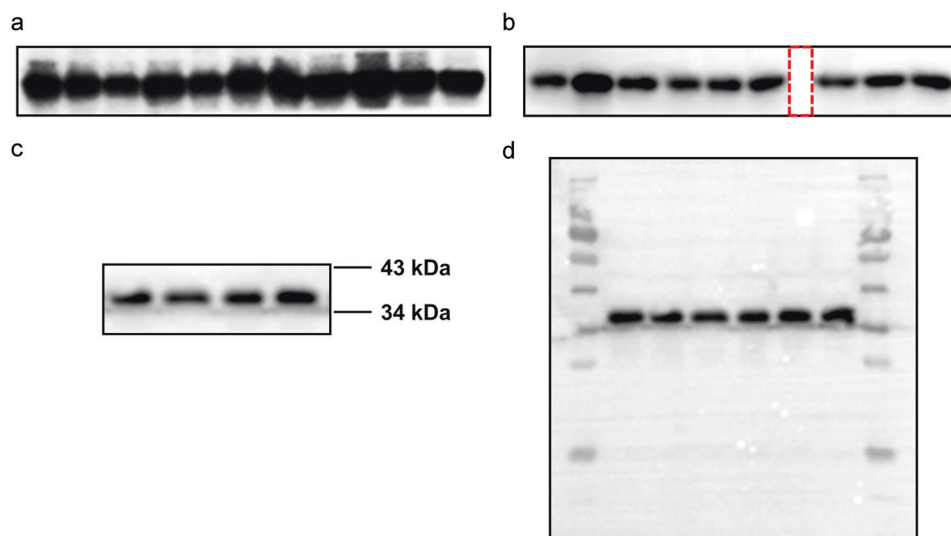


Fig. 1 Representative WB bands. **a** Oversaturated bands in the WB panel. **b** The space (red dotted line) indicates blot splicing. **c** The cut blot. **d** The full blot.

is eliminated or misrepresented. Figures in TIFF format are preferred. For WB images, a minimum resolution of 300 dpi is required.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Lu Tie¹, Han Xiao², Da-lei Wu³, Ye Yang⁴ and Pei Wang^{5,6}

¹Department of Pharmacology, School of Basic Medical Sciences, Peking University and Beijing Key Laboratory of Tumor Systems Biology, Peking University, Beijing 100191, China; ²Department of Cardiology and Institute of Vascular Medicine, Peking University Third Hospital, NHC Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides, Key Laboratory of Molecular Cardiovascular Science, Ministry of Education, Beijing Key Laboratory of Cardiovascular Receptors Research, Beijing 100191, China; ³Helmholtz International Lab, State Key Laboratory of Microbial Technology, Shandong University, Qingdao 266237, China; ⁴School of Medicine & Holistic Integrative Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, China; ⁵Department of Pharmacology, Second Military Medical University, Shanghai 200433, China and ⁶Department of Pharmacy, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China

Correspondence: Lu Tie (tielu@bjmu.edu.cn) or Han Xiao (xiaohan@bjmu.edu.cn) or Da-lei Wu (dlwu@sdu.edu.cn)

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Transparency Is the Key to Quality

Amanda J. Fosang and Roger J. Colbran

A workshop held last June by the National Institutes of Health (NIH) Director's Office, Nature Publishing Group, and *Science* focused on the role that journals play in supporting scientific research that is reproducible, robust, and transparent. The "Principles and Guidelines for Reporting Preclinical Research" (<http://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research>) that emerged from the workshop have since been endorsed by nearly 80 societies, journals, and associations.

Rigorous, objective peer review was widely acknowledged as the key to publication of high quality science. The expert, dedicated members of the JBC Editorial Board provide an invaluable service to the community of JBC authors and readers by ensuring the rigor, reproducibility, and transparency of research reported in the Journal. Over the past year, the JBC Associate Editors have been working to make sure that JBC reviewing editors, and ultimately our readers, have the information they need from authors for rigorous evaluation of the scientific content of JBC manuscripts. This effort has led to extensive revisions of our Instructions for Authors (<http://www.jbc.org/site/misc/ifora.xhtml>) for reporting experimental uncertainty, animal studies, biological materials, immunoblot data, and imaging results.

The JBC has identified three major gaps in overall data reporting. We expect that filling these gaps will have an immediate impact on improving transparency in our journal. These gaps, which will be readily recognized by much of the bioscience community, include the need for (i) more complete disclosure of experimental design and reporting of experimental uncertainty and reproducibility, (ii) improved statistical and graphical presentation of quantitative data, and (iii) revised guidelines for the presentation and quantitation of immuno ("Western") blots.

Experimental Design and Reporting of Experimental Uncertainty and Reproducibility

Editors, reviewers, and the general JBC readership want to know about the reproducibility and also the variation in the observations among multiple experiments. To this end it is critically important that the number of independent biological replicates, the number of technical replicates, and the number of repeated experiments are clearly separated and specified. Surprisingly, this simple rule is often broken or misrepresented. Sometimes, the value of N is, and can only be, one. An example of this is an experiment to compare drug treatments in a line of patient-derived stem cells. Although there may be numerous technical replicates for such an experiment, and the experiment could be repeated several times, the patient is one *independent biological sample*. As another example, if six metatarsals were harvested from the front paws of a single mouse and cultured as six individual explant cultures, the number of biological replicates (again, the value of N) is equal to one, but with six technical replicates. The JBC now requires authors to include explicit information describing N and its value in the figure legends and to distinguish between the biological (independent) and technical replicates for each experiment. More uncertainty is generally seen in the former.

Statistical and Graphical Presentation of Quantitative Data

Many experiments published in the JBC yield qualitative data that are not amenable to statistical analyses, *e.g.* electrophoresis, histology, chromatography, electron microscopy. In these cases authors need to clearly indicate the number of independent replicates that the figure represents. However, when quantitative data are presented, appropriate statistical analyses to portray experimental reproducibility and support an interpretation that experimental manipulations yield significant differences are needed. The JBC encourages the use of the 95% confidence interval (CI) as error bars because they are easier to interpret; the 95% CI is defined as the interval that encompasses 95 out of 100 independent samples from a population. Use of standard deviation (S.D.) or standard error of the mean (S.E.) is also permitted. Both S.E. and CI are inferential statistics, which are used to make inferences about the data; when $N = 3$, the 95% CI is $\sim \text{mean} \pm 4 \text{ S.E.}$, but when $N \geq 10$, the 95% CI is $\sim \text{mean} \pm 2 \text{ S.E.}$

As a complementary measure to graphically improve transparency, the JBC now strongly encourages the use of scatter plots for small data sets (<30 independent samples) or box and whisker plots to compare large data sets. These plots, inclusive of appropriate error bars, provide more transparent information about the variability within the data than the ubiquitous dynamite plunger plots (bar graphs) that historically dominate scientific publications, including JBC (1). Statistical analyses of variation and precision for establishing differences between experimental groups can be reported in the same plot, preferably using the S.D. or 95% CI. The JBC now requires authors to include specific information describing experimental uncertainty and reproducibility of each data set in the figure legends.

Presentation and Quantitation of Western Blots

Western blots have become a standard technology in the tool kit of most biology or biochemistry laboratories, particularly because commercial antibodies are now available for many proteins, even those that have barely appeared in the literature. The JBC requires users of Western blot technologies to define the species of origin and source of all antibodies used, including catalogue/lot numbers, in the "Experimental Procedures" section of their manuscripts. A description of the data supporting the specificity of all antibodies is required. In cases where novel antibodies are used, we are asking authors to describe how the antibody was made, including preparation and purification of the epitope/antigen, and also to provide data validating the specificity of the antibody. As far as possible, data showing loss of immunoreactivity in samples following genetic or other molecular modifications to the antigen are a welcome addition to confirm monospecificity of the antibodies. The specificity of antibodies designed to specifically detect post-translational modifications, *e.g.* methylation, oxidation, phosphorylation, glycosylation, or neoepitopes (2), should also be validated as appropriate and be reported.

An increasing number of journals, including the JBC, do *not* allow surreptitious splicing of Western blots. If it is essential to remove lanes from an original blot for presentation purposes, then the splice positions must be clearly marked and explained in the figure legend. Of course, splicing together lanes from more than one blot is not allowed under any circumstances.

Authors should also be careful to avoid "overcropping" sections of Western blots for presentation in figures. Sufficient surrounding background regions should be retained including the positions of at least one, but preferably more, molecular weight markers above and below the band of interest.

Quantitation of Western blots is not always required but it can be fraught with traps for the unwary investigator and often sparks lively debate among scientists. It is not uncommon to "correct" Western blot signals for protein loading by normalizing to a second Western blot for a housekeeper protein, *e.g.* β -actin, α -tubulin, transferrin, GAPDH, HPRT1. The problem with this approach is that a linear relationship between signal intensity and the mass or volume of sample loaded must be confirmed for every antigen. This is further complicated by the fact that some detection methods, in particular enhanced chemiluminescence using x-ray film, have a very restricted linear range, and careful attention to the experimental conditions is necessary to ensure linearity. It is typically better to normalize Western blots using total protein loading as the denominator (3–11). To avoid potential pitfalls and with a focus on improving transparency, the JBC strongly recommends that authors describe their methods used to quantify signal intensity, how the linearity of signal intensity with antigen loading was established, and how protein loading was normalized between lanes. We prefer that signal intensities are normalized to total protein by staining membranes with Coomassie Blue, Ponceau S, or other protein stains, and we strongly caution against the use of housekeeping proteins for normalization, unless there is a clear demonstration that expression of the housekeeping protein is unaffected by the experimental treatments.

Authors should be prepared to submit raw data showing original Western blots or validating their reagents and quantitative analyses during the review of a manuscript upon request from the reviewers or an Associate Editor. JBC also reserves the right to digitally analyze all figures for undisclosed splicing of gels or other inappropriate image manipulation (<http://www.jbc.org/site/misc/ifora.xhtml#manipulation>).

It is worth reiterating a point made by other transparency advocates (12–15) that while statistics is a necessary mainstay for data interpretation by clinical researchers, psychologists, and epidemiologists, whose conclusions depend wholly on statistics, the interpretation of data in papers published in the biological sciences, including the JBC, do not always require sophisticated statistical analyses. JBC papers are selected because they provide novel and important mechanistic insights into cellular or biological processes at the molecular level. To this end, the JBC requires diligent data reporting and transparency so that readers, reviewers, and journal editors can identify sound papers with reliable data.

Acknowledgments—We acknowledge Prof. Susan Donath, University of Melbourne, Australia, and Prof. David Vaux, Walter & Eliza Hall Institute, Melbourne, Australia, for their advice and helpful discussions.

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Publications have developed more stringent review guidelines for western blot data, based on recommendations arising from a 2014 meeting organized by the National Institutes of Health (NIH), and the journals Science and Nature.

<https://www.sciencedirect.com/science/article/pii/S0021925820394801?via%3Dihub>

Nature:

<https://www.nature.com/nature-portfolio/editorial-policies/image-integrity#electrophoretic-gels-and-blots>

Electrophoretic gels and blots

- Quantitative comparisons between samples on different gels/blots are strongly discouraged; if this is unavoidable, the figure legend must state that the samples derive from the same experiment or parallel experiments and that gels/blots were processed in parallel.
- Re-arranged lanes that are non-adjacent in the gel must be clearly indicated in a manner that delineates the boundary between the lanes. Re-arrangement of lanes should be stated as such in the figure legend.
- Loading controls (e.g. GAPDH, actin) must be run on the same blot. When sample processing controls are run on different gels, they must be identified as such in the figure legend. Cropped gels in the paper must retain all important bands.
- High-contrast gels and blots are discouraged, as overexposure may mask additional bands.
- Authors should take care to check their manuscripts for the following (1) check figures for duplications (2) check blots and gels for splicing of lanes (3) indicate whether panels are sample processing or loading controls (4) ensure that the unprocessed scans provided match the figures.

J Mol Med (springer) :

<https://www.springer.com/journal/109/submission-guidelines>

Western blots and protein quantification

For manuscripts that contain cropped gels/blots, J Mol Med requests the additional submission of a file* containing whole uncropped/unedited images of the original blots (for example Western blots) from which figures have been derived.

For studies reporting semi-quantitative analyses of immunoblots, authors should clearly explain how quantitative data were obtained, and how protein loading was normalized among lanes.

Housekeeping proteins should not be used for normalization without evidence that experimental manipulations do not affect their expression.

Authors must state the number of independent samples (biological replicates) and the number of replicate samples (technical replicates) and report how many times each experiment was repeated.

Key statements about increases, decreases, or lack of changes in protein abundance, phosphorylation, posttranslational modification, association, and activation must be supported by quantification of data amalgamated from at least 3 Western blots (that represent independent biological replicates) and statistical analysis where appropriate. Showing the densitometry from a single Western blot is not acceptable. When quantifying signals from lysates, the signal for the protein of interest must be normalized to that of a loading control. The signal for a phosphorylated form of a protein must be normalized to that for the total abundance of that protein, a requirement that also applies to other posttranslational modifications. When quantifying changes in protein-protein interactions, the signal for the immunoprecipitated protein must be normalized to that in the total lysate.

*Please submit as Supplementary Figure(s). Each gel should be annotated as “full unedited gel for Figure X,” and the authors should highlight which lanes of the unedited gel correspond to those shown in the cropped images within the manuscript.

neuropharmacology

<https://www.elsevier.com/journals/neuropharmacology/0028-3908/guide-for-authors#txt5002>

Electrophoretic blots and gels

Whilst *Neuropharmacology* appreciates the value of concise representation of electrophoretic blots or gels in the main figures of a manuscript, authors should provide the full, untruncated image of the gel or blot as a supplemental figure (DOC, PDF or PPT), not as a compressed file.

From: Hoau-yan Wang
Sent time: 11/17/2021 12:41:26 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

POL 87(2)(a)

Hoau

From: Walker, Joseph <joseph.walker@wsj.com>
Sent: Tuesday, November 16, 2021 3:19 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

Hi, Dr. Wang,

This is Joe Walker from the Wall Street Journal. I just wanted to check back with you to see if you wanted to comment on any of the allegations made pertaining to your work. I know you haven't responded to my emails or calls in the past, but please know that I'm following up now to ensure that you know you still have an opportunity to get across your side in the story. But it will likely have to be tonight as the story could really run any time now.

In addition, we had understood that CUNY was reviewing these allegations -- do you know if that is still the case? Has the matter been resolved?

You can also reach me at 917-689-9598 if you'd like to discuss further.

Joe

On Sun, Oct 17, 2021 at 6:06 PM Walker, Joseph <joseph.walker@wsj.com> wrote:

Professor Wang,

I'm a reporter at the Wall Street Journal and I'm working on a story with my colleague Dave Michaels about the recent allegations of data manipulation and scientific misconduct made against Cassava Sciences and collaborators including yourself regarding work related to Simufilam.

The allegations were filed in a Citizen Petition in August that is posted online here <https://www.regulations.gov/docket/FDA-2021-P-0930/document>

Many of the allegations pertain to western blot images published in papers of yours.

Can you speak with us by phone to discuss the allegations? We're hoping to talk sometime this week.

Absent that, can you comment on the matter by email?

How do you respond to the allegations of cutting and pasting images in the western blots?

Are you aware of whether any institutions, such as the FDA, NIH or CUNY are investigating the allegations?

We understand that your lab has shared the raw data from the experiments with some of the journals where the papers were published? Is that accurate?

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Are you aware of any other forthcoming corrections or retractions to your work on Simuflam or Filamin A?

Thank you for considering our request. You may reach me anytime at the number below.

Regards,

Joe

--

Joseph Walker
917-689-9598
1211 Avenue of the Americas, 5th Fl, NY, NY 10036
THE WALL STREET JOURNAL.
IAPE Local 1096:
We
Power Dow Jones.

--

Joseph Walker
917-689-9598
1211 Avenue of the Americas, 5th Fl, NY, NY 10036
THE WALL STREET JOURNAL.
IAPE Local 1096:
We
Power Dow Jones.

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent time: 11/17/2021 12:48:14 PM
To: Hoau-yan Wang
Subject: Re: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

POL 87(2)(a)

[REDACTED]

Jennifer Beidel
Jennifer.beidel@saul.com
(215) 470-0667

On Nov 17, 2021, at 12:41 PM, Hoau-yan Wang wrote:

****EXTERNAL EMAIL**** - This message originates from outside our Firm. Please consider carefully before responding or clicking links/attachments.

[REDACTED]

Hoau

From: Walker, Joseph
Sent: Tuesday, November 16, 2021 3:19 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

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Joe

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Many of the allegations pertain to western blot images published in papers of yours.

Can you speak with us by phone to discuss the allegations? We're hoping to talk sometime this week.

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Are you aware of any other forthcoming corrections or retractions to your work on Simufilam or Filamin A?

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Regards,

Joe

--

Joseph Walker

917-689-9598

1211 Avenue of the Americas, 5th Fl, NY, NY 10036

[The Wall Street Journal]

IAPE Local 1096: We Power Dow Jones.

--

Joseph Walker

917-689-9598

1211 Avenue of the Americas, 5th Fl, NY, NY 10036

[The Wall Street Journal]

IAPE Local 1096: We Power Dow Jones.

"Saul Ewing Arnstein & Lehr LLP (saul.com) " made the following annotations:

+~~~~~+

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+~~~~~+

From: Lindsay Burns <lburns@cassavasciences.com>
Sent time: 11/17/2021 12:53:58 PM
To: Juan Lerma Gomez <jlerma.nsc@umh.es>; Hoau-yan Wang
Cc: Weerd-Wilson, Donna (ELS-AMS) <D.Weerd-Wilson@elsevier.com>
Subject: [EXTERNAL] RE: Suspicious figures in your Neuroscience 2005 paper

Dear Prof. Lerma,

Dr. Wang has spent 20 hours looking for these 16-year-old files in back-up disks (since his hard drive was destroyed a decade or so ago), and he is making some progress. Please stay tuned. We hope that your statement can also address the other paper you examined of Dr. Wang that showed no evidence of duplication of bands.

Best regards,
Lindsay

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Monday, November 15, 2021 9:52 AM
To: Lindsay Burns <lburns@cassavasciences.com>; Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Weerd-Wilson, Donna (ELS-AMS) <D.Weerd-Wilson@elsevier.com>
Subject: Suspicious figures in your Neuroscience 2005 paper

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Drs. Wang and Burns,

Thanks very much for your responses, Please be advised that we have requested information from Professor Wesson on the research that CUNY appears to be conducting. In the mean time, we decided to publish an expression of concern until a conclusion arises from this investigation. This is the text of the note:

Expression of concern

Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and G β γ signaling

[H.-Y.Wang](#), [E.Friedman](#), [M.C. Olmstead](#), [L.H.Burns](#)

Neuroscience [Volume 135, Issue 1](#), 2005, Pages 247-261. <https://doi.org/10.1016/j.neuroscience.2005.06.003>

The Editor in Chief would like to note an expression of concern related to the above-mentioned publication, arising from the apparent duplication and insertion of spurious bands in Western Blots that raise concerns about the data in the article. Upon request to the authors, no evidence has so far been submitted to the journal to confirm 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.

I hope you understand that we must keep our readers informed of any vicissitudes that may arise from the data published in the Journal.

Best regards,

Juan

Prof. Juan Lerma
Editor-in-Chief of Neuroscience, the IBRO Journal.
EMBO Member

Instituto de Neurociencias CSIC-UMH
San Juan de Alicante, Spain

P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39



[Brain Imaging Special Issue](#)

On 30 Sep 2021, at 15:35, Lindsay Burns <lburns@cassavasciences.com> wrote:

Dear Dr. Gomez,

It is not appropriate to call these figures fraudulent before any investigation. This has been guilty until proven innocent. We have already responded to JNS with original blots (exonerating claims of fraud) and a corrected IHC figure that was human error. We are having trouble accessing files for this 16-year-old paper. Hopefully Dr. Wesson can be helpful to you.

Thank you,
Lindsay

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Thursday, September 30, 2021 8:09 AM

To: Juan Lerma Gomez <jlerma.nsc@umh.es>

Cc: Lindsay Burns <lburns@cassavasciences.com>

Subject: Re: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. Gomez,

Sorry for my late reply. Please contact Dr. Rosemarie Wesson.

Rosemarie D. Wesson, Ph.D., P.E.
Interim Associate Provost for Research
Professor of Chemical Engineering
The Grove School of Engineering
The City College of New York

Steinman Hall, Suite 152
160 Convent Avenue
New York, NY 10031

Phone: 212-650-6902
Fax: 212-650-5768
Email: rwesson@ccny.cuny.edu

Thank you.

Sincerely,

Hoau-Yan Wang

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Monday, September 27, 2021 9:01 AM
To: Lindsay Burns
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

Dear Dr Burns,

Thanks very much for your email. Before making any further movement, I wonder whether you could please provide the name of the CUNY committee and a contact person.

Thanks very much.

Best regards,

Juan

Prof. Juan Lerma
Editor-in-Chief of Neuroscience, the IBRO Journal.
EMBO Member

Instituto de Neurociencias CSIC-UMH
San Juan de Alicante, Spain

P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39

<image001.jpg>
[Brain Imaging Special Issue](#)

On 20 Sep 2021, at 21:34, Lindsay Burns <lburns@cassavasciences.com> wrote:

Dear Dr. Gomez,

Dr. Wang has handed over all electronic files for an investigation. CUNY has committed to making their findings of this investigation public. I do not have any files from this paper that is 16 years old.

Thank you,
Lindsay Burns

Lindsay H. Burns, PhD
SVP, Neuroscience
Cassava Sciences, Inc.
O: 512-501-2484 C: 512-574-4238
www.cassavasciences.com
<image001.png>

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, September 20, 2021 1:30 PM
To: Lindsay Burns <lburns@cassavasciences.com>
Subject: Fw: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

I don't have access to anything at the moment. Can you please help with dealing with this.

Thanks.

Best,

Hoau

From: Juan Lerma Gomez <jlerma.nsc@umh.es>
Sent: Wednesday, September 15, 2021 7:35 AM
To: Hoau-yan Wang
Cc: Weerd-Wilson, Donna (ELS-AMS)
Subject: [EXTERNAL] Fraudulent figures in your Neuroscience 2005 paper

Dear Dr Wang,

It has been brought to our attention that several figures from your 2005 Neuroscience paper (<https://doi.org/10.1016/j.neuroscience.2005.06.003>) have problems that make some figures fraudulent. Please see <https://pubpeer.com/publications/5E71DFFFC843817787A90968A16765> for understanding what the problems are. I have personally checked these issues and I find them reasonable source of concern so I am requesting your collaboration to clarify the situation, as the Ctte of Publication Ethics (COPE) requires.

We will wait to a maximum of 30 days for your response. In case we don't have a reasonable explanation, we will proceed to retract your paper from our Journal.

Best regards,

Juan

Prof. Juan Lerma
Editor-in-Chief of Neuroscience, the IBRO Journal.
EMBO Member

Instituto de Neurociencias CSIC-UMH
San Juan de Alicante, Spain

P.A.: Laura Navío, PhD
lnavio@umh.es
Tel: +34 965919238/39

[The Neurobiology of Social and Affective Touch](#)

<PastedGraphic-5.tiff>

From: Pubpeer <alerts@pubpeer.com>
Sent time: 11/17/2021 01:52:59 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau-Yan Wang,

There's a new comment on your article entitled: **PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiology of Aging**

This link will log you in so that you can respond to the comment; please do not share the link with anyone else

See comment and respond

Regards,
PubPeer

If you're having trouble clicking the "See comment and respond" button, copy and paste the URL below into your web browser:

<https://pubpeer.com/publications/80DD10169D3C375C5828BC2711A49B/author-response/29583036?signature=0cc8fcfd3e13bc58c6dcaeadf75cd0a200b7883f7ba6b9b2ac3e403fc3df6f7>

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From: Hoau-yan Wang
Sent time: 11/18/2021 10:56:59 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Re: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

POL 87(2)(a)

[REDACTED]

[REDACTED]

Hoau

From: Beidel, Jennifer L.
Sent: Wednesday, November 17, 2021 12:48 PM
To: Hoau-yan Wang
Subject: Re: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

[REDACTED]

Jennifer Beidel
Jennifer.beidel@saul.com
(215) 470-0667

On Nov 17, 2021, at 12:41 PM, Hoau-yan Wang wrote:

****EXTERNAL EMAIL**** - This message originates from outside our Firm. Please consider carefully before responding or clicking links/attachments.

[REDACTED]

Hoau

From: Walker, Joseph
Sent: Tuesday, November 16, 2021 3:19 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wall Street Journal request - re: Simufilam

Hi, Dr. Wang,

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You can also reach me at 917-689-9598 if you'd like to discuss further.

Joe

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The allegations were filed in a Citizen Petition in August that is posted online here https://urldefense.proofpoint.com/v2/url?u=https-3A__www.regulations.gov_docket_FDA-2D2021-2DP-2D0930_document&d=DwIGaQ&c=4NmamNZG3KTnUCoC6InoLJ6KV1tbVKrkZXHRwtIMGmo&r=YAnDdIh9IEWHiy_3lavsTLajOSlrKTXLS4AccHSzT3c&m=HV7FgTJ_ffOhHDnK0AOdbBSTX9vCm7zntHZzme6d7Wk&s=LKJhtPIuJvKvzd9sXeGrgsfYUNhJGDEm3Wwoz5aVeeA&e=

Many of the allegations pertain to western blot images published in papers of yours.

Can you speak with us by phone to discuss the allegations? We're hoping to talk sometime this week.

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1211 Avenue of the Americas, 5th Fl, NY, NY 10036

[The Wall Street Journal]

IAPE Local 1096: We Power Dow Jones.

--

Joseph Walker

917-689-9598

1211 Avenue of the Americas, 5th Fl, NY, NY 10036

[The Wall Street Journal]

IAPE Local 1096: We Power Dow Jones.

"Saul Ewing Arnstein & Lehr LLP (saul.com) " made the following annotations:

+~~~~~+

This e-mail may contain privileged, confidential, copyrighted, or other legally protected information. If you are not the intended recipient (even if the e-mail address is yours), you may not use, copy, or retransmit it. If you have received this by mistake please notify us by return e-mail, then delete.

+~~~~~+

From: jane.wang@acme.com
Sent time: 11/19/2021 02:49:02 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Update of Acme Bioscience-Chemistry Based CRO
Attachments: Acme Handout.pdf

Dear Dr. Wang,

Hope all is going well for you at CUNY and Cassava Sciences. Thanks for your support of Acme. Please take Acme Bioscience into consideration when you need chemistry outsourcing support.

We can help all your chemistry programs: medchem, process chem R&D, IND enabling tox batch, scale up to multi kilo grams, and non-GMP manufacturing on hundreds kgs to tons scale of materials.

A few benefits of working with Acme:

- Hybrid Model: We have sites in both the US and China to maintain high quality while keeping costs low.
- We have no internal discovery, investment arms, and risk/profit sharing projects. Your IP is safe with us.
- We are Chemistry based CRO. Chemistry is our main focus and we're pretty good at it.
- A true partner. We care about our clients We provide weekly updates and work with you to resolve any issues.

Acme is also selected as a vendor to JLABS companies.

Please check Acme out at the JLABS website at below link:

<https://jllabs.jninnovation.com/resource-hub>

We have experience in ADC research if needed, we can synthesize linker, drug, and linker-drug. Most of our customers choose to do the conjugation with proteins in house.

Acme Update: Acme has about 15 PhD bench chemists in Palo Alto and over 200 chemists at Shanghai.

At Acme Shanghai: An additional 100 fume hoods are ready to use this month, November 2021. GMP pilot lab can make kgs scales of GMP drug substances to support customers' Phase 1 Clinical Trials.

We also co-own a non-GMP manufacturing facility outside of Shanghai (from hundreds kilo grams to tons scale).

We currently have a total of five scale up labs at Acme Shanghai site. We have reactors ranging from 10, 20, 50, and 100 L, and can handle temperatures from 150 °C to -78 °C. We also have done several manufacturing projects with 5000 L reactor and produced 4000 kg (each batch) of raw material for GMP. We shipped the material to a European country.

You can choose to work with either or both sites of Acme.

There is no conflict of interest since we have none internal research programs. Your IP is fully protected.

By the way, Acme Bioscience provides service for nucleoside triphosphate synthesis. We have a validated and reliable method for triphosphate synthesis and purification. A minimum of 10 mg nucleoside starting material is required. We provide the product in a solid form as its triethylammonium salt. A complete analytical package including H-NMR, P-NMR, LCMS, and HPLC will be provided. The turnaround time is two weeks. Please try out our triphosphate synthesis service when needed.

Acme has a strong management team and experienced chemists with extensive knowledge in medicinal chemistry and organic synthesis. Our current unique positions with both Palo Alto, U.S. and Shanghai sites enable us to support our customers with great flexibility and efficiency. Customers have been using our hybrid model for FTE projects at both Palo Alto and Shanghai sites to obtain good quality and cost effective services and products. We also support companies on fee for services based projects at both sites.

Besides providing medicinal chemistry support, Acme can help your API development projects in the following areas:

- Search for GMP raw materials (Shanghai site has a chemical search team)
- Make GMP raw materials for hundreds kg scales and up
- Make reference compounds, impurities markers, metabolites, and degradants
- non-GMP materials scale up work (hundreds kg scales)

Acme is well equipped and has a strong track record to support many successful companies. We hope to work with your team and contribute to the continued success of your company.

Most recent examples:

XenoPort, Inc.: working with the company for many years, sold for \$467 million to Arbor Pharma.

Flexus Biosciences: working with the company for just one year, sold for 1.3 billion to BMS.

Anacor Pharmaceuticals: Working with the company for over 14 years, sold for 5.2 billion to Pfizer.

A brief background about our management team members.

(1) Jason Zhang, President and CEO

Got PhD at Emory, worked at Microcide for 8 years, founded Acme Bioscience in 2001, and expanded Acme Shanghai in 2009.

(2) Zhi-Jie (ZJ) Ni, Chief Scientific Officer

Got PhD from China, did postdoc at Ohio State and Emory, worked at Affymax, Versicor, and Chiron/Novartis for over 13 years before Acme in 2007.

(3) Ian (Yingcai) Wang, SVP of Chemistry

Got PhD at Texas A&M, worked at Tularik/Amgen, Endocyte, and Purdue U for over 13 years before Acme in 2015.

(4) Jane Wang, VP of Business Development

Got PhD at Emory, worked at Gilead medchem for 13 years and Regulatory CMC for 4.5 years before Acme in 2011.

We look forward to supporting your projects.

Best regards,

Jane

Jane Jianying Wang

Acme Bioscience, Inc.

3941 E. Bayshore Road

Palo Alto, CA 94303

Jane.Wang@acmeca.com

Phone: (650) 969-8000 Ext. 505

Fax: (650) 969-8001

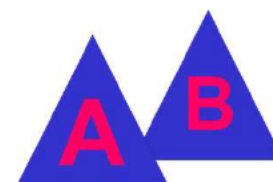
Cell: (650) 533-2718

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Palo Alto, CA 94303, USA
(650) 969-8000

info@acmeca.com



Shanghai Zhang-Jiang Hi-Tech Park
509 Renqing Road, Building 3
Pudong, Shanghai 201201, China

info@acmeca.com

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- Lead optimization
 - Optimize potency
 - Secure IP
 - Improve ADME properties of lead molecules
- Pro-drugs

Process Chemistry R&D and Manufacturing

- Route selection and optimization
- Develop non-GMP API for IND enabling tox studies
- Scale up to multi kilograms of materials
- Produce hundreds kilograms to tons scale of non-GMP starting materials
- Manage GMP materials through alliances

Project Based Custom Synthesis

- Nucleotides, nucleosides, and triphosphates
- Reference compounds
- Building blocks and small libraries
- Intermediates and catalog products
- Impurities, degradants, and metabolites
- Chiral synthesis and separation
- Stable isotopes

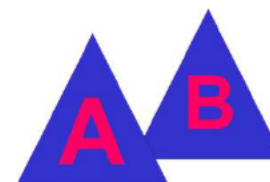
Other Services

- Regulatory CMC consulting
- Analytical services (HPLC, LCMS, NMR, X-ray, chiral analysis and separation, etc.)
- Biological tests, *In vitro* & *in vivo* PKDM through alliances

Acme Bioscience, Inc.

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Two Sites to Support Your Business
San Francisco - Shanghai



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USA Site

- All Have PhDs in Organic Chemistry
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- Motivated, Independent, and Efficient

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- 11,000 sqf of Office and Lab Space
- Three State-of-the-Art Chemistry Labs
- Twenty-Six Standard Fume Hoods

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- High-Pressure Reactor (2000 psi)
- Microwave Synthesizer
- Photo Reactor & Polarimeter
- Lyophilizer & Biotage Flash System
- Reaxys and SciFinder Database
- In House 20L, 50L, 100L Reactors
- Manufacture: 1000L, 2000L, 5000L

China Site

- Local Managers Familiar with Chinese Rules/Regulations
- Combination of PhD, MS, and BS Scientists with Prior Industry Experience

- 65,000 sqf of Office and Lab Space
- Over 200 Standard Fume Hoods
- Five Scale-up Labs
- Manufactures

3941 E. Bayshore Road, Palo Alto, California 94303, USA
Shanghai Zhang-Jiang Hi-Tech Park (East), Building No. 3, 509 Renqing Road, Pudong New Area, Shanghai 201201, China
Tel: (650) 969-8000 Email: info@acmeca.com

From: Peter Rapp <peter@nbaging.com>
Sent time: 11/20/2021 10:59:14 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Wang et al. (2017), NBA, 55, 99-114

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Editor-in-Chief
Neurobiology of Aging

From: Peter Rapp <peter@nbaging.com>
Sent time: 11/21/2021 05:17:16 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

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[Peter R. Rapp, PhD](#)
Editor-in-Chief
[Neurobiology of Aging](#)

From: Hoau-yan Wang
Sent time: 11/22/2021 09:44:26 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

POL 87(2)(a)

Hoau

From: Peter Rapp <peter@nbaging.com>
Sent: Sunday, November 21, 2021 5:17 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

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[Peter R. Rapp, PhD](#)
Editor-in-Chief
[Neurobiology of Aging](#)

From: Hoau-yan Wang
Sent time: 11/22/2021 10:20:10 AM
To: Peter Rapp <peter@nbaging.com>
Cc: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Re: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

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[Neurobiology of Aging](#)

From: Hoau-yan Wang
Sent time: 11/22/2021 11:01:13 AM
To: [REDACTED]@gmail.com
Subject: Fw: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

From: Hoau-yan Wang
Sent: Monday, November 22, 2021 10:20 AM
To: Peter Rapp
Cc: Beidel, Jennifer L.
Subject: Re: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

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From: Peter Rapp <peter@nbaging.com>
Sent time: 11/22/2021 07:07:03 PM
To: Hoau-yan Wang
Cc: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Re: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

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From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 11/23/2021 01:51:49 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] You have a new full-text request

ResearchGate



Daniel Siehl requested the full-text of your article:

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

You can use a stored copy of this full-text to quickly fulfill this request

[View request](#)

This message was sent to hywang@sci.cny.cuny.edu by ResearchGate. To make sure you receive our updates, add ResearchGate to your address book or safe list. [See instructions](#)

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From: Hoau-yan Wang
Sent time: 11/23/2021 08:43:56 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

From: Peter Rapp <peter@nbaging.com>
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From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 11/24/2021 01:24:58 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Hoau-Yan, a recent article cited your research

ResearchGate



Hoau-Yan, we found a recent citation of your research:



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

Recent advances in molecular pathways and therapeutic implications targeting neuroinflammation for Alzheimer's disease

Citing article

Nov 2021 · Inflammopharmacology

Rishika Dhapola · Subhendu Shekhar Hota · Phulen Sarma · Anusuya Bhattacharyya · [...]

[View citing research](#)

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ResearchGate GmbH, Chausseestr. 20, 10115 Berlin, Germany. [Imprint](#).
See our [Privacy Policy](#) and [Terms of Service](#).

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent time: 11/24/2021 02:32:03 PM
To: Sharki Ahmed; Candice Baptiste-Sexton
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION
Attachments: Other supports-CUNY-Wang-upated.docx

Dear Sharki,

Finally I heard from USC. Please prepare Just-In-Time materials and send them to both Ms. Roxanne Odom (rododom@med.usc.edu) and Ms. Patricia Corona (pcorona@usc.edu).. Enclosed is my updated other supports document using the new format. Please copy me when you send the documents.

Thank you for your help.

Happy Thanksgiving.

Best,

Hoau-Yan Wang

On Tue, Nov 23, 2021 at 4:53 PM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Any update?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, November 9, 2021 11:41 AM
To: Hoau-Yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Noted, thanks for the update!

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Tuesday, November 9, 2021 11:39 AM
To: Sharki Ahmed
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

NOT YET. I will forward to you once I hear back from the primary PI.

Thanks.

Hoau-Yan Wang

On Tue, Nov 9, 2021 at 11:14 AM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Just circling back to this. Any update?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
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160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, November 2, 2021 9:42 AM
To: Hoau-Yan Wang
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Hi Dr. Wang,

Noted. Thank you for the update.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Tuesday, November 2, 2021 9:29 AM
To: Sharki Ahmed
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Sharki,

I am waiting for a description on a pending project, once I have the description I will then send my other supports document to you.

Thanks.

Best,

Hoau-Yan Wang

On Mon, Nov 1, 2021 at 1:22 PM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Based on the information that I have when I assisted you on submitting, there are no human/animal subjects. That being said it seems that only the Other Support document is needed, please confirm.

Use the attached template and fill it out according to the instructions on the template and in the email below. Once done, please return it to me for review.

Best,

Sharki Ahmed
Grants Associate

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160 Convent Avenue SH-Room 16
New York, NY 10031
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sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Monday, November 1, 2021 1:13 PM
To: Candice Baptiste-Sexton
Cc: Hoau-Yan wang; Hoau-yan Wang; Grants Preaward
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Hi Candice,

I worked with Dr. Wang on this submission and will follow up directly.

Dr. Wang- I will email you separately.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Candice Baptiste-Sexton
Sent: Monday, November 1, 2021 1:02 PM
To: Grants Preaward
Cc: Hoau-Yan wang; Hoau-yan Wang
Subject: FW: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Dear PreAward Team,

Who worked with Dr. Wang on the submission referenced below? Once identified, kindly assist with the JIT submission. Sharki, please facilitate.

Thanks.

Best regards,

Candice Baptiste-Sexton

Director, Grants and Sponsored Programs – CCNY

PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Monday, November 1, 2021 12:59 PM
To: Candice Baptiste-Sexton <csexton@ccny.cuny.edu>
Subject: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Dear Candice,

I am forwarding this email to inform you of a request for the just-in-time document.

Thank you.

Best regards,

Hoau-Yan Wang

----- Forwarded message -----

From: **Hussein Yassine** <hyassine@usc.edu>

Date: Sat, Oct 30, 2021 at 4:10 PM

Subject: Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

To: Zoe Arvanitakis <Zoe_Arvanitakis@rush.edu>, Hoau-Yan wang <[REDACTED]@gmail.com>

Cc: Roxanne Odom <rodom@med.usc.edu>

Please prepare JIT documents

Hussein

Begin forwarded message:

From: era-notify@mail.nih.gov

Date: October 30, 2021 at 12:54:57 PM PDT

To: Hussein Yassine <hyassine@usc.edu>

Cc: USC Award <uscaward@usc.edu>

Subject: REQUEST FOR JUST-IN-TIME INFORMATION

*** This is an automated notification - Please do not reply to this message. ***

Principal Investigator: Hussein Yassine

Application 1 R01 AG076124-01A1 entitled Brain cPLA2 as a mechanism for neuroinflammation in AD/ADRD with and without APOE4 has completed the first phase of peer review.

REQUEST FOR JUST-IN-TIME INFORMATION

THIS IS NOT A NOTICE OF GRANT AWARD NOR SHOULD IT BE CONSTRUED AS AN INDICATOR OF POSSIBLE AWARD

This is a standard notice and request for information from all principal investigators with grant applications receiving an impact score of 30 or less (regardless of the IC's payline) which reflects NIH's current tightened paylines and new Impact Scoring system. This notice is a request for Just-In-Time Information. NIH Institutes and Centers (ICs) have varying pay lines and funding strategies that determine which grants will be funded.

If a decision is made to fund this application, the assigned IC will need the following information PRIOR to making an award.

- **Current Other Support:** Provide active and pending support information for all individuals designated in an application as senior/key personnel—those devoting measurable effort to a project. Other support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards. Training awards, prizes or gifts are not included. There is no form page for providing other

support, although sample format pages are available at <https://grants.nih.gov/grants/funding/phs398/othersupport.doc> and <https://grants.nih.gov/grants/funding/phs398/othersupport.pdf>. Note that effort devoted to projects must be measured in person-months.

- For all senior/key personnel, provide details on how you would adjust any budgetary, scientific, or effort overlap if this application is funded.
- For Career Development Award applications, information on all active support for the candidate, sponsor(s), co-sponsor(s), and Senior/Key Personnel may be requested by the awarding component prior to award.

- **Certifications:**

- **IRB Approval:** If the proposed project involves human subjects research, the certification date of IRB review and approval must be submitted. Pending or out-of-date approvals are not acceptable.
- **IACUC Approval:** If the proposed project involves research with live vertebrate animals, the verification of the date of IACUC approval of those sections of the application that involve use of vertebrate animals along with any IACUC-imposed changes must be submitted. Pending or out-of-date approvals are not acceptable.
- **Human Subjects Education:** If the proposed project involves human subjects research, certification that any person identified as senior/key personnel involved in human subjects research has completed an education program in the protection of human subjects must be submitted.
- **Human Embryonic Stem Cells (hESCs):** If the proposed project involves hESCs and the applicant did not identify a hESC line from the NIH Human Embryonic Stem Cell Registry in the application, the line(s) should be included
- **Institutional Certification for Human Genomic Data Sharing:** If the proposed project involves a genomic data sharing plan for the generation of human genomic data, investigators must submit an Institutional Certification, or, in some cases, a Provisional Institutional Certification. Institutional certification forms and directions for completing them are available on the NIH GDS: <https://osp.od.nih.gov/scientific-sharing/institutional-certifications/>. This certification should be submitted as a "Genome Data Sharing Certification" in the eRA Commons Just-in-Time module.
- **SBIR Funding Agreement:** For SBIR applicants, provide only upon request the SBIR Funding Agreement Certification described in Section 2.18 of the Supplemental Grant Application Instructions. The certification is available in fillable formats at: https://grants.nih.gov/grants/forms/manage_a_small_business_award.htm. This should be submitted as an "Other Upload" in the eRA Commons Just-in-Time module.
- **STTR Funding Agreement:** For STTR applicants, provide only upon request the STTR Funding Agreement Certification described in Section 2.19 of the Supplemental Grant Application Instructions. The certification is available in fillable formats at: https://grants.nih.gov/grants/forms/manage_a_small_business_award.htm <https://grants.nih.gov/grants/forms.htm#sbir>. This should be submitted as an "Other Upload" in the eRA Commons Just-in-Time module.

- **Other Information Requested by the Awarding IC:** NIH IC's may also request additional Just-in-Time information on a case-by-case basis, such as revised budgets or changes to the human subjects or vertebrate animal sections of the application. These changes should be submitted as an "Other Upload" file in the eRA Commons Just-In-Time module.

Applicants must submit their information at least 60 days before the proposed project period start date. However, you should contact the IC for specific guidance. We understand that obtaining IRB and/or IACUC approval may take more than two weeks. Therefore, you may submit these approvals at the earliest date they are available.

All of the information must be submitted electronically using the Just-In-Time feature of the eRA Commons found in the Commons **Status** section. Department and Division assignments may be changed or added by the organization's Signing Official (SO) via the eRA Commons found in the Commons Status section, under Re-Assign Award. For information on the Commons see: <https://public.era.nih.gov/commons/index.jsp>.

Timely submission of the requested information will enable NIH staff to expedite an award should an

application be identified for funding. Institute staff will contact you if they have not received the requested information or if additional information is required. If you have any additional questions, please contact the assigned Grants Management Specialist. Contact information for these individuals can be found in Commons Status.

Please be reminded that this notice and request for information applies only to principal investigators with grant applications receiving an impact score of 30 or less (regardless of the IC's payline). For additional information on the Just-in-Time procedures, see section 2.5.1 of the NIH Grants Policy Statement.

Wang, Hoau-Yan

Active research support

R21 AG065890 (Li, Wang) 4/1/2020-1/31/2022 0.66 Academic
NIA \$50,000

Translating the function of *C. elegans* APL-1 into understanding the function of human APP.

The primary goal of this study is to examine the function and interactors of APP in *c. elegans*, mice and postmortem human brain tissues for their role in Alzheimer's disease pathogenesis.

R44 AG 065152-01 (Burns) 08/1/2020-07/31/2022 1 Academic
NIA \$76,542

Open-label extension of a 3-month blinded clinical trial for PTI-125.

The primary goal of this study is to determine the anti-Alzheimer's disease (AD) therapeutic efficacy of the PTI-125 in a clinical trial setting.

1R42AG057329 (Thorton, Wang, Burns) 09/30/2018-06/30/2021 1 Academic
NIA \$89,259

Development of PTI-125 DX, a blood-based diagnostic for Alzheimer's disease.

The primary goal of this study is to develop a blood biomarker specific for Alzheimer's disease.

1 R01 AG057658-01 (Talbot) 5/15/2018-2/28/2023 1 Academic
NIA \$123,403

Treating Alzheimer's Disease by reducing insulin resistance with incretin receptor agonists.

The primary goal of this study is to examine whether reducing brain insulin resistance by incretin receptor agonists attenuates Alzheimer's disease pathologies.

RF1AG059621 (Arvanitakis) 8/15/2018-6/30/2023 1.1 Academic
NIA \$129,497

Linking peripheral and brain insulin resistance to AD neuropathology and cognition.

The primary goal of this study is to examine whether peripheral insulin resistance contribute to central insulin resistance and Alzheimer's disease pathologies as well as cognitive decline.

1 R01 MH116463 (Hahn, Wang) 4/1/2019-3/31/2024 1 Academic
NIMH \$75,742

mGluR5 hypoactivity is integral to glutamatergic dysregulation in schizophrenia.

The primary goal of this study is to examine the mechanism responsible for mGluR5 hypoactivity that leads to dysregulated glutamatergic systems in schizophrenia.

Pending research supports

R21MH127273 (Hahn, Wang) 7/1/2021-6/30/2023 0.5 Academic

BDNF-Glucocorticoid interplay in antidepressant responsiveness.

This study aims to study signaling interplay between BDNF and glucocorticoid in olfactory neuron cultures to assess the responsivity of antidepressants.

1 R01 AG076124-01 **(Yasseine, Arvanitakis, Wang)** 4/1/2022-3/31/2027 1 Academic

This project will elucidate a novel mechanism for APOE4 induced brain inflammation in AD/ADRD. The study of available brain tissues from well-characterized autopsied persons with a range of clinical and pathologic phenotypes will provide deep insights into cell specific cPLA2 activation profiles in relation to APOE4 and markers of inflammation.

OVERLAP

There is no scientific or budgetary overlap among the active grants and two applications under consideration.

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent time: 11/24/2021 02:38:44 PM
To: Sharki Ahmed; Candice Baptiste-Sexton
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION
Attachments: Other supports-CUNY-Wang-upated.docx

Sorry. Please use this one.

Thanks.

Hoau

On Wed, Nov 24, 2021 at 2:32 PM Hoau-Yan Wang <[REDACTED]@gmail.com> wrote:

Dear Sharki,

Finally I heard from USC. Please prepare Just-In-Time materials and send them to both Ms. Roxanne Odom (rododom@med.usc.edu) and Ms. Patricia Corona (pcorona@usc.edu).. Enclosed is my updated other supports document using the new format. Please copy me when you send the documents.

Thank you for your help.

Happy Thanksgiving.

Best,

Hoau-Yan Wang

On Tue, Nov 23, 2021 at 4:53 PM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Any update?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, November 9, 2021 11:41 AM
To: Hoau-Yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Noted, thanks for the update!

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Tuesday, November 9, 2021 11:39 AM
To: Sharki Ahmed
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

NOT YET. I will forward to you once I hear back from the primary PI.

Thanks.

Hoau-Yan Wang

On Tue, Nov 9, 2021 at 11:14 AM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Just circling back to this. Any update?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, November 2, 2021 9:42 AM
To: Hoau-Yan Wang
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Hi Dr. Wang,

Noted. Thank you for the update.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
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To: Sharki Ahmed
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Sharki,

I am waiting for a description on a pending project, once I have the description I will then send my other supports document to you.

Thanks.

Best,

Hoau-Yan Wang

On Mon, Nov 1, 2021 at 1:22 PM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

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Grants Associate

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The City College of New York
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sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Monday, November 1, 2021 1:13 PM
To: Candice Baptiste-Sexton
Cc: Hoau-Yan wang; Hoau-yan Wang; Grants Preaward

Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Hi Candice,

I worked with Dr. Wang on this submission and will follow up directly.

Dr. Wang- I will email you separately.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
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Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Candice Baptiste-Sexton
Sent: Monday, November 1, 2021 1:02 PM
To: Grants Preaward
Cc: Hoau-Yan wang; Hoau-yan Wang
Subject: FW: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Dear PreAward Team,

Who worked with Dr. Wang on the submission referenced below? Once identified, kindly assist with the JIT submission. Sharki, please facilitate.

Thanks.

Best regards,

Candice Baptiste-Sexton

Director, Grants and Sponsored Programs – CCNY

PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Monday, November 1, 2021 12:59 PM

To: Candice Baptiste-Sexton <csexton@ccny.cuny.edu>
Subject: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Dear Candice,

I am forwarding this email to inform you of a request for the just-in-time document.

Thank you.

Best regards,

Hoau-Yan Wang

----- Forwarded message -----

From: Hussein Yassine <hyassine@usc.edu>
Date: Sat, Oct 30, 2021 at 4:10 PM
Subject: Fwd: REQUEST FOR JUST-IN-TIME INFORMATION
To: Zoe Arvanitakis <Zoe_Arvanitakis@rush.edu>, Hoau-Yan wang <[REDACTED]@gmail.com>
Cc: Roxanne Odom <rodom@med.usc.edu>

Please prepare JIT documents

Hussein

Begin forwarded message:

From: era-notify@mail.nih.gov
Date: October 30, 2021 at 12:54:57 PM PDT
To: Hussein Yassine <hyassine@usc.edu>
Cc: USC Award <uscaward@usc.edu>
Subject: REQUEST FOR JUST-IN-TIME INFORMATION

*** This is an automated notification - Please do not reply to this message. ***

Principal Investigator: Hussein Yassine

Application 1 R01 AG076124-01A1 entitled Brain cPLA2 as a mechanism for neuroinflammation in AD/ADRD with and without APOE4 has completed the first phase of peer review.

REQUEST FOR JUST-IN-TIME INFORMATION

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 - For all senior/key personnel, provide details on how you would adjust any budgetary, scientific, or effort overlap if this application is funded.
 - For Career Development Award applications, information on all active support for the candidate, sponsor(s), co-sponsor(s), and Senior/Key Personnel may be requested by the awarding component prior to award.
- **Certifications:**
 - **IRB Approval:** If the proposed project involves human subjects research, the certification date of IRB review and approval must be submitted. Pending or out-of-date approvals are not acceptable.
 - **IACUC Approval:** If the proposed project involves research with live vertebrate animals, the verification of the date of IACUC approval of those sections of the application that involve use of vertebrate animals along with any IACUC-imposed changes must be submitted. Pending or out-of-date approvals are not acceptable.
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 - **Institutional Certification for Human Genomic Data Sharing:** If the proposed project involves a genomic data sharing plan for the generation of human genomic data, investigators must submit an Institutional Certification, or, in some cases, a Provisional Institutional Certification. Institutional certification forms and directions for completing them are available on the NIH GDS: <https://osp.od.nih.gov/scientific-sharing/institutional-certifications/>. This certification should be submitted as a "Genome Data Sharing Certification" in the eRA Commons Just-in-Time module.
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- **Other Information Requested by the Awarding IC:** NIH IC's may also request additional Just-in-Time information on a case-by-case basis, such as revised budgets or changes to the human subjects or vertebrate animal sections of the application. These changes should be submitted as an "Other Upload" file in the eRA Commons Just-In-Time module.

Applicants must submit their information at least 60 days before the proposed project period start date. However, you should contact the IC for specific guidance. We understand that obtaining IRB and/or IACUC approval may take more than two weeks. Therefore, you may submit these approvals at the earliest date they are available.

All of the information must be submitted electronically using the Just-In-Time feature of the eRA

Commons found in the Commons **Status** section. Department and Division assignments may be changed or added by the organization's Signing Official (SO) via the eRA Commons found in the Commons Status section, under Re-Assign Award. For information on the Commons see: <https://public.era.nih.gov/commons/index.jsp>.

Timely submission of the requested information will enable NIH staff to expedite an award should an application be identified for funding. Institute staff will contact you if they have not received the requested information or if additional information is required. If you have any additional questions, please contact the assigned Grants Management Specialist. Contact information for these individuals can be found in Commons Status.

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Wang, Hoau-Yan

Active research support

R21 AG065890 (Li, Wang) 4/1/2020-1/31/2022 0.66 Academic
NIA \$50,000

Translating the function of *C. elegans* APL-1 into understanding the function of human APP.

The primary goal of this study is to examine the function and interactors of APP in *c. elegans*, mice and postmortem human brain tissues for their role in Alzheimer's disease pathogenesis.

R44 AG 065152-01 (Burns) 08/1/2020-07/31/2022 1 Academic
NIA \$76,542

Open-label extension of a 3-month blinded clinical trial for PTI-125.

The primary goal of this study is to determine the anti-Alzheimer's disease (AD) therapeutic efficacy of the PTI-125 in a clinical trial setting.

1R42AG057329 (Thorton, Wang, Burns) 09/30/2018-06/30/2021 1 Academic
NIA \$89,259

Development of PTI-125 DX, a blood-based diagnostic for Alzheimer's disease.

The primary goal of this study is to develop a blood biomarker specific for Alzheimer's disease.

1 R01 AG057658-01 (Talbot) 5/15/2018-2/28/2023 1 Academic
NIA \$123,403

Treating Alzheimer's Disease by reducing insulin resistance with incretin receptor agonists.

The primary goal of this study is to examine whether reducing brain insulin resistance by incretin receptor agonists attenuates Alzheimer's disease pathologies.

RF1AG059621 (Arvanitakis) 8/15/2018-6/30/2023 1.1 Academic
NIA \$129,497

Linking peripheral and brain insulin resistance to AD neuropathology and cognition.

The primary goal of this study is to examine whether peripheral insulin resistance contribute to central insulin resistance and Alzheimer's disease pathologies as well as cognitive decline.

1 R01 MH116463 (Hahn, Wang) 4/1/2019-3/31/2024 1 Academic
NIMH \$75,742

mGluR5 hypoactivity is integral to glutamatergic dysregulation in schizophrenia.

The primary goal of this study is to examine the mechanism responsible for mGluR5 hypoactivity that leads to dysregulated glutamatergic systems in schizophrenia.

Pending research supports

R21MH127273 (Hahn, Wang) 7/1/2021-6/30/2023 0.5 Academic

BDNF-Glucocorticoid interplay in antidepressant responsiveness.

This study aims to study signaling interplay between BDNF and glucocorticoid in olfactory neuron cultures to assess the responsivity of antidepressants.

Program Director/Principal Investigator (Last, First, Middle):

1 R01 AG076124-01 (Yasseine, Arvanitakis, Wang) 4/1/2022-3/31/2027 1 Academic
Brain cPLA2 as a mechanism for neuroinflammation in AD/ADRD with and without APOE4.

This project will elucidate a novel mechanism for APOE4 induced brain inflammation in AD/ADRD. The study of available brain tissues from well-characterized autopsied persons with a range of clinical and pathologic phenotypes will provide deep insights into cell specific cPLA2 activation profiles in relation to APOE4 and markers of inflammation.

OVERLAP

There is no scientific or budgetary overlap among the active grants and two applications under consideration.

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent time: 11/25/2021 10:52:11 AM
To: Sharki Ahmed
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION
Attachments: Other supports-CUNY-Wang-upated.docx

Dear Sharki,

Please find the updated and revised other support document. All the indicated errors had been corrected. Please forward all the JIT documents to USC (Ms. Odom and Ms. Corona) as soon as you can. The primary wants to send it by this coming week.

Thanks

Best,

Hoau-Yan Wang

On Wed, Nov 24, 2021 at 2:52 PM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Please see our review comments below and send me a revised version.

- Missing PI name at the top in the header
- Project #3 is listed as active but the end date has passed
- Pending Support entries are missing the source (such as NIH, NIMH, NIA, etc...)

FYI- Our office closes at 3pm today.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Wednesday, November 24, 2021 2:48 PM
To: Hoau-Yan Wang
Cc: Hoau-yan Wang; Candice Baptiste-Sexton
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Hi Dr. Wang,

We will review and let you know if any changes are needed.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Wednesday, November 24, 2021 2:38 PM
To: Sharki Ahmed; Candice Baptiste-Sexton
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Sorry. Please use this one.

Thanks.

Hoau

On Wed, Nov 24, 2021 at 2:32 PM Hoau-Yan Wang <[REDACTED]@gmail.com> wrote:
Dear Sharki,

Finally I heard from USC. Please prepare Just-In-Time materials and send them to both Ms. Roxanne Odom (rodome@med.usc.edu) and Ms. Patricia Corona (pcorona@usc.edu).. Enclosed is my updated other supports document using the new format. Please copy me when you send the documents.

Thank you for your help.

Happy Thanksgiving.

Best,

Hoau-Yan Wang

On Tue, Nov 23, 2021 at 4:53 PM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Any update?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Tuesday, November 9, 2021 11:41 AM
To: Hoau-Yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Noted, thanks for the update!

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Tuesday, November 9, 2021 11:39 AM
To: Sharki Ahmed
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

NOT YET. I will forward to you once I hear back from the primary PI.

Thanks.

Hoau-Yan Wang

On Tue, Nov 9, 2021 at 11:14 AM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Just circling back to this. Any update?

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed

Sent: Tuesday, November 2, 2021 9:42 AM
To: Hoau-Yan Wang
Cc: Hoau-yan Wang
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Hi Dr. Wang,

Noted. Thank you for the update.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Tuesday, November 2, 2021 9:29 AM
To: Sharki Ahmed
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Sharki,

I am waiting for a description on a pending project, once I have the description I will then send my other supports document to you.

Thanks.

Best,

Hoau-Yan Wang

On Mon, Nov 1, 2021 at 1:22 PM Sharki Ahmed <sahmed9@ccny.cuny.edu> wrote:

Hi Dr. Wang,

Based on the information that I have when I assisted you on submitting, there are no human/animal subjects. That being said it seems that only the Other Support document is needed, please confirm.

Use the attached template and fill it out according to the instructions on the template and in the email below. Once done, please return it to me for review.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sharki Ahmed
Sent: Monday, November 1, 2021 1:13 PM
To: Candice Baptiste-Sexton
Cc: Hoau-Yan wang; Hoau-yan Wang; Grants Preaward
Subject: Re: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Hi Candice,

I worked with Dr. Wang on this submission and will follow up directly.

Dr. Wang- I will email you separately.

Best,

Sharki Ahmed
Grants Associate

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue SH-Room 16
New York, NY 10031
Ph:212-650-7915 F: 212-650-7906
sahmed9@ccny.cuny.edu

GSP- <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Candice Baptiste-Sexton
Sent: Monday, November 1, 2021 1:02 PM
To: Grants Preaward
Cc: Hoau-Yan wang; Hoau-yan Wang
Subject: FW: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Dear PreAward Team,

Who worked with Dr. Wang on the submission referenced below? Once identified, kindly assist with the JIT submission. Sharki, please facilitate.

Thanks.

Best regards,

Candice Baptiste-Sexton

Director, Grants and Sponsored Programs – CCNY

PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Monday, November 1, 2021 12:59 PM
To: Candice Baptiste-Sexton <csexton@ccny.cuny.edu>
Subject: [EXTERNAL] Fwd: REQUEST FOR JUST-IN-TIME INFORMATION

Dear Candice,

I am forwarding this email to inform you of a request for the just-in-time document.

Thank you.

Best regards,

Hoau-Yan Wang

----- Forwarded message -----

From: Hussein Yassine <hyassine@usc.edu>
Date: Sat, Oct 30, 2021 at 4:10 PM
Subject: Fwd: REQUEST FOR JUST-IN-TIME INFORMATION
To: Zoe Arvanitakis <Zoe_Arvanitakis@rush.edu>, Hoau-Yan wang <[REDACTED]@gmail.com>
Cc: Roxanne Odom <rodom@med.usc.edu>

Please prepare JIT documents

Hussein

Begin forwarded message:

From: era-notify@mail.nih.gov
Date: October 30, 2021 at 12:54:57 PM PDT
To: Hussein Yassine <hyassine@usc.edu>
Cc: USC Award <uscaward@usc.edu>
Subject: REQUEST FOR JUST-IN-TIME INFORMATION

*** This is an automated notification - Please do not reply to this message. ***

Principal Investigator: Hussein Yassine

Application 1 R01 AG076124-01A1 entitled Brain cPLA2 as a mechanism for neuroinflammation in AD/ADRD with and without APOE4 has completed the first phase of peer review.

REQUEST FOR JUST-IN-TIME INFORMATION

THIS IS NOT A NOTICE OF GRANT AWARD NOR SHOULD IT BE CONSTRUED AS AN INDICATOR OF POSSIBLE AWARD

This is a standard notice and request for information from all principal investigators with grant applications receiving an impact score of 30 or less (regardless of the IC's payline) which reflects NIH's current tightened paylines and new Impact Scoring system. This notice is a request for Just-In-Time Information. NIH Institutes and Centers (ICs) have varying pay lines and funding strategies that determine which grants will be funded.

If a decision is made to fund this application, the assigned IC will need the following information PRIOR to making an award.

- **Current Other Support:** Provide active and pending support information for all individuals designated in an application as senior/key personnel—those devoting measurable effort to a project. Other support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards. Training awards, prizes or gifts are not included. There is no form page for providing other support, although sample format pages are available at <https://grants.nih.gov/grants/funding/phs398/othersupport.doc> and <https://grants.nih.gov/grants/funding/phs398/othersupport.pdf>. Note that effort devoted to projects must be measured in person-months.
 - For all senior/key personnel, provide details on how you would adjust any budgetary, scientific, or effort overlap if this application is funded.
 - For Career Development Award applications, information on all active support for the candidate, sponsor(s), co-sponsor(s), and Senior/Key Personnel may be requested by the awarding component prior to award.
- **Certifications:**
 - **IRB Approval:** If the proposed project involves human subjects research, the certification date of IRB review and approval must be submitted. Pending or out-of-date approvals are not acceptable.
 - **IACUC Approval:** If the proposed project involves research with live vertebrate animals, the verification of the date of IACUC approval of those sections of the application that involve use of vertebrate animals along with any IACUC-imposed changes must be submitted. Pending or out-of-date approvals are not acceptable.
 - **Human Subjects Education:** If the proposed project involves human subjects research, certification that any person identified as senior/key personnel involved in human subjects research has completed an education program in the protection of human subjects must be submitted.
 - **Human Embryonic Stem Cells (hESCs):** If the proposed project involves hESCs and the applicant did not identify a hESC line from the NIH Human Embryonic Stem Cell Registry in the application, the line(s) should be included
 - **Institutional Certification for Human Genomic Data Sharing:** If the proposed project involves a genomic data sharing plan for the generation of human genomic data, investigators must submit an Institutional Certification, or, in some cases, a Provisional Institutional Certification. Institutional certification forms and directions for completing them are available on the NIH GDS: <https://osp.od.nih.gov/scientific-sharing/institutional-certifications/>. This certification should be submitted as a "Genome Data Sharing Certification" in the eRA Commons Just-in-Time module.
 - **SBIR Funding Agreement:** For SBIR applicants, provide only upon request the SBIR Funding Agreement Certification described in Section 2.18 of the Supplemental Grant Application Instructions. The certification is available in fillable formats at: https://grants.nih.gov/grants/forms/manage_a_small_business_award.htm. This should be submitted as an "Other Upload" in the eRA Commons Just-in-Time module.
 - **STTR Funding Agreement:** For STTR applicants, provide only upon request the STTR Funding Agreement Certification described in Section 2.19 of the Supplemental Grant Application Instructions. The certification is available in fillable formats at: https://grants.nih.gov/grants/forms/manage_a_small_business_award.htm

<https://grants.nih.gov/grants/forms.htm#sbir>. This should be submitted as an "Other Upload" in the eRA Commons Just-in-Time module.

- **Other Information Requested by the Awarding IC:** NIH IC's may also request additional Just-in-Time information on a case-by-case basis, such as revised budgets or changes to the human subjects or vertebrate animal sections of the application. These changes should be submitted as an "Other Upload" file in the eRA Commons Just-In-Time module.

Applicants must submit their information at least 60 days before the proposed project period start date. However, you should contact the IC for specific guidance. We understand that obtaining IRB and/or IACUC approval may take more than two weeks. Therefore, you may submit these approvals at the earliest date they are available.

All of the information must be submitted electronically using the Just-In-Time feature of the eRA Commons found in the Commons **Status** section. Department and Division assignments may be changed or added by the organization's Signing Official (SO) via the eRA Commons found in the Commons Status section, under Re-Assign Award. For information on the Commons see: <https://public.era.nih.gov/commons/index.jsp>.

Timely submission of the requested information will enable NIH staff to expedite an award should an application be identified for funding. Institute staff will contact you if they have not received the requested information or if additional information is required. If you have any additional questions, please contact the assigned Grants Management Specialist. Contact information for these individuals can be found in Commons Status.

Please be reminded that this notice and request for information applies only to principal investigators with grant applications receiving an impact score of 30 or less (regardless of the IC's payline). For additional information on the Just-in-Time procedures, see section 2.5.1 of the NIH Grants Policy Statement.

Program Director/Principal Investigator (Last, First, Middle): Wang, Hoau-Yan

Wang, Hoau-Yan

Active research support

R21 AG065890 (Li, Wang) 4/1/2020-1/31/2022 0.66 Academic
NIA \$50,000

Translating the function of *C. elegans* APL-1 into understanding the function of human APP.

The primary goal of this study is to examine the function and interactors of APP in *c. elegans*, mice and postmortem human brain tissues for their role in Alzheimer's disease pathogenesis.

R44 AG 065152-01 (Burns) 08/1/2020-07/31/2022 1 Academic
NIA \$76,542

Open-label extension of a 3-month blinded clinical trial for PTI-125.

The primary goal of this study is to determine the anti-Alzheimer's disease (AD) therapeutic efficacy of the PTI-125 in a clinical trial setting.

1 R01 AG057658-01 (Talbot) 5/15/2018-2/28/2023 1 Academic
NIA \$123,403

Treating Alzheimer's Disease by reducing insulin resistance with incretin receptor agonists.

The primary goal of this study is to examine whether reducing brain insulin resistance by incretin receptor agonists attenuates Alzheimer's disease pathologies.

RF1AG059621 (Arvanitakis) 8/15/2018-6/30/2023 1.1 Academic
NIA \$129,497

Linking peripheral and brain insulin resistance to AD neuropathology and cognition.

The primary goal of this study is to examine whether peripheral insulin resistance contribute to central insulin resistance and Alzheimer's disease pathologies as well as cognitive decline.

1 R01 MH116463 (Hahn, Wang) 4/1/2019-3/31/2024 1 Academic
NIMH \$75,742

mGluR5 hypoactivity is integral to glutamatergic dysregulation in schizophrenia.

The primary goal of this study is to examine the mechanism responsible for mGluR5 hypoactivity that leads to dysregulated glutamatergic systems in schizophrenia.

Pending research supports

R21MH127273 (Hahn, Wang) 7/1/2021-6/30/2023 0.5 Academic
NIMH

BDNF-Glucocorticoid interplay in antidepressant responsiveness.

This study aims to study signaling interplay between BDNF and glucocorticoid in olfactory neuron cultures to assess the responsiveness of antidepressants.

1 R01 AG076124-01 (Yassine, Arvanitakis, Wang) 4/1/2022-3/31/2027 1 Academic
NIA

Brain cPLA2 as a mechanism for neuroinflammation in AD/ADRD with and without APOE4.

This project aims to elucidate a novel mechanism for APOE4 induced brain inflammation in AD/ADRD. The

Program Director/Principal Investigator (Last, First, Middle): Wang, Hoau-Yan

study of available brain tissues from well-characterized autopsied persons with a range of clinical and pathologic phenotypes will provide deep insights into cell specific cPLA2 activation profiles in relation to APOE4 and markers of inflammation.

OVERLAP

There is no scientific or budgetary overlap among the active grants and two applications under consideration.

From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 12/02/2021 12:48:05 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Ian A Blair published an article

ResearchGate



This week's research from your network



Suggested for you

Basal and stimulated hippocampal adenylate cyclase activity in the experimentally lesioned rat...

Article Nov 1999 · Acta Neuropathologica

[View article](#)



Ian A Blair · a researcher you follow
published an article

Glutamine deprivation triggers NAGK-dependent hexosamine salvage

Article Nov 2021 · eLife Sciences

[View article](#)

[Discover more](#) on ResearchGate

Hoau-Yan, are these your publications?



H-Y Wang

Article: PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients

The Journal of Prevention of Alzheimer s Disease 09/2020; 7(4):256-264.

[Confirm authorship](#)

[Not me](#)



Hoau-Yan Wang *(Correspondence)

Article: Hyper-activated Insulin Signaling Cascade in Human Glioblastoma Cells

Critical Reviews in Oncogenesis 01/2019; 24(3).

[Confirm authorship](#)

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From: PLOS ONE <alerts@e.plos.org>
Sent time: 12/06/2021 03:06:54 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] PLOS ONE New Articles Published

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PUBLISHED: November 27, 2021 to December 03, 2021

Engineering and technology

Energy and power

Nanotechnology

Physical sciences

Chemistry

Materials science

Physics

New articles, sorted by publication date

Ringed seal (*Pusa hispida*) breeding habitat on the landfast ice in northwest Alaska during spring 1983 and 1984

Donna D. W. Hauser, Kathryn J. Frost, John J. Burns

An optimized LC-HRMS untargeted metabolomics workflow for multi-matrices investigations in the three-spined stickleback

Emmanuelle Lebeau-Roche, Gaëlle Daniele, Aurélie Fildier, Cyril Turies, Odile Dedourge-Geffard, Jean-Marc Porcher, Alain Geffard, Emmanuelle Vulliet

Provider views on rapid diagnostic tests and antibiotic prescribing for respiratory tract infections: A mixed methods study

Shana A. B. Burrowes, Tamar F. Barlam, Alexandra Skinner, Rebecca Berger, Pengsheng Ni, Mari-Lynn Drainoni

Advantages of score-based delirium detection compared to a clinical delirium assessment—a retrospective, monocentric cohort study

Markus Jäckel, Nico Aicher, Xavier Bemtgen, Jonathan Rilinger, Viviane

Zotzmann, Paul Marc Biever, Alexander Supady, Peter Stachon, Daniel
Duerschmied, Tobias Wengenmayer, Christoph Bode, Dawid Leander Staudacher

Employment outcomes and experiences of people with seeing disability in Canada: An analysis of the Canadian Survey on Disability 2017

Shikha Gupta, Mahadeo Sukhai, Walter Wittich

Admission criteria in critically ill COVID-19 patients: A physiology-based approach

Samuele Ceruti, Andrea Glotta, Maira Biggiogero, Pier Andrea Maida, Martino
Marzano, Patrizia Urso, Giovanni Bona, Christian Garzoni, Zsolt Molnar

Health co-inquiry in migraine: Online participation and stakeholder experiences before and during the COVID-19 pandemic

Camden L. Baucke, Lauren S. Seifert, Kara Kaelber

Antibiotic use for respiratory syncytial virus in the Middle East: A surveillance study in hospitalized Jordanian children

Danielle A. Rankin, Nikhil K. Khankari, Zaid Haddadin, Olla Hamdan, Ahmad Yanis,
Samir Faouri, Asem Shehabi, John V. Williams, Najwa Khuri-Bulos, Natasha B.
Halasa

Prognostic value of right ventricular native T1 mapping in pulmonary arterial hypertension

Ryotaro Asano, Takeshi Ogo, Yoshiaki Morita, Akiyuki Kotoku, Tatsuo Aoki, Kyoko
Hirakawa, Sayuri Nakayama, Jin Ueda, Akihiro Tsuji, Mark T. Waddingham,
Yasutoshi Ohta, Tetsuya Fukuda, Keiko Ohta-Ogo, Hatsue Ishibashi-Ueda, Teruo
Noguchi, Satoshi Yasuda

Impacts of COVID-19 on rural livelihoods in Bangladesh: Evidence using panel data

Marcel Gatto, Abu Hayat Md Saiful Islam

Polling India via regression and post-stratification of non-probability online samples

Roberto Cerina, Raymond Duch

Anthropometric failures and its associated factors among preschool-aged children in a rural community in southwest Ethiopia

Kebebe Bidira, Dessalegn Tamiru, Tefera Belachew

Direct-to-consumer genetic testing: Prospective users'

attitudes toward information about ancestry and biological relationships

James W. Hazel, Catherine Hammack-Aviran, Kathleen M. Brelsford, Bradley A. Malin, Laura M. Beskow, Ellen Wright Clayton

The effect of bio-banding on the anthropometric, physical fitness and functional movement characteristics of academy soccer players

Calum MacMaster, Matt Portas, Guy Parkin, Sean Cumming, Chris Wilcox, Christopher Towilson

Virus-infection in cochlear supporting cells induces audiosensory receptor hair cell death by TRAIL-induced necroptosis

Yushi Hayashi, Hidenori Suzuki, Wataru Nakajima, Ikuno Uehara, Atsuko Tanimura, Toshiki Himeda, Satoshi Koike, Tatsuya Katsuno, Shin-ichiro Kitajiri, Naoto Koyanagi, Yasushi Kawaguchi, Koji Onomoto, Hiroki Kato, Mitsutoshi Yoneyama, Takashi Fujita, Nobuyuki Tanaka

A machine learning framework for the evaluation of myocardial rotation in patients with noncompaction cardiomyopathy

Marcelo Dantas Tavares de Melo, Jose de Arimatéia Batista Araujo-Filho, José Raimundo Barbosa, Camila Rocon, Carlos Danilo Miranda Regis, Alex dos Santos Felix, Roberto Kalil Filho, Edimar Alcides Bocchi, Ludhmila Abrahão Hajjar, Mahdi Tabassian, Jan D'hooge, Vera Maria Cury Salemi

Influences of study design on the effectiveness of consensus messaging: The case of medicinal cannabis

Asheley R. Landrum, Brady Davis, Joanna Huxster, Heather Carrasco

Effects of *Salmonella enterica* ser. Enteritidis and Heidelberg on host CD4⁺CD25⁺ regulatory T cell suppressive immune responses in chickens

Revathi Shanmugasundaram, Keila Acevedo, Mohamad Mortada, Gabriel Akerele, Todd J. Applegate, Michael H. Kogut, Ramesh K. Selvaraj

Central nervous system infection in the intensive care unit: Development and validation of a multi-parameter diagnostic prediction tool to identify suspected patients

Hugo Boechat Andrade, Ivan Rocha Ferreira da Silva, Justin Lee Sim, José Henrique Mello-Neto, Pedro Henrique Nascimento Theodoro, Mayara Secco Torres da Silva, Margareth Catoia Varela, Grazielle Viana Ramos, Aline Ramos da Silva, Fernando Augusto Bozza, Jesus Soares, Ermias D. Belay, James J. Sejvar, José Cerbino-Neto, André Miguel Japiassú

Men and infertility in The Gambia: Limited biomedical knowledge and awareness discourage male involvement and exacerbate gender-based impacts of infertility

Susan Dierickx, Kelvin Onyango Oruko, Ed Clarke, Sainey Ceesay, Allan Pacey, Julie Balen

Deep learning algorithm in detecting intracranial hemorrhages on emergency computed tomographies

Almut Kundisch, Alexander Hönning, Sven Mutze, Lutz Kreissl, Frederik Spohn, Johannes Lemcke, Maximilian Sitz, Paul Sparenberg, Leonie Goelz

COVID-19 vaccine confidence and hesitancy among health care workers: A cross-sectional survey from a MERS-CoV experienced nation

Mazin Barry, Mohamad-Hani Temsah, Abdullah Alhuzaimi, Nurah Alamro, Ayman Al-Eyadhy, Fadi Aljamaan, Basema Saddik, Ali Alhaboob, Fahad Alsohime, Khalid Alhasan, Abdulkarim Alrabiaah, Ali Alaraj, Rabih Halwani, Amr Jamal, Sarah Alsubaie, Fatimah S. Al-Shahrani, Ziad A. Memish, Jaffar A. Al-Tawfiq

Contextual factors influencing a training intervention aimed at improved maternal and newborn healthcare in a health zone of the Democratic Republic of Congo

Malin Bogren, Sylvie Nabintu Mwambali, Marie Berg

Geometric morphometric wing analysis as a tool to discriminate female mosquitoes from different suburban areas of Chiang Mai province, Thailand

Danita Champakaew, Anuluck Junkum, Narin Sontigun, Sangob Sanit, Kwankamol Limsopatham, Atiporn Saeung, Pradya Somboon, Benjawan Pitasawat

Predicting the risk of atherosclerotic cardiovascular disease among adults living with HIV/AIDS in Addis Ababa, Ethiopia: A hospital-based study

Minyahil Woldu, Omary Minzi, Workineh Shibeshi, Aster Shewaamare, Ephrem Engidawork

Setting a standard for low reading proficiency: A comparison of the bookmark procedure and constrained mixture Rasch model

Tabea Feseker, Timo Gnambs, Cordula Artelt

Prediction of the importance of auxiliary traits using computational intelligence and machine learning: A

simulation study

Antônio Carlos da Silva Júnior, Michele Jorge da Silva, Cosme Damião Cruz, Isabela de Castro Sant'Anna, Gabi Nunes Silva, Moysés Nascimento, Camila Ferreira Azevedo

Using allocative efficiency analysis to inform health benefits package design for progressing towards Universal Health Coverage: Proof-of-concept studies in countries seeking decision support

Nicole Fraser-Hurt, Xiaohui Hou, Thomas Wilkinson, Denizhan Duran, Gerard J. Abou Jaoude, Jolene Skordis, Adanna Chukwuma, Christine Lao Pena, Opope O. Tshivuila Matala, Marelize Gorgens, David P. Wilson

Health promotion interventions for the control of hypertension in Africa, a systematic scoping review from 2011 to 2021

Jinhee Shin, Kennedy Diema Konlan, Eugenia Mensah

Diagnostic value of virtual autopsy using pm-MRI at 3T on malformed second trimester fetuses vs classic autopsy

Adelina Staicu, Camelia Albu, Roxana Popa-Stanila, Cosmina Ioana Bondor, Ioana Cristina Rotar, Florin Stamatian, Daniel Muresan

Acoustic wave response to groove arrays in model ears

Brian W. Keeley, Annika T. H. Keeley

Absolute quantification of *E. coli* virulence and housekeeping genes to determine pathogen loads in enumerated environmental samples

K. B. Hoorzook, T. G. Barnard

Examining patient trust towards physicians between clinical departments in a Chinese hospital

Judy Yang, Yuanzheng Lu, Xiaoxing Liao, Mary P. Chang

Collective language creativity as a trade-off between priming and antipriming

Sergei Monakhov

The effectiveness of Non-pharmaceutical interventions in reducing the COVID-19 contagion in the UK, an observational and modelling study

Giorgos Galanis, Corrado Di Guilmi, David L. Bennett, Georgios Baskozos

Microglial-stimulation of glioma invasion involves the EGFR ligand amphiregulin

Salvatore J. Coniglio, Jeffrey E. Segall

***Panax Ginseng* alleviates thioacetamide-induced liver injury in ovariectomized rats: Crosstalk between inflammation and oxidative stress**

Rasha E. Mostafa, Nermeen M. Shaffie, Rasha M. Allam

Family context and individual characteristics in antenatal care utilization among adolescent childbearing mothers in urban slums in Nigeria

Akanni Ibukun Akinyemi, Temitope Peter Erinfolami, Samuel Olinapekun Adebayo, Iqbal Shah, Reni Elewonbi, Elizabeth Omoluabi

Transparency in peer review: Exploring the content and tone of reviewers' confidential comments to editors

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Correction: Coherent detection-based photonic radar for autonomous vehicles under diverse weather conditions

The PLOS ONE Staff

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***L*-Menthol increases extracellular dopamine and c-Fos-like immunoreactivity in the dorsal striatum, and promotes ambulatory activity in mice**

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Alien woody plants are more versatile than native, but both share similar therapeutic redundancy in South Africa

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The mucosal barrier and anti-viral immune responses can eliminate portions of the viral population during transmission and early viral growth

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High-dose drug heat map analysis for drug safety and efficacy in multi-spheroid brain normal cells and GBM patient-derived cells

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Parkinson's patients situation during the SARS CoV-2 pandemic and their interest in telemedicine *A cross-sectional study*

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Evaluation of the Abbott BinaxNOW COVID-19 Test Ag Card for rapid detection of SARS-CoV-2 infection by a local public health district with a rural population

Rachel E. Pollreis, Clay Roscoe, Rachel J. Phinney, Surabhi S. Malesha, Matthew C. Burns, Aimee Ceniseros, Charles H. Washington, Andrew J. Nutting, Christopher L. Ball

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Assessing BRCA1 activity in DNA damage repair using human induced pluripotent stem cells as an approach to assist classification of BRCA1 variants of uncertain significance

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Female mentors positively contribute to undergraduate STEM research experiences

Saili Moghe, Katelyn Baumgart, Julie J. Shaffer, Kimberly A. Carlson

Intrathecal IGF2 siRNA injection provides long-lasting anti-allodynic effect in a spared nerve injury rat model of neuropathic pain

Wei-Hung Chan, Nian-Cih Huang, Yi-Wen Lin, Feng-Yen Lin, Chien-Sung Tsai, Chun-Chang Yeh

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Yanyun Xu, Junyong Ye, Ahlam Khalofah, Ali Tan Kee Zuan, Rehmat Ullah, Ahmed M. El-Shehawi

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M. Arantxa Colchero, Guillermo Paraje, Barry M. Popkin

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Hasan Selcuk Ozger, Resul Karakus, Elif Nazli Kuscu, Umit Emin Bagriacik, Nihan Oruklu, Melek Yaman, Melda Turkoglu, Gonca Erbas, Aysegul Yucel Atak, Esin Senol

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Luis Paixao, Haoqi Sun, Jacob Hogan, Katie Hartnack, Mike Westmeijer, Anudeepthi Neelagiri, David W. Zhou, Lauren M. McClain, Eyal Y. Kimchi, Patrick L. Purdon, Oluwaseun Akeju, M. Brandon Westover

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Masahiro Yamawaki, Yosuke Honda, Kenji Makino, Takahide Nakano, Yasunori Iida, Fumiaki Yashima, Hiroshi Ueno, Kazuki Mizutani, Minoru Tabata, Norio Tada, Kensuke Takagi, Futoshi Yamanaka, Toru Naganuma, Yusuke Watanabe, Masanori Yamamoto, Shinichi Shirai, Kentaro Hayashida, on behalf of OCEAN-TAVI registry

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Paulina Rewers, Jacek Diakun

Epidemiology of clubfoot in Sweden from 2016 to 2019: A national register study

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Ebenezer Zaabaar, Samuel Kyei, Maame Ama Amamoah Parkson Brew, Samuel Bert Boadi-Kusi, Frank Assiamah, Kofi Asiedu

Allopurinol to reduce cardiovascular morbidity and mortality: A systematic review and meta-analysis

Karel H. van der Pol, Kimberley E. Wever, Mariette Verbakel, Frank L. J. Visseren, Jan H. Cornel, Gerard A. Rongen

How do patients and physicians communicate about hereditary angioedema in the United States?

Gagan Jain, Lauren Walter, Carolyn Reed, Patricia O'Donnell, Jeffrey Troy

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Habtamu B. Derseh, Jason Q. D. Goodger, Jean-Pierre Y. Scheerlinck, Chrishan S. Samuel, Ian E. Woodrow, Enzo A. Palombo, Alistair Cumming, Ken Snibson

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Analysis of anticholinergic adverse effects using two large databases: The US Food and Drug Administration Adverse Event Reporting System database and the Japanese Adverse Drug Event Report database

Junko Nagai, Yoichi Ishikawa

Phenotypic characterization of carbapenem non-susceptible gram-negative bacilli isolated from clinical specimens

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Yang Shu, Jinqi Zhang, Wei Li, Pengwu Zhao, Qiyue Zhang, Mei Zhou

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Heidi S. West, Mary E. Robbins, Corrina Moucheraud, Abdur Razzaque, Randall Kuhn

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Bhargavi Bhat, Shuhao Liu, Yu-Ting Lin, Martin L. Sentmanat, Joseph Kwon, Mustafa Akbulut

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Maria Paola Tramonti Fantozzi, Ugo Faraguna, Adrien Ugon, Gastone Ciuti, Andrea Pinna

The impact of hypoglycemia on quality of life and related outcomes in children and adolescents with type 1 diabetes: A systematic review

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Jardin A. Leleux, Tina C. Albershardt, Rebecca Reeves, Reice James, Jordan Krull, Andrea J. Parsons, Jan ter Meulen, Peter Berglund

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Ashadun Nobi, Kamrul Hasan Tuhin, Jae Woo Lee

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Suniti Yadav, Imnameren Longkumer, Priyanka Rani Garg, Shipra Joshi, Sunanda Rajkumari, Naorem Kiranmala Devi, Kallur Nava Saraswathy

Diversity and heterogeneity of immune states in non-small cell lung cancer and small cell lung cancer

Shawn J. Rice, Chandra P. Belani

Improving uptake of prevention of mother-to-child HIV transmission services in Benue State, Nigeria through a faith-based congregational strategy

Michele Montandon, Timothy Efuntoye, Ijeoma U. Itanyi, Chima A. Onoka, Chukwudi Onwuchekwa, Jerry Gwamna, Amee Schwitters, Chibuzor Onyenuobi, Amaka G. Ogidi, Mahesh Swaminathan, John Okpanachi Oko, Gbenga Ijaodola, Deborah Odoh, Echezona E. Ezeanolue

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Eugene Enah Fang, Raymond Babila Nyasa, Emmanuel Menang Ndi, Denis Zofou, Tebit Emmanuel Kwenti, Edith Pafoule Lepezeu, Vincent P. K. Titanji, Roland N. Ndip

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Stephen Franklin Weng, Ralph Kwame Akyea, Kenneth KC Man, Wallis C. Y. Lau, Barbara Iyen, Joseph Edgar Blais, Esther W. Chan, Chung Wah Siu, Nadeem Qureshi, Ian C. K. Wong, Joe Kai

Improved HIV case finding among key populations after differentiated data driven community testing approaches in Zambia

Joseph Kamanga, Kayla Stankevitz, Andres Martinez, Robert Chiegil, Lameck Nyirenda, Florence Mulenga, Mario Chen, Mulamuli Mpofu, Sam Lubasi, Moses Bateganya

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Sai Kyauk, Howard Y. Cajucum-Uy, Hla Myint Htoon, Z. Zaw Htoi Aung, Jodhbir S. Mehta, Arundhati Anshu

Comparison of *TCF4* repeat expansion length in corneal endothelium and leukocytes of patients with Fuchs endothelial corneal dystrophy

Eric D. Wieben, Ross A. Aleff, Tommy A. Rinkoski, Keith H. Baratz, Shubham Basu, Sanjay V. Patel, Leo J. Maguire, Michael P. Fautsch

Prevalence of common mental health issues among migrant workers: A systematic review and meta-analysis

Siti Idayu Hasan, Anne Yee, Ariyani Rinaldi, Adlina Aisya Azham, Farizah Mohd Hairi, Amer Siddiq Amer Nordin

Walking on the bright side: Associations between affect, depression, and gait

Divya Kumar, Dario J. Villarreal, Alicia E. Meuret

A green-lipped mussel reduces pain behavior and chondrocyte inflammation and attenuated experimental osteoarthritis progression

JooYeon Jhun, Hyun Sik Na, Keun-Hyung Cho, Jiyoung Kim, Young-Mee Moon, Seung Yoon Lee, Jeong Su Lee, A. Ram Lee, Seok Jung Kim, Mi-La Cho, Sung-Hwan Park

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Sonia Roura, Gerard Álvarez, Ivan Solà, Francesco Cerritelli

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Mentalized affectivity in a nutshell: Validation of the Italian version of the Brief-Mentalized Affectivity Scale

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Spatial and time domain analysis of eye-tracking data during screening of brain magnetic resonance images

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An investigation into the deep learning approach in sentimental analysis using graph-based theories

Mohamed Kentour, Joan Lu

Identifying agricultural disaster risk zones for future climate actions

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Vitamin D related genetic polymorphisms affect serological response to high-dose vitamin D supplementation in multiple sclerosis

Max Mimpen, Linda Rolf, Geert Poelmans, Jody van den Ouweland, Raymond Hupperts, Jan Damoiseaux, Joost Smolders

Fears of disclosure and misconceptions regarding domestic violence reporting amongst patients in two US emergency departments

Leigh Kimberg, Juan A. Vasquez, Jennifer Sun, Erik Anderson, Clarissa Ferguson, Mireya Arreguin, Robert M. Rodriguez

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Factors associated with female students' past year experience of sexual violence in South African public higher education settings: A cross-sectional study

Mercilene T. Machisa, Esnat D. Chirwa, Pinky Mahlangu, Yandisa Sikweyiya, Ncediswa Nunze, Elizabeth Dartnall, Managa Pillay, Rachel Jewkes

The Alaska Native/American Indian experience of hepatitis C treatment with sofosbuvir-based direct-acting antivirals

Lisa Townshend-Bulson, Elena Roik, Youssef Barbour, Dana J. T. Bruden, Chriss E. Homan, Hannah G. F. Espera, Timothy J. Stevenson, Annette M. Hewitt, Wileina

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Vegetation characteristics control local sediment and nutrient retention on but not underneath vegetation in floodplain meadows

Lena Kretz, Elisabeth Bondar-Kunze, Thomas Hein, Ronny Richter, Christiane Schulz-Zunkel, Carolin Seele-Dilbat, Fons van der Plas, Michael Vieweg, Christian Wirth

ThinPrep cytology combined with HPV detection in the diagnosis of cervical lesions in 1622 patients

Sulaiya Husaiyin, Zhen Jiao, Kailibinuer Yimamu, Reyilanmu Maisaidi, Lili Han, Mayinuer Niyazi

Nest parasitism, promiscuity, and relatedness among wood ducks

Kayla Harvey, Philip Lavretsky, Justyn Foth, Christopher K. Williams

A mixed methods evaluation of medication reconciliation in the primary care setting

Michael R. Gionfriddo, Vanessa Duboski, Allison Middernacht, Melissa S. Kern, Jove Graham, Eric A. Wright

The effects of environmental enrichment on hatchery-performance, smolt migration and capture rates in landlocked Atlantic salmon

Matti Janhunnen, Jorma Piironen, Anssi Vainikka, Pekka Hyvärinen

Gene mining, codon optimization and analysis of binding mechanism of an aldo-keto reductase with high activity, better substrate specificity and excellent solvent tolerance

Wei Jiang, Xiaoli Fu, Weiliang Wu

Taylor's rule, political cycle, and Latin America—An analysis of time series in search of responsibility for monetary stabilization

Nadja Simone Menezes Nery de Oliveira, Paulo Reis Mourao

Determinants of dental caries among adolescent patients attending Hospitals in West Wollega Zone, Western Ethiopia: A case-control study

Tsega Tola Guracho, Emiru Merdassa Atomssa, Obsa Amante Megersa, Tadesse Tolossa

Effect of HIV status and retinol on immunogenicity to oral cholera vaccine in adult population living in an endemic area of Lukanga Swamps, Zambia

Charlie Chaluma Luchen, John Mwaba, Harriet Ng'ombe, Peter Ibukun Oluwa Alabi, Michelo Simuyandi, Obvious N. Chilyabanyama, Luiza Miyanda Hatyoka, Cynthia Mubanga, Samuel Bosomprah, Roma Chilengi, Cleopatra Caroline Chisenga

A model framework for projecting the prevalence and impact of Long-COVID in the UK

Chris Martin, Michiel Luteijn, William Letton, Josephine Robertson, Stuart McDonald

Functional response of *Amblyseius eharai* (Acari: Phytoseiidae) on *Tetranychus urticae* (Acari: Tetranychidae)

Young-Gyun Park, Joon-Ho Lee, Un Taek Lim

Comparison of post-activation performance enhancement (PAPE) after isometric and isotonic exercise on vertical jump performance

Salvador Vargas-Molina, Ulises Salgado-Ramírez, Iván Chulvi-Medrano, Leandro Carbone, Sergio Maroto-Izquierdo, Javier Benítez-Porres

Prediction of suicidal ideation risk in a prospective cohort study of medical interns

Tyler L. Malone, Zhou Zhao, Tzu-Ying Liu, Peter X. K. Song, Srijan Sen, Laura J. Scott

Comprehensive analysis of an immune infiltrate-related competitive endogenous RNA network reveals potential prognostic biomarkers for non-small cell lung cancer

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Sub-lethal doses of Nucleopolyhedrosis Virus and synthetic insecticides alter the biological parameters of *Helicoverpa armigera* Hübner (Lepidoptera: Noctuidae)

Allah Dita Abid, Syed Muhammad Zaka, Shafqat Saeed, Naeem Iqbal, Muhammad Nadir Naqqash, Muhammad Sohail Shahzad

Fire behaviors along timber linings affixed to tunnel walls in mines

Ke Gao, Zimeng Liu, Changfa Tao, Zhiqiang Tang, Yisimayili Aiyiti, Lianzeng Shi

High-gamma mirror activity patterns in the human brain during reach-to-grasp movement observation, retention, and execution—An MEG study

Alexander M. Dreyer, Jochem W. Rieger

The association between socioeconomic disadvantage and children's working memory abilities: A systematic review and meta-analysis

Kate E. Mooney, Stephanie L. Prady, Mary M. Barker, Kate E. Pickett, Amanda H. Waterman

Three weeks of a home-based “sleep low-train low” intervention improves functional threshold power in trained cyclists: A feasibility study

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Niclosamide shows strong antiviral activity in a human airway model of SARS-CoV-2 infection and a conserved potency against the Alpha (B.1.1.7), Beta (B.1.351) and Delta variant (B.1.617.2)

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Effect of homophily and correlation of beliefs on COVID-19 and general infectious disease outbreaks

Claus Kadelka, Audrey McCombs

Prevalence and clinical profile of glaucoma patients in rural Nigeria—A hospital based study

Ngozika E. Ezinne, Chukwuebuka S. Ojukwu, Kingsley K. Ekemiri, Obinna F. Akano, Edgar Ekure, Uchechukwu Levi Osuagwu

Antifungal activity of volatile compounds generated by endophytic fungi *Sarocladium brachiariae* HND5 against *Fusarium oxysporum* f. sp. *cubense*

Yang Yang, Yipeng Chen, Jimiao Cai, Xianbao Liu, Guixiu Huang

Male coloration affects female gestation period and timing of fertilization in the guppy (*Poecilia reticulata*)

Aya Sato, Ryu-ichi Aihara, Kenji Karino

Potential role of the ABCG2-Q141K polymorphism in type 2 diabetes

Edit Szabó, Anna Kulin, Orsolya Móznér, László Korányi, Botond Literáti-Nagy, Márta Vitai, Judit Cserepes, Balázs Sarkadi, György Várady

Whole blood viscosity is associated with extrahepatic metastases and survival in patients with hepatocellular carcinoma

Ji Won Han, Pil Soo Sung, Jeong Won Jang, Jong Young Choi, Seung Kew Yoon

Treatment of necrotizing enterocolitis by conditioned medium derived from human amniotic fluid stem cells

Joshua S. O'Connell, Bo Li, Andrea Zito, Abdalla Ahmed, Marissa Cadete, Niloofar Ganji, Ethan Lau, Mashriq Alganabi, Nassim Farhat, Carol Lee, Simon Eaton, Robert Mitchell, Steve Ray, Paolo De Coppi, Ketan Patel, Agostino Pierro

SARS-CoV-2 spike protein displays sequence similarities with paramyxovirus surface proteins; a bioinformatics study

Ehsan Ahmadi, Mohammad Reza Zabihi, Ramin Hosseinzadeh, Leila Mohamed Khosroshahi, Farshid Noorbakhsh

Advancing the representation of reservoir hydropower in energy systems modelling: The case of Zambesi River Basin

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Vague data analysis using neutrosophic Jarque–Bera test

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Estimation of sodium consumption by novel formulas derived from random spot and 12-hour urine collection

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Low frequency weak electric fields can induce structural changes in water

Iman Rad, Rainer Stahlberg, Kurt Kung, Gerald H. Pollack

Geometrical model of lobular structure and its importance for the liver perfusion analysis

Eduard Rohan, Jana Camprová Turjanicová, Václav Liška

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Retraction: miR-24-3p Suppresses Malignant Behavior of Lacrimal Adenoid Cystic Carcinoma by Targeting PRKCH to Regulate p53/p21 Pathway

The PLOS ONE Editors

Correction: Ecological assessment and environmental niche modelling of Himalayan rhubarb (*Rheum webbianum* Royle) in northwest Himalaya

The PLOS ONE Staff

Correction: Estimation of the cardiovascular risk using world health organization/international society of hypertension risk prediction charts in Central Vietnam

Ho Anh Hien, Nguyen Minh Tam, Vo Tam, Huynh Van Minh, Nguyen Phuong Hoa, Stefan Heytens, Anselme Derese, Dirk Devroey

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Yi Zhang, Yi Yuan

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From: Hoau-yan Wang
Sent time: 12/09/2021 11:21:09 PM
To: [REDACTED]@gmail.com
Subject: Fw: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

From: Peter Rapp <peter@nbaging.com>
Sent: Monday, November 22, 2021 7:07 PM
To: Hoau-yan Wang
Cc: Beidel, Jennifer L.
Subject: Re: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

Dear Dr. Wang:

Thank you very much for this quick reply. I look forward to resolving the issues raised.

Sincerely,
Peter R. Rapp
[Peter R. Rapp, PhD](#)
Editor-in-Chief
[Neurobiology of Aging](#)

On Mon, Nov 22, 2021 at 10:20 AM Hoau-yan Wang <hywang@med.cuny.edu> wrote:

Dear Dr. Rapp,

We will provide a full response to your inquiries as soon as possible. The primary antibody from Santa Cruz against nicotinic alpha7 receptor should be **SC-65607** as indicated below. My laboratory has never worked on alpha1 nicotinic receptors so that we do not possess and use SC-65844. We will also include this correction in our full response.

Anti-Nicotinic Acetylcholine Receptor alpha 7/CHRNA7 Antibody (319): sc-58607

Thank you.

Best regards,

Hoau-Yan Wang

From: Peter Rapp <peter@nbaging.com>
Sent: Sunday, November 21, 2021 5:17 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

Dr. Wang:

One additional issue needing attention in your report, the primary antibody from Santa Cruz listed in your Methods against nicotinic alpha7 receptor (i.e., SC-65844) appears to bind a different subunit, not the alpha7 subunit reportedly examined.

Again, I appreciate your attention to these matters.

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Peter R. Rapp
[Peter R. Rapp, PhD](#)
Editor-in-Chief
[Neurobiology of Aging](#)

On Sat, Nov 20, 2021 at 10:59 AM Peter Rapp <peter@nbaging.com> wrote:

Dear Dr. Wang:

I write regarding your article, Wang et al., (2017) PTI-125 binds and reverses an altered confirmation of filamin A to reduce Alzheimer's disease pathogenesis. *Neurobiol. Aging*, 55, 99-114, for which you serve as corresponding author. A reader has brought to our attention credible concerns that, as Editor-in-Chief of the journal, I must take seriously.

The specific substance of the concerns is copied below:

1. Figure 12:

- **All blots in this figure contain 13 bands, corresponding to the 13 different conditions indicated at the bottom. However, the NR1 normalization blot shown at the top contains only 12 bands.**
- **The right-most four bands of the NR1 blot appear to show a different background than the left lanes of that blot**
- **The right-most three bands of the PLCgamma1 blot (and other blots) appear to show a different background than the left lanes of that blot**

Editor's Note: Consistent with this description, each of the 7 blots in Fig. 12 in your originally submitted manuscript (NBA 16-1080) includes two separately selectable items, one of 3 or 4 lanes on the right, and a second panel with the remaining lanes.

2. Figure 3:

- **One of the bands representing a 10-month sample, in the right blot, appears to be surrounded by a rectangle of a different background than the rest of the blot.**

3. Figure 6:

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Please provide a full response to these complaints of figure manipulation, ideally including uncropped copies of the blots or photomicrographs used to configure Figs 3, 6, and 12. I would appreciate a response at your earliest convenience, within 30 days. Consistent with COPE guidelines, we anticipate informing the complainant regarding the response.

Please note that, in the absence of a satisfactory timely response, the journal may be obligated to pursue other corrective action.

Thank you for your attention to this important issue, and for supporting the accuracy and integrity of data published at *Neurobiology of Aging*.

Sincerely,
Peter R. Rapp
[Peter R. Rapp, PhD](#)
[Editor-in-Chief](#)
[Neurobiology of Aging](#)

From: Hoau-yan Wang
Sent time: 12/09/2021 11:26:05 PM
To: [REDACTED]@gmail.com
Subject: Fw: [EXTERNAL] Wang et al. (2017), NBA, 55, 99-114

From: Peter Rapp <peter@nbaging.com>
Sent: Saturday, November 20, 2021 10:59 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Wang et al. (2017), NBA, 55, 99-114

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Peter R. Rapp, PhD
Editor-in-Chief
Neurobiology of Aging

From: Hoau-yan Wang
Sent time: 12/11/2021 09:56:05 AM
To: [REDACTED]@gmail.com
Subject: Fw: [EXTERNAL] Re: Wang et al. (2017), NBA, 55, 99-114

From: Peter Rapp <peter@nbaging.com>
Sent: Monday, November 22, 2021 7:07 PM
To: Hoau-yan Wang
Cc: Beidel, Jennifer L.
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From: Pubpeer <alerts@pubpeer.com>
Sent time: 12/12/2021 05:03:27 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

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To: Hoau-yan Wang
Subject: [EXTERNAL] Shashank Agarwal published an article

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Hoau-Yan, are these your publications?



H-Y Wang

Article: PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients

The Journal of Prevention of Alzheimer's Disease 09/2020; 7(4):256-264.

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Hoau-Yan Wang *(Correspondence)

Article: Hyper-activated Insulin Signaling Cascade in Human Glioblastoma Cells

Critical Reviews in Oncogenesis 01/2019; 24(3).

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From: Saad Dar <saad.dar@baselane.com>
Sent time: 12/20/2021 06:42:25 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Cassava concerns - CUNY Alumni Seeking your guidance and clarification

Dear Mr. Wang,

My name is Saad Majeed Dar. I'm an alumnus of Baruch College and CUNY Honors Program, class of 07'

I'm an enthusiastic investor of Cassava (stock SAVA) and also have a member of my family that has Alzheimer's. I'm very hopeful that this drug can make a difference.

I'm am very concerned about the reports and the current accusations laid against the research and analysis you have published. (ref. Wang et al., 2021).

Are you planning to defend yourself against all the accusations and provide clarifications for all the disparities that many have pointed out? How is it possible that the COGS-ADS 11 scores were promising and yet people are questioning your western blots analysis? What is the correlation between the two?

I would very much appreciate your response.

Kind regards.

Thank you
Saad Dar

--

Head of BD and Partnerships | saad.dar@baselane.com | +1 347 252 9021

From: Hoau-yan Wang
Sent time: 12/20/2021 07:35:33 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] Cassava concerns - CUNY Alumni Seeking your guidance and clarification

From: Saad Dar <saad.dar@baselane.com>
Sent: Monday, December 20, 2021 6:42 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Cassava concerns - CUNY Alumni Seeking your guidance and clarification

Dear Mr. Wang,

My name is Saad Majeed Dar. I'm an alumnus of Baruch College and CUNY Honors Program, class of 07'

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Saad Dar

--

Head of BD and Partnerships | saad.dar@baselane.com | +1 347 252 9021

From: Pubpeer <alerts@pubpeer.com>
Sent time: 12/21/2021 07:51:37 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau-Yan Wang,

There's a new comment on your article entitled: **PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiology of Aging**

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From: Ana Carrillo
Sent time: 12/22/2021 06:14:31 AM
To: Hoau-yan Wang
Cc: Marc Scullin
Subject: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

Dear Prof. Wang,

Good morning. I hope this email finds you in good health. This is a reminder to please certify the academic effort for the following semesters:

Fall 2020

Kindly be reminded to complete the other categories (Instruction, Departmental Administration, Other instructional activities etc..) as you see fit. Please use the link provided and be reminded to log in first for the link to work: <https://www.rfcuny.org/effortreporting/certification/>.

Emp Name	Semester Code	Project	Project Department	Project Name	Start Date	End Date	Certification Status	Grant Effort %	PI Name
Wang, Hoau-yan	FALL2020	72762-00 02	Molecular, Cellular Sciences	HYPOACTIVITY IS INTEGRAL TO GLUTAMATERGI	12/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan
Wang, Hoau-yan	FALL2020	72587-00 02	Molecular, Cellular Sciences	OPEN-LABEL EXTENSION STUDY OF PTI-125	09/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan

Happy Holidays,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: Hoau-yan Wang
Sent time: 12/22/2021 09 56:00 AM
To: Ana Carrillo
Cc: Marc Scullin
Subject: Re: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

Ana,

Do you mean Fall 2021? This can only be done after 1/15/2022.

Thanks.

Best,

Hoau

From: Ana Carrillo
Sent: Wednesday, December 22, 2021 6:14 AM
To: Hoau-yan Wang
Cc: Marc Scullin
Subject: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

Dear Prof. Wang,

Good morning. I hope this email finds you in good health. This is a reminder to please certify the academic effort for the following semesters:

Fall 2020

Kindly be reminded to complete the other categories (Instruction, Departmental Administration, Other instructional activities etc..) as you see fit. Please use the link provided and be reminded to log in first for the link to work: <https://www.rfcuny.org/effortreporting/certification/>.

Emp Name	Semester Code	Project	Project Department	Project Name	Start Date	End Date	Certification Status	Grant Effort %	PI Name
Wang, Hoau-yan	FALL2020	72762-00 02	Molecular, Cellular Sciences	HYPOACTIVITY IS INTEGRAL TO GLUTAMATERGI	12/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan
Wang, Hoau-yan	FALL2020	72587-00 02	Molecular, Cellular Sciences	OPEN-LABEL EXTENSION STUDY OF PTI-125	09/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan

Happy Holidays,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: Hoau-yan Wang
Sent time: 12/22/2021 10 03:16 AM
To: Ana Carrillo
Cc: Marc Scullin
Subject: Re: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

I got it. Fall 2020 is now certified.

Thanks. Happy holidays.

Best,

Hoau

From: Ana Carrillo
Sent: Wednesday, December 22, 2021 6:14 AM
To: Hoau-yan Wang
Cc: Marc Scullin
Subject: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

Dear Prof. Wang,

Good morning. I hope this email finds you in good health. This is a reminder to please certify the academic effort for the following semesters:

Fall 2020

Kindly be reminded to complete the other categories (Instruction, Departmental Administration, Other instructional activities etc..) as you see fit. Please use the link provided and be reminded to log in first for the link to work: <https://www.rfcuny.org/effortreporting/certification/>.

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Happy Holidays,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: paul greenaway <[REDACTED]@yahoo.com>
Sent time: 12/22/2021 12:19:56 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] A THANK YOU from thousands

Hello Dr Wang you do not know me my name is Paul Greenaway I am a long term investor in cassava science.. a family member of mine also had Alzheimer's and suffered greatly with it.

But that's not the reason I wanted to email..

I do not know if others have emailed you, but I know I speak for thousands, we all see the attacks being made on you and your work, by people in the stock market - simply money motivated - it's disgusting..

I wanted to say stay tough, do not listen to these evil people, you are fighting a great fight and myself and literally thousands of people appreciate you and your work sir. Thank you

I hope this email finds you well - all things considered - and have a good holiday period with your family, and then the Chinese New year if you celebrate that sir..

Kind regards.

Paul Greenaway

From: Hoau-yan Wang
Sent time: 12/22/2021 04:45:59 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] A THANK YOU from thousands

From: paul greenaway <[REDACTED]@yahoo.com>
Sent: Wednesday, December 22, 2021 12:19 PM
To: Hoau-yan Wang
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Kind regards.

Paul Greenaway

From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 12/28/2021 11:35:14 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Hoau-Yan Wang published an article

ResearchGate



This week's research from your network



Suggested for you

Anaesthetic neurotoxicity and neuroplasticity: An expert group report and statement based on the...

Article May 2013 · BJA British Journal of Anaesthesia

[View article](#)



[Hoau-Yan Wang](#) · a researcher in your field
published an article

Editorial note: "Ultra-low-dose naloxone suppresses opioid tolerance, dependence, associated...

Article Dec 2021 · Neuroscience

[View article](#)



[Bengt Winblad](#) · a researcher in your field
published an article

Changes in mortality trends amongst common diseases during the COVID-19 pandemic in Sweden

Article Dec 2021 · Scandinavian Journal of Public Health

[View article](#)

[Discover more](#) on ResearchGate

Hoau-Yan, are these your publications?



H-Y Wang

Article: PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients

The Journal of Prevention of Alzheimer s Disease 09/2020; 7(4):256-264.

[Confirm authorship](#)

[Not me](#)



Hoau-Yan Wang *(Correspondence)

Article: Hyper-activated Insulin Signaling Cascade in Human Glioblastoma Cells

Critical Reviews in Oncogenesis 01/2019; 24(3).

[Confirm authorship](#)

[Not me](#)

[View all suggestions](#)

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ResearchGate GmbH, Chausseestr. 20, 10115 Berlin, Germany. [Imprint](#)
See our [Privacy Policy](#) and [Terms of Service](#).

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent time: 01/04/2022 11:52:13 AM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Dr. Wang,

Acct# 72587-0002 had ended back in December. Do you have any pending invoices on this account? In addition, there is about \$31k on direct, will you be asking for an extension? I'm not sure if that is possible, but please let me know.

Thanks,

Yan

Yan Bing Li
Project Administrator
Grants & Contracts
Office Hours Mon – Tues
Remote Hours Wed – Fri
212-417-8473
Yan_Bing_Li@rfcuny.org

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, October 4, 2021 7:42 PM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

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Thanks.

Hoau

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent: Monday, October 4, 2021 3:13 PM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] 72587-0002-Cassava

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Yan Bing Li
Project Administrator
Grants & Contracts

230 West 41st Street
New York, NY 10036
212-417-8473
212-417-6473 Fax
Yan_Bing_Li@rfcuny.org
<http://www.rfcuny.org>

|

From: Ana Carrillo
Sent time: 01/04/2022 04:44:12 PM
To: Hoau-yan Wang
Cc: Marc Scullin
Subject: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort for Spring 2021

Dear Prof Wang,

Happy New Year! I hope you are well. Recently a new entry was processed in the system for the spring 2021. May you please certify it? Kindly be reminded to complete the other categories (Instruction, Departmental Administration, Other instructional activities etc..) as you see fit. Please use the link provided and be reminded to log in first for the link to work: <https://www.rfcuny.org/effortreporting/certification/>.

Emp Name	Semester Code	Project	Project Department	Project Name	Start Date	End Date	Certification Status	Grant Effort %	PI Name	PI Email
Wang, Hoau-yan	SPRING2021	72598-00 04	Molecular, Cellular Sciences	TREAT ALZHEIMER'S DISEASE-REDUCE INSULIN	03/01/2021	05/31/2021	Not Done	10.14	Wang, Hoau-Yan	hywang@med.cuny.edu

Thank you in advance,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: Hoau-yan Wang
Sent: Wednesday, December 22, 2021 10:03 AM
To: Ana Carrillo
Cc: Marc Scullin
Subject: Re: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort

I got it. Fall 2020 is now certified.

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From: Ana Carrillo
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Wang, Hoau-yan	FALL2020	72762-00 02	Molecular, Cellular Sciences	HYPOACTIVITY IS INTEGRAL TO GLUTAMATERGI	12/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan
Wang, Hoau-yan	FALL2020	72587-00 02	Molecular, Cellular Sciences	OPEN-LABEL EXTENSION STUDY OF PTI-125	09/01/2020	01/15/2021	Not Done	7.00	Wang, Hoau-Yan

Happy Holidays,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: Hoau-yan Wang
Sent time: 01/05/2022 10 33 55 AM
To: Ana Carrillo
Cc: Marc Scullin
Subject: Re: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort for Spring 2021

DONE

From: Ana Carrillo
Sent: Tuesday, January 4, 2022 4:44 PM
To: Hoau-yan Wang
Cc: Marc Scullin
Subject: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort for Spring 2021

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Thank you in advance,

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Grants Administrator
acarrillo@ccny.cuny.edu

From: Hoau-yan Wang
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To: Ana Carrillo
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acarrillo@ccny.cuny.edu

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Thank you!

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: Hoau-yan Wang
Sent: Wednesday, January 5, 2022 10:33 AM
To: Ana Carrillo
Cc: Marc Scullin
Subject: Re: Hi Prof. Wang- REMINDER-- Please Certify Academic Effort for Spring 2021

DONE

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Happy Holidays,

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: Hoau-yan Wang
Sent time: 01/05/2022 10:39:34 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>
Cc: Maria Agosto
Subject: Re: 72587-0002-Cassava

Hi Yan,

Can you please let me know of the title of the account (grant). I am not sure whether I can ask for extension as there were a lot of things going on I have no control over, but I will do my best.

Thanks. Stay safe!

Hoau

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent: Tuesday, January 4, 2022 11:52 AM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Dr. Wang,
Acct# 72587-0002 had ended back in December. Do you have any pending invoices on this account? In addition, there is about \$31k on direct, will you be asking for an extension? I'm not sure if that is possible, but please let me know.
Thanks,
Yan

Yan Bing Li
Project Administrator
Grants & Contracts
Office Hours Mon – Tues
Remote Hours Wed – Fri
212-417-8473
Yan_Bing_Li@rfcuny.org

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, October 4, 2021 7:42 PM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

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Thanks.

Hoau

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Cc: Maria Agosto
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Yan Bing Li
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230 West 41st Street
New York, NY 10036
212-417-8473
212-417-6473 Fax
Yan_Bing_Li@rfcuny.org
<http://www.rfcuny.org>

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent time: 01/05/2022 11:02:58 AM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Hi Dr. Wang,
Sure. Title is: *Analyzing Patient Samples from a 1-Year Open-Label Extension Study of PTI-125 Using SavaDx and Other Biomarkers*
Yan

Maria,
Any eays for this project? End date must be prior to 12/31/21
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Yan Bing Li
Project Administrator
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Office Hours Mon – Tues
Remote Hours Wed – Fri
212-417-8473
Yan_Bing_Li@rfcuny.org

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 5, 2022 10:40 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

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Subject: Re: 72587-0002-Cassava

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230 West 41st Street
New York, NY 10036
212-417-8473
212-417-6473 Fax
Yan_Bing_Li@rfcuny.org
<http://www.rfcuny.org>

From: Maria Agosto
Sent time: 01/05/2022 11:10:47 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>; Hoau-yan Wang
Subject: RE: 72587-0002-Cassava

Hello Yan,

No pending e-pays for this project.

Best,
Maria

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent: Wednesday, January 5, 2022 11:03 AM
To: Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Hi Dr. Wang,
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Yan Bing Li
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212-417-8473
Yan_Bing_Li@rfcuny.org

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 5, 2022 10:40 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

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230 West 41st Street
New York, NY 10036
212-417-8473
212-417-6473 Fax
Yan_Bing_Li@rfcuny.org
<http://www.rfcuny.org>

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent time: 01/05/2022 11:43:22 AM
To: Maria Agosto; Hoau-yan Wang
Subject: [EXTERNAL] RE: 72587-0002-Cassava

OK. Thanks Maria for confirming!

Yan Bing Li
Project Administrator
Grants & Contracts
Office Hours Mon – Tues
Remote Hours Wed – Fri
212-417-8473
Yan_Bing_Li@rfcuny.org

From: Maria Agosto <magosto@med.cuny.edu>
Sent: Wednesday, January 5, 2022 11:11 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>; Hoau-yan Wang <hywang@med.cuny.edu>
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From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 5, 2022 10:40 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

Hi Yan,

Can you please let me know of the title of the account (grant). I am not sure whether I can ask for extension as there were a lot of things going on I have no control over, but I will do my best.

Thanks. Stay safe!

Hoau

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent: Tuesday, January 4, 2022 11:52 AM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Dr. Wang,
Acct# 72587-0002 had ended back in December. Do you have any pending invoices on this account? In addition, there is about \$31k on direct, will you be asking for an extension? I'm not sure if that is possible, but please let me know.
Thanks,
Yan

Yan Bing Li
Project Administrator
Grants & Contracts
Office Hours Mon – Tues
Remote Hours Wed – Fri
212-417-8473
Yan_Bing_Li@rfcuny.org

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, October 4, 2021 7:42 PM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

will do.

Thanks.

Hoau

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent: Monday, October 4, 2021 3:13 PM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] 72587-0002-Cassava

Hi Prof. Wang
Please note that your account with Cassava will be ending in two months (12/31/2021) & I see you have over \$30k to spend. Please try to spend it down as best you can. Otherwise, try to request an extension. I wanted to send this to you early in case Cassava denies any extension requested late in the budget period.
Best,
Yan

Yan Bing Li
Project Administrator
Grants & Contracts

230 West 41st Street
New York, NY 10036
212-417-8473
212-417-6473 Fax
Yan_Bing_Li@rfcuny.org
<http://www.rfcuny.org>

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent time: 01/05/2022 03:44:01 PM
To: Zoe Arvanitakis <Zoe_Arvanitakis@rush.edu>
Cc: SEARNOLD@mgh.harvard.edu; Hoau-yan Wang; Rexford Ahima <ahima@jhmi.edu>; Ana Capuano <Ana_Capuano@rush.edu>
Subject: [EXTERNAL] Re: FW: Alzheimer's & Dementia: Translational Research & Clinical Interventions: Your Submission TRCI-D-21-00113
Attachments: Adipokine signaling-AD- Alzheimer's ^0 dementia finalized4.docx Reviewers cooment - ADTC.docx

Dear All,

Enclosed are mildly edited manuscript and a draft rebuttal letter that is clearly on the anemic side. The first reviewer requested a more thorough description of the study cohort that I think he/she meant to tell us to add a Table. Inadvertently, I indicated table 1 in the first part of the result section that reviewer 2 picked up. I think it may be appropriate to add a Table 1B to describe the study cohort (Ana please help!) with Table 1A describing the antibody used in the ex vivo study.

The reviewer 3 complains about typos and writing style (not by an English-first person) that he/she requested a revision made by English-first persons. Since English is indeed not my first language even though I don't think such a statement is accurate, your help in thoroughly revising the manuscript is appreciated.

Lastly, I am going into 2 months of extremely heavy teaching that I shoulder 90% of the CNS pharmacology and other parts and 60% of a graduate course, both as the course director. On many days, my lecture hours come to 6 hours (with 30 min in between). Please forgive me If I don't respond to your request quickly. I am doing everything in my limited abilities to stay on top of things.

Thanks for your understanding and again your help in getting this manuscript revised and re-submitted on time.

Best,

Hoau

On Thu, Dec 30, 2021 at 4:18 PM Zoe Arvanitakis <Zoe_Arvanitakis@rush.edu> wrote:

Dear all,

We received the journal review last week from Alz&Dem: TRCI, for our BIRA paper on adipokines. Please see below. Should not take too long to respond.

Hoau,

Are you able to take a first stab at the response? Can you then send to all, indicating where you specifically may have questions and for whom? I will then do a final review.

Please note that the resubmission date is set at JANUARY 20 and I will need at least a week before that to do a review. I think this is achievable.

Thank you all and happy new year!

Zoe

Zoe Arvanitakis, MD, MS, FAAN, FANA
Medical Director of the Rush Memory Clinic and Neuroscientist, Rush Alzheimer's Disease Center
Professor and Section Head of Cognitive Neuroscience, Department of Neurological Sciences
Rush University Medical Center, Rush University System for Health (RUSH)

Administrative Assistant: Veronica_Hernandez@rush.edu

rush.edu/radc

-----Original Message-----

From: em.trci.0.78260a.1a939eb8@editorialmanager.com [mailto:em.trci.0.78260a.1a939eb8@editorialmanager.com] On Behalf Of Alzheimer's & Dementia TRCI

Sent: Tuesday, December 21, 2021 10:49 AM

To: Zoe Arvanitakis <Zoe_Arvanitakis@rush.edu>

Subject: Alzheimer's & Dementia: Translational Research & Clinical Interventions: Your Submission TRCI-D-21-00113

Rush Email Security

****WARNING**** This email originated from outside of Rush University Medical Center. ****DO NOT CLICK**** links or attachments unless you recognize the sender and know the content is safe. Remember, Rush IS will never ask for user ID information via email communication.

CC: adj_xed@kra.net

Alzheimer's & Dementia: Translational Research & Clinical Interventions Ms. Ref. No.: TRCI-D-21-00113

Title: Human brain leptin and adiponectin signaling, neuropathology, and cognition

Decision: Revise

Dear Dr. Arvanitakis,

The reviewers have now commented on your paper. Regrettably, we will be unable to publish your manuscript referenced above. However, you may resubmit the manuscript as a revision, if you can fully respond to the reviewers' comments. Please note: the revised manuscript may be rejected by the editors if it is regarded as below the priority standard of the Journal, even if revised to the satisfaction of the referees. It is the policy of the Journal to allow one opportunity to make substantive revisions.

Please carefully consider the referee reports, along with any additional editorial comments (if included). If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. The revised manuscript will be due on Jan 20, 2022.

For your guidance, reviewers' comments are appended below.

To submit a revision, please go to

[https://urldefense.com/v3/https://www.editorialmanager.com/trci/;!!OlavHw!qnKnKw7d4_hk31pqQzeepAR-bGVCypjP846VglPygM1x8JeWyMNtbpUkui7LSaIx0aMj_w\\$](https://urldefense.com/v3/https://www.editorialmanager.com/trci/;!!OlavHw!qnKnKw7d4_hk31pqQzeepAR-bGVCypjP846VglPygM1x8JeWyMNtbpUkui7LSaIx0aMj_w$) and login as an Author.

Your username is: zarvanit

If you need to retrieve password details please go to: [https://urldefense.com/v3/https://www.editorialmanager.com/trci/l.asp?i=79580&l=EO5TIEI3;!!OlavHw!qnKnKw7d4_hk31pqQzeepAR-bGVCypjP846VglPygM1x8JeWyMNtbpUkui7LSaLzfJEPow\\$](https://urldefense.com/v3/https://www.editorialmanager.com/trci/l.asp?i=79580&l=EO5TIEI3;!!OlavHw!qnKnKw7d4_hk31pqQzeepAR-bGVCypjP846VglPygM1x8JeWyMNtbpUkui7LSaLzfJEPow$)

On your Main Menu page is a folder entitled "Submissions Needing Revision". You will find your submission record there. Along with addressing all reviewer and/or editor comments, please be sure to provide the following items:

1. New cover letter
2. Point by point response to comments with "comments" followed by "response" and some reference (page and line number) of where the corrections appear
3. Marked-up manuscript (highlighted) - this should be uploaded under the 'Marked Revision' file designation
4. Revised manuscript - this should be uploaded under the 'Manuscript' file designation. *Please note that, if accepted, this file will be the one typeset and published.
5. Abstract, in the format outlined in our Guide for Authors.
6. Research in Context, as described in our Guide for Authors
7. References must follow AMA style, and be serially numbered. Please note that no web addresses should appear unless cite as references.
8. Figures must be uploaded as individual files in TIFF, EPS, JPG, or PDF format, of at least 300 DPI.

Please feel free to contact the editorial office, at ADJEdOffice@jjeditorial.com with any questions.

Yours sincerely,

Ara S. Khachaturian, Ph.D.

Editor-in-Chief

Alzheimer's & Dementia: Translational Research & Clinical Interventions

Reviewers' comments:

Reviewer #1: Wang et al presented ELISA and ex vivo data using postmortem samples to show that leptin and adiponectin signaling functions were not associated with the global pathology of Alzheimer's disease, amyloid burden, or neurofibrillary tangle density. Instead, leptin signaling was suggested to be associated with more microinfarcts in the cortical regions. While potentially useful, this work suffers significant deficiencies at its present form. Major concerns are:

1. The exclusive use of the dorsolateral prefrontal cortex to examine the link between AD pathology and leptin/adiponectin is unjustified. The presence of neurofibrillary tangles at this region indicates late Braak stages. Animal studies demonstrated that AD is a self-propagating tauopathy, suggesting that the progression of cognitive defects may not require the initial, nucleating factors. If leptin or adiponectin is associated with AD, entorhinal regions should be the most likely area to search for the link.
2. The description of the subjects is practically absent. Other than the total number of postmortem samples, mean ages, and gender, there is no indication of the stages of AD, or the severity of T2D. Data interpretation is therefore rudimentary.

Reviewer #2: Manuscript entitled "Human brain leptin and adiponectin signaling, neuropathology, and cognition" by Wang et al., report no relationship between leptin signaling and AD pathologies and cognitive impairment, while authors suggest that the leptin signaling may associate with micro infarcts and amyloid angiopathy. This paper followed the previous publication by same authors (Neurobiol. Aging 2019) and may include interesting findings. However, overall, the manuscript is immature compared to authors' previous publication, and the discussion session is verbose along with poor presentation of results.

This reviewer has concerns as follows

1. Table 1 shows the information of antibodies used in this study, while Table 1 indicates subject information in page 10. In the sessions 3.1 and 3.2, authors describe APOE e4 but not data for APOE isoforms are shown (maybe a table is missing).
2. The experimental procedure is unclear. This reviewer guesses that activated protein kinase, which is phosphorylated at a specific amino acid (such as pY705STAT3), is isolated by immunoprecipitation with pan-kinase antibody (anti-STAT3), and detected it by immunoblotting with phosphorylation state specific antibody (pTyr706 specific antibody). The phosphorylation ratio seems to be quantified and compared. However, no blot results are shown. It is impossible to evaluate the results.

Overall, the manuscript should be reconstructed largely prior to submission.

Reviewer #3: The regulation of CNS function by adipokines (adiponectin and leptin) is complex and remains confusing. This paper adds more fuel to this complexity by examining the role of adipokines in CNS pathology by examining signaling capacity of these adipokines (with and without insulin) in postmortem human brain tissue (DLPFC was chosen - it may be obvious but it would still be helpful to say why). The samples were obtained from the Religious Orders Study which features annual cognitive testing, and fairly short postmortem interval. These studies follow an earlier study that demonstrated the technical feasibility of running a cell signaling measurement in postmortem human tissue in an ex vivo manner. The authors used pY1007/1008JAK2 relative to total JAK2, pY705STAT3 relative to total JAK2 as measures of leptin signaling, and pT183/172AMPK α 1/2 relative to total AMPK as a measure of adiponectin signaling. 10 nM leptin and 10 μ g/ml adiponectin with and without 1 nM insulin were used to stimulate these pathways. This pharmacologist reviewer would suggest using a concentration response curve for leptin and adiponectin to better understand any changes in signaling potency and efficacy - one can be misled by responses to single concentrations. Possibly insufficient post-mortem brain material is available.

The authors found that leptin signaling was linked more strongly to vascular insults: micro-infarcts and amyloid angiopathy. Signaling pathways for either adipokine are not correlated with cognitive outcomes. They suggest that the new findings lead to an integrated hypothesis describing the association of leptin, but not adiponectin signaling with cerebrovascular pathology but not with Alzheimer's disease (AD) pathology or cognition, among elderly persons with or without diabetes.

The presentation of the data in tables makes it difficult for the non-expert reader to study and make sense of the results. A diagram summarizing the effects of leptin, adiponectin and insulin with the signaling pathways measured would be helpful for the reader, for following the various correlations (or lack thereof) in the tables, as well as for formulating future hypotheses to test.

The paper is generally well-written although there are numerous typos and expressions that were clearly not written by a native English speaker. A review by a native English speaker would be helpful.

In compliance with data protection regulations, you may request that we remove your personal registration details at any time.
(Use the following URL: [https://urldefense.com/v3/__https://www.editorialmanager.com/trci/login.asp?a=r_!!OlavHw!qnKnKw7d4_hk31pqQzeepAR-bGVCypjP846VglPygM1x8JeWyMNtbpUkui7LSaLBmihJsw\\$](https://urldefense.com/v3/__https://www.editorialmanager.com/trci/login.asp?a=r_!!OlavHw!qnKnKw7d4_hk31pqQzeepAR-bGVCypjP846VglPygM1x8JeWyMNtbpUkui7LSaLBmihJsw$)). Please contact the publication office if you have any questions.

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Response: Neurofibrillary tangles are present in dorsolateral prefrontal and entorhinal cortex in AD. AD animal models are mostly genetically modified partial models so that animal models can not accurately reflect AD pathology progression. In this study, we aim to assess whether there are any correlations between leptin or adiponectin signaling with AD. In this regard, dorsolateral prefrontal cortex is a suitable brain area to assess the whether the levels of leptin/adiponectin signaling are related to AD progression.

2. The description of the subjects is practically absent. Other than the total number of postmortem samples, mean ages, and gender, there is no indication of the stages of AD, or the severity of T2D. Data interpretation is therefore rudimentary.

Response: Table 1B is added to better describe the characteristic of the subjects including the APOE ϵ genotypes (Ana please add the table).

Reviewer #2: Manuscript entitled "Human brain leptin and adiponectin signaling, neuropathology, and cognition" by Wang et al., report no relationship between leptin signaling and AD pathologies and cognitive impairment, while authors suggest that the leptin signaling may associate with micro infarcts and amyloid angiopathy. This paper followed the previous publication by same authors (Neurobiol. Aging 2019) and may include interesting findings. However, overall, the manuscript is immature compared to authors' previous publication, and the discussion session is verbose along with poor presentation of results.

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which is phosphorylated at a specific amino acid (such as pY705STAT3), is isolated by immunoprecipitation with pan-kinase antibody (anti-STAT3), and detected it by immunoblotting with phosphorylation state specific antibody (pTyr706 specific antibody). The phosphorylation ratio seems to be quantified and compared. However, no blot results are shown. It is impossible to evaluate the results.

Response: The ex vivo stimulation method had been thoroughly described in our earlier 2019 Neurobiology of Aging paper (Wang HY, Capuano AW, Khan A, Pei Z, Lee KC, Bennett DA, et al. Insulin and adipokine signaling and their cross-regulation in postmortem human brain. *Neurobiol Aging*. 2019; 84:119-130). The focus of the current manuscript is to assess the correlations of adiponectin and leptin signaling with cerebrovascular and AD pathology, the quantification of the signaling described in the tables is sufficient to achieve these objectives.

Overall, the manuscript should be reconstructed largely prior to submission.

Reviewer #3: The regulation of CNS function by adipokines (adiponectin and leptin) is complex and remains confusing. This paper adds more fuel to this complexity by examining the role of adipokines in CNS pathology by examining signaling capacity of these adipokines (with and without insulin) in postmortem human brain tissue (DLPFC was chosen - it may be obvious but it would still be helpful to say why). The samples were obtained from the Religious Orders Study which features annual cognitive testing, and fairly short postmortem interval. These studies follow an earlier study that demonstrated the technical feasibility of running a cell signaling measurement in postmortem human tissue in an ex vivo manner. The authors used pY1007/1008JAK2 relative to total JAK2, pY705STAT3 relative to total JAK2 as measures of leptin signaling, and pT183/172AMPK α 1/2 relative to total AMPK as a measure of adiponectin signaling. 10 nM leptin and 10 μ g/ml adiponectin with and without 1 nM insulin were used to stimulate these pathways. This pharmacologist reviewer would suggest using a concentration response curve for leptin and adiponectin to better understand any changes in signaling potency and efficacy - one can be misled by responses to single concentrations. Possibly insufficient post-mortem brain material is available.

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The paper is generally well-written although there are numerous typos and expressions that

were clearly not written by a native English speaker. A review by a native English speaker would be helpful.

Response: We have thoroughly review to eliminate typos and re-write where appropriate.

Human brain leptin and adiponectin signaling, neuropathology, and cognition

Hoau-Yan Wang, PhD^{1,2}; Ana W. Capuano, PhD³; Steven E. Arnold, MD⁴;
Amber Khan, PhD^{1,2}; Bouchra Taïb, PhD⁵; Frederick Anokye-Danso, PhD⁵; Julie A. Schneider,
MD, MS³; David A. Bennett, MD³; Rexford S. Ahima, MD, PhD⁵; Zoe Arvanitakis, MD, MS³

¹Department of Molecular, Cellular and Biomedical Science, City University of New York School of Medicine, 160 Convent Avenue, New York, New York 10031, USA.

²Department of Biology, Neuroscience Program, Graduate School of the City University of New York,
365 Fifth Avenue, New York, New York 10061, U.S.A.

³Rush Alzheimer's Disease Center and Department of Neurological Sciences, Rush University Medical Center, 1750 W. Harrison Street, Suite 1000, Chicago, Illinois 60612, USA.

⁴Department of Neurology and the Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Charlestown, <https://www.editorialmanager.com/TRCI/> Massachusetts 02129, USA.

⁵Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine,
333 East Monument Street, Baltimore, Maryland 21205, USA.

Correspondence to:

Hoau-Yan Wang, Ph.D.

Department of Molecular, Cellular and Biomedical Sciences,

City University of New York School of Medicine,

160 Convent Avenue, New York, New York 10031

Phone: 212-650-8813

Fax: 212-650-7726

Email: hywang@med.cuny.edu

Running Head (max: 50 characters): Brain adipokine and cerebrovascular disease

Number of characters in the title: 67 characters; in the running head: 39 characters

Number of words in the Abstract: 149 words; Introduction: 411 words; Discussion: 1433 words; the body of the manuscript (not including abstract or references, figure legends, etc.): 3500 words

Number of figures, color figures, and tables: 0 figures, 7 tables.

Keywords: Diabetes, adiponectin, leptin, insulin, signaling, Alzheimer's disease, cerebrovascular disease, infarcts, cognition, memory

Abstract

INTRODUCTION: The associations of leptin and adiponectin signaling with neuropathology and cognitive function in diabetes is currently unclear.

METHODS: We use ELISA and *ex vivo* stimulation of postmortem dorsolateral prefrontal cortical tissue with insulin (+/- leptin or adiponectin).

RESULTS: Leptin signaling measured by pY^{1007/1008}JAK2 and pY⁷⁰⁵STAT3, adiponectin by pT¹⁷²AMPK, were not associated with the global AD pathology, amyloid burden or tau tangle density scores. A higher leptin+insulin-induced pY^{1007/1008}JAK2 level was associated with more microinfarcts in cortical regions (OR= 2.68, p= 0.005). Also, pY⁷⁰⁵STAT3 level was positively associated with amyloid angiopathy (OR= 1.87, p= 0.004). There were no associations with global or domain-specific cognitive measures: episodic memory or perceptual speed.

DISCUSSION: Our results suggest that leptin, but not adiponectin signaling is associated with cerebrovascular pathology but not with Alzheimer's disease (AD) pathology or cognition, among elderly persons with or without diabetes.

Abbreviations:

AD: Alzheimer's disease; **ADP:** Adiponectin; **AMPK:** adenosine monophosphate dependent protein kinase; **CSF:** Cerebrospinal fluid; **DMSO:** dimethyl sulfoxide; **EDTA:** ethylenediaminetetraacetic acid; **EGTA:** aminopolycarboxylic acid; **ELISA:** Enzyme-linked immunosorbent assay; **INS:** insulin; **IR:** insulin receptor; **IRS1:** insulin receptor substrate 1; **JAK2:** Janus kinase 2; **LEP:** Leptin; **PAGE:** polyacrylamide gel electrophoresis; **PBS:** phosphate buffered saline; **PMI:** postmortem interval; **SDS:** sodium dodecyl sulfate; **STAT:** signal transducer and activator of transcription 3; **T2D:** Type 2 Diabetes Mellitus; **TMB:** 3, 3', 5, 5'-tetramethylbenzidine

1. INTRODUCTION

Metabolic perturbation resulting from type 2 diabetes mellitus (T2D) is a risk factor for brain dysfunction including cognitive decline and dementia in the elderly [1, 2]. Although the neurobiological mechanisms for this heightened risk remain elusive, T2D-associated insulin resistance has been demonstrated in Alzheimer's disease (AD) brains [3, 4]. T2D is most often associated with obesity and altered levels of leptin and adiponectin, two prominent insulin signaling regulators [5-8]. Leptin signaling in the hypothalamus regulates feeding and energy homeostasis [9-12]. Leptin also modulates cortical and hippocampal neuronal and glial proteins, brain development, synaptic plasticity, cognitive function, and neuroprotection [13-16]. Epidemiological studies indicate that the development of AD is associated with mid-life obesity and leptin deficiency [16-18]. Adiponectin, discovered years later after leptin but the most abundant adipokine identified to date, improves insulin sensitivity and protects against oxidative injury and inflammation [19] [20-25]. Studies in rodents demonstrate that adiponectin protects against neuronal injury and promotes learning and memory [26-28]. Furthermore, adiponectin levels are associated with mild cognitive impairment and AD [29-32].

Adipokines can regulate brain function. Indeed, leptin and adiponectin receptors are expressed in the human brain [33-35], and leptin and adiponectin are present in cerebrospinal fluid (CSF). However, it remains unclear whether insulin, adiponectin, leptin, or their concurrent signaling is associated with neuropathology of AD or cerebrovascular disease, the major underlying neuropathologies of cognitive impairment and dementia in the elderly [3, 36-38]. Further, little data are available on the relation of adipokines in brain, and human brain specifically, to the clinical expression of common aging-related neuropathology, namely cognitive impairment.

In this study, we examined the associations of key signaling molecules in leptin ([JAK2] and [STAT3]) and adiponectin ([AMPK]) signaling with AD and cerebrovascular neuropathology and cognitive function, among deceased and autopsied elderlies with or without diabetes. We used 150 postmortem dorsolateral prefrontal gyrus cortex (DLPFC) from age-/education-balanced, gender-matched 1:1 subjects (75 with and 75 without diabetes) from a community-based, clinical-pathologic aging study, as described previously [39]. We performed ELISAs to quantify pY⁷⁰⁵STAT3, pT¹⁷²AMPK and pS²⁴⁴⁸mTOR. We also used an *ex vivo* brain stimulation method to measure leptin (+/- insulin)-induced pY^{1007/1008}JAK2 and pY⁷⁰⁵STAT3, as well as adiponectin (+/- insulin)-induced pT^{183/172}AMPK [40]. We tested the associations of brain insulin, leptin, and adiponectin signaling measures with global and specific AD neuropathology, cerebrovascular disease (brain infarcts and vessel pathologies), and global cognitive function and five separate cognitive domains proximate-to-death.

2. METHODS

2.1 Study approval.

The Rush Institutional Review Board (IRB) approves the study. The City College of New York and City University of New York Medical School human research committee had determined that this study that use postmortem brain tissues does not meet the definition of human subject research as defined by the federal regulations (45 CFR 46.102(d) (f)) and therefore does not require further IRB review or approval.

2.2 Study sample, and clinical and neuropathologic data

The Religious Orders Study (ROS) is an ongoing, prospective, community-based clinical-pathologic aging study. Catholic nuns, priests, and brothers from about 40 convents and monasteries across the US were invited to participate, starting in 1994 [41]. Once a year, subjects undergo a detailed clinical evaluation including a medical history, physical examination, and neuropsychological testing with 17 previously described neuropsychological tests [42] grouped to assess composite measures of global cognition and five cognitive domains [43]. To create composite scores, individual test results were converted to z scores (using the baseline mean and standard deviation from the entire cohort), and scores for all tests in each domain were averaged. The presence of diabetes was determined by the medical history and the use of anti-diabetes medications [44].

A standardized brain autopsy protocol was applied and tissues from one hemisphere were frozen at -80°C, and from the other hemisphere were paraformaldehyde-fixed [43]. The ROS autopsy rate is >90%, with a mean postmortem interval (PMI) of 9.6 hours. Gross and histologic postmortem neuropathologic evaluations were conducted blinded to clinical data [45]. The square root of a continuous standardized AD pathological measure including neuritic plaques, diffuse plaques, and neuronal neurofibrillary tangles counts by a modified silver stain [45]. Immunohistochemical measures of the square root of global amyloid β ($A\beta$) burden and tau tangle density were also determined [46].

Evaluation for cerebrovascular disease was conducted as described earlier [45, 47, 48]. The number, volume (in mm²) and location of the gross (macroscopic) infarcts were identified on gross examination [45]. Each gross infarct was dissected, inspected under the microscope by H&E, and categorized by age (only chronic infarcts were considered in analyses). Micro-infarcts were identified in paraffin-embedded sections with H&E staining, and location and age were

recorded [47]. Cerebral vessel pathology data are systematically collected [48]. Atherosclerosis severity was graded using a semi-quantitative scale by visual inspection of vessels in the Circle of Willis. Arteriolosclerosis severity was determined by H&E stained sections of the anterior basal ganglia, and vessel wall thickening graded by a semi-quantitative scale. Amyloid angiopathy severity was graded in several neocortical brain regions according to the magnitude of anti-amyloid- β immunohistochemical labeling [47, 49]. The severity of each of the vessel pathologies was grouped into two or three levels as described below.

Study case selection

We selected 150 ROS autopsied subjects, 75 with and 75 without diabetes matched sex, and balanced by age-at-death and education, from which we collected new brain ELISA data. We used a randomization algorithm to select 39 pairs of subjects with or without diabetes who had a PMI ≤ 12 hours for *ex vivo* stimulation assays. This PMI cutoff was previously determined to be responsive to leptin and adiponectin stimulation, either alone or in combination with insulin, in postmortem human brain tissue using an *ex vivo* stimulation method [40].

2.3 Brain leptin and adiponectin signaling molecules by ELISA

Frozen DLPFC brain samples were thawed, homogenized in lysis buffer containing protease and phosphatase inhibitors, and 50 μ g supernatant proteins were assayed in duplicate using Pathscan ELISA kits (Cell Signaling, Danvers, MA) according to manufacturer's instructions. The following ELISAs were performed: PathScan® Phospho-Stat3 (Tyr705) Sandwich ELISA Kit #7300, PathScan® Total Stat3 Sandwich ELISA Kit #7305, Phospho-AMPK α (Thr172) Sandwich ELISA Kit #7959, PathScan® Total AMPK α Sandwich ELISA Kit

#7961, Phospho-mTOR (Ser2448) Sandwich ELISA Kit #7976, and PathScan® Total mTOR Sandwich ELISA Kit #7974.

2.4 Assessing leptin and adiponectin signaling using an *ex vivo* stimulation method

The leptin and adiponectin receptor-mediated responses were measured using antibodies described in Table 1A by methods published earlier [40]. The leptin signaling was assessed by the levels of 1) activated Janus kinase 2 (JAK2), pY^{1007/1008}JAK2 relative to total JAK2 immunoprecipitated by anti-JAK2 antibodies, and 2) activated signal transducer and activator of transcription 3 (STAT3), pY⁷⁰⁵STAT3 relative to total JAK2 immunoprecipitated by anti-STAT3 antibodies. The adiponectin signaling was assessed by the levels of activated adenosine monophosphate dependent protein kinase (AMPK), pT^{183/172}AMPK α 1/2 relative to total AMPK immunoprecipitated by anti-AMPK antibodies. The magnitude of leptin signaling was expressed as the fold increase induced by 10 nM leptin with and without 1 nM insulin compared to Krebs's Ringer (KR)-incubated basal levels. The level of adiponectin signaling was expressed as the fold increase evoked by 10 μ g/ml adiponectin with and without 1 nM insulin compared to KR-incubated basal levels. Leptin (10 nM) increased pY^{1007/1008}JAK2 4.2-4.3-fold and increased pY⁷⁰⁵STAT3 4.3-fold. Co-incubation of leptin with insulin but not adiponectin increased levels of pY^{1007/1008}JAK2 and pY⁷⁰⁵STAT3 by 22.1 \pm 2.5%. Adiponectin at 10 μ g/ml increased pT^{183/172}AMPK α 1/2 by 470%. Co-incubation of insulin but not leptin with adiponectin resulted in a 20.2 \pm 4.4% decrease in the adiponectin-evoked pT^{183/172}AMPK α 1/2 levels.

2.5 Statistical approach

We examined the data distribution, identified possible extremes, and examined the correlation structure of various variables. All brain adipokine signaling variables were z-score to facilitate the comparison of effects. There were two categories of adipokine signaling variables. The ELISA with three main variables: the pY⁷⁰⁵STAT3/total STAT3 ratio, the pT¹⁷²AMPK/total AMPK ratio, and the pS²⁴⁴⁸mTOR/total mTOR ratio. The *ex vivo* stimulation data with six variables: pY^{1007/1008}JAK2, pY⁷⁰⁵STAT3, and pT^{183/172}AMPK, each with and without co-incubation with insulin. We used a Bonferroni corrected alpha for each category (for ELISA we used $0.05/3=0.016$, and for *ex vivo* stimulation we used $0.05/6=0.008$). We used t-tests or the Wilcoxon Rank Sum to compare brain leptin and adiponectin signaling variables and basic subject characteristics between those with and without diabetes. We examined the association of each brain adipokine signaling with measures of AD neuropathology, infarcts and other vessel pathology, and cognition proximate-to-death, in separate models controlling for age-at-death, and sex. Specifically, the linear regression model was used for the square root of AD neuropathology and for cognition proximate-to-death. The cumulative ordinal model assuming proportional odds was used for arteriolosclerosis (none, mild, and moderate/severe), amyloid angiopathy (none, mild, and moderate/severe), total infarct (none, single, and multiple), and for skewed pathology outcomes, A β plaques and tau tangles. The logistic regression model was used for infarcts of specific sizes (microscopic and gross) and locations (presence versus absence in the cortical or subcortical regions), and atherosclerosis vessel pathology (at least moderate versus less than moderate severity). Standard diagnostic methods and graphical examinations demonstrate that the assumptions underlying the statistical models were adequately met. All analyses were conducted using SAS/STAT software, Version 9.4 of the SAS® system for Linux.

3. RESULTS

3.1 Sample characteristics

This study included 75 non-diabetic and 75 diabetic subjects (Table 1B). The mean age-at-death was 86.6 years and education 18.1 years, and 50% of the study group were women. There were no differences in the demographic characteristics among those with and without diabetes. Cognitive function and AD pathology levels were similar between diabetes and non-diabetes groups [39]. There was no association between *APOE* $\epsilon 4$ and diabetes ($\chi^2(1)=1.316$; $p=0.251$).

3.2 Brain leptin and adiponectin signaling in relation to diabetes and *APOE*

The median and interquartile ranges of the z-score of the nine measures of leptin and adiponectin signaling by diabetes status (Wilcoxon Two-Sample Test with t Approximation, all $p \geq 0.0256$) is provided in Table 2. Analyses examining ELISA-based adipokine and related markers and *APOE* $\epsilon 4$ revealed no association between *APOE* $\epsilon 4$ and pT¹⁷²AMPK, pY⁷⁰⁵STAT3 or pS²⁴⁴⁸mTOR (as the outcomes) in models adjusting for age and sex (all $p \geq 0.666$). Similarly, examining *ex vivo* stimulation adipokine markers and *APOE* $\epsilon 4$ indicated no association between *APOE* $\epsilon 4$ and leptin-induced pY^{1007/1008}JAK2 or pY⁷⁰⁵STAT3, as well as adiponectin-induced pT^{183/172}AMPK, in models adjusting for age and sex (all $p \geq 0.242$).

3.3 Brain adipokine signaling and AD neuropathology

Because diabetes increases dementia risk, we examined the association of adipokine signaling levels in brain tissue with AD, the most common underlying neuropathology in dementia. We examined global AD pathology, and separately amyloid burden and tau tangle density. In Table 3, there was no association between the ELISA measures of pY⁷⁰⁵STAT3, pT¹⁷²AMPK, or pS²⁴⁴⁸mTOR with the composite global AD pathology score. Similarly, there was no association between AD pathology score with leptin and adiponectin signaling determined using *ex vivo* stimulation without and with insulin. Secondary analyses showed there was no association of pY⁷⁰⁵STAT3, pT¹⁷²AMPK, or pS²⁴⁴⁸mTOR with amyloid burden or tangle density. There was no association of amyloid burden or tangle density score with adiponectin and leptin signaling determined using *ex vivo* stimulation without and with insulin.

3.4 Brain adipokine signaling and cerebrovascular pathology

Because diabetes increases the risk of vascular pathology, we examined the association of the key signaling molecules in the leptin and adiponectin signaling pathways in brain tissue with number, size, and location of brain infarcts and three cerebral vessel pathologies (atherosclerosis, arteriolosclerosis, and amyloid angiopathy). Tables 4, 5, and 6 show results of separate regression models with cerebrovascular pathology as outcomes for leptin and adiponectin signaling ELISA and *ex vivo* stimulation measures. All models adjusted for age-at-death and sex. After Bonferroni correction, we found no association between the adipokine signaling and the number (0, 1, or >1), size (gross and micro infarcts), and location (cortical and subcortical) of infarcts (Table 4). In secondary analyses (Table 5), we found pY^{1007/1008}JAK2 (IN) was positively associated with cortical micro-infarcts (Table 5). In analyses of vessel pathology outcomes, we found pY⁷⁰⁵STAT3 but no other measures were positively associated with amyloid angiopathy (Table 6).

3.5 Brain adipokine signaling and cognitive function

We conducted further analyses, adjusted for age-at-death, sex, and education, of the relation domains (episodic memory, semantic memory, working memory, perceptual speed, and of the adipokine signaling measures with global cognitive function and five separate cognitive visuospatial abilities). We found that there was no association between the adipokine signaling measures and any of the cognitive outcomes (Table 7).

4. DISCUSSION

We previously demonstrated leptin and adiponectin signaling, as well as their separate and reciprocal interaction with the insulin signaling pathway, in postmortem human brains from cognitively normal controls [40]. In this study, we utilized these established experimental systems and found that leptin but not adiponectin signaling is positively associated with the number of micro-cortical infarcts, and with amyloid angiopathy, a cerebrovascular amyloidosis that is associated with both ischemic and hemorrhagic infarcts. In accordance with our earlier demonstration that adiponectin increases but leptin decreases insulin signaling [40], leptin, but not adiponectin signaling may be associated with cerebrovascular pathology but not with cognition, among elderly persons with and without diabetes. Specifically, we found correlations between leptin/insulin-induced pY^{1007/1008}JAK2 and increased abundance of micro-cortical infarcts, as well as increased amyloid angiopathy and elevated pY⁷⁰⁵STAT3. Together, these findings suggest that brain micro infarcts in cortical regions, and amyloid angiopathy may be related to brain insulin resistance. The insulin resistance may be at least in part resulted from a heightened suppression of insulin signaling caused by an elevated leptin signaling. In support,

epidemiological studies have found that higher blood leptin levels are associated with lower risk of dementia including that due to AD [50-52]. Moreover, lower circulating blood but not CSF leptin levels have been reported in AD patients [51, 53]. In brain, leptin modulates learning and memory by influencing synaptic plasticity [16, 54], neuronal excitability [55, 56], firing frequency of dopaminergic neurons in ventral tegmental area [57], and the dendritic morphology in the hippocampus [58]. However, our data showing there are no associations of the leptin or adiponectin related measurements with the level of global cognition or five separate cognitive domains, such as memory (Table 6) suggest that altered leptin signaling is likely not a major mediator of cognitive impairment in AD .

Leptin is also associated with cerebrovascular health. Leptin augments cerebral hemodynamic reserve following experimental vessel occlusion in rats [59]. Leptin's neuroprotective effect on various pathologies had also been demonstrated in experimental models [60, 61]. Treatment with leptin reduces oxygen/glucose deprivation induced ischemic damage in primary rat neuronal cultures and focal ischemia/reperfusion injury in mice [60, 62-64]. Leptin expression was increased in the ischemic cerebrocortex, perhaps representing an adaptive attempt to reverse neuronal damage [65]. In addition, leptin treatment potentiates the cerebral hemodynamic reserve in a three-vessel occlusion cerebral ischemic model [59]. Further, leptin receptor deficiency induces early, transient and hyperglycemia-independent blood-brain barrier dysfunction that presumably can lead to invasion of peripheral proteins [66]. In concert with the protective effects of leptin observed in experimental models, larger infarct volume following focal cerebral ischemia is noted in leptin-null ob/ob mice, compared to wild-type mice with normal leptin and insulin signaling [67]. In a permanent cerebral ischemia rat model, leptin reduced the brain infarct volume and neurological deficit up to seven days after the induction of ischemia [68]. Leptin's beneficial effects correlate with increased pY⁷⁰⁵STAT3 and

are partly mediated by promoting energy metabolism via JAK-STAT3 signaling pathways that increases anti-apoptotic protein Bcl-xL expression, stabilization of mitochondrial membrane potential with reduced mitochondrial oxidative stress, and elevating expression of tissue inhibitor of matrix metalloproteinases-1 (MMP-1) [60, 68, 69]. In striking contrast to leptin's protective effect against cerebral ischemia in animal studies, epidemiological studies demonstrated that high circulating blood leptin levels are associated with ischemic cerebrovascular disease, including an increased propensity for hemorrhagic stroke in men with insulin resistance [70-73]. The association of elevated circulating leptin with ischemic stroke observed in these studies may indicate a compensatory overproduction in response to leptin resistance, itself resulting in decreased neuroprotection by the leptin system [74]. This hypothesis is also supported by our current finding that heightened pY^{1007/1008}JAK2 induced by insulin and leptin is associated with amyloid angiopathy, although the mechanisms need further elucidation.

Cerebrovascular pathology is associated with impaired cerebral circulation and metabolism, including a decreased oxygen supply to the brain cells. Since poor cerebrovascular function is associated with, and considered as an early marker of cognitive decline, in healthy postmenopausal women [75], it is conceivable that leptin may protect against neuropathology and dementia. This hypothesis is supported by published data showing that leptin decreases A β production, increases A β clearance and degradation, and inhibits A β aggregation, thereby reducing A β levels as well as tau phosphorylation by inhibiting β secretase, and decreasing GM1 ganglioside activating PI3K/Akt/mTOR, sirtuins and AMPK [76-80]. The leptin's beneficial effects on AD pathology and cognition are supported by studies conducted in humans and transgenic AD mouse models [51, 81-84] although negative data also exist [85, 86]. The findings that plasma leptin levels are lower in AD subjects compared to normal controls independent of adiposity and body weight [87-89] support the possibility of a

decreased neuroprotective effects of leptin due to the reduced leptin signaling. This reduced leptin signaling may in turn accelerate AD pathology progression and promote cognitive decline. Hence, our current observations that leptin signaling is positively associated with micro cortical infarcts and amyloid angiopathy but does not correlate with AD pathology or global cognitive function, may suggest that our study subjects are predominantly in the early AD and the increased leptin signaling is a compensatory response aiming to offset cerebrovascular pathology.

Using *ex vivo* stimulation paradigm, our earlier report showed that exogenous human recombinant adiponectin potentiates insulin signaling and increases pT^{183/172}AMPK α 1/2 levels [40]. In the current work, we utilized pT^{183/172}AMPK α 1/2 levels as well as pT^{183/172}AMPK α 1/2 production by adiponectin alone or in combination with insulin, to assess the correlations of adiponectin signaling and neuropathology and cognitive function. While the pT^{183/172}AMPK α 1/2 levels tend to negatively associate with the extent of cerebrovascular pathology, adiponectin- and adiponectin/insulin-induced pT^{183/172}AMPK α 1/2 levels trend to positively correlate with infarct levels and AD pathology. Our data therefore suggest that levels of cerebrovascular pathology and cognition are not influenced by adiponectin signaling, or vice versa.

In contrast to leptin, low circulating adiponectin levels were associated with higher incidence of ischemic cerebrovascular diseases such as cerebral infarction [90-92]. Low circulating adiponectin levels can correlate with neurological dysfunction severity and poor outcomes and are associated with mortality after ischemic stroke [93, 94]. There is also evidence showing that circulating adiponectin levels may be temporarily reduced during cerebrovascular insults [91]. The neuroprotective effects counteracting ischemic stroke were demonstrated in a focal cerebral ischemia mouse model that increased adiponectin expression

reduced brain atrophy and improved the overall neuronal function by promoting angiogenesis [95]. Adiponectin appears to prevent ischemic injury by activating endothelial nitric oxide synthase-dependent hemodynamic mechanisms and protecting against ischemia-reperfusion damage by blocking the NF- κ B pathway to promote an anti-inflammatory effect [96, 97]. Although these studies collectively suggest that adiponectin, like leptin, can protect against ischemic stroke, our results however did not show any clear relationship between adiponectin signaling and cerebrovascular pathology. Several possibilities as to why we did not show a relationship between adiponectin signaling and cerebrovascular pathology including the relatively small sample size and that other molecules not measured are involved.

We have illustrated that the postmortem human brain within 10 hours PMI under optimally oxygenated and normothermic conditions, remains responsive to insulin, adiponectin and leptin [3, 4, 39, 40]. Others and we have found that postmortem brain can withstand some ischemic insults and retain functions and ability to signal, despite the differential agonal states [98-104]. While these data indicate that postmortem brain research can produce functional data and assess disease states, there are many limitations and confounds with such studies. Most notably, various brain cells and molecules are differentially vulnerable to postmortem changes, hence some may lose more integrity and functionality than others. We use rigorous methods including tightly controlled tissue storage temperature and detailed tissue preservation procedures, to preserve the integrity of the receptors and signaling molecules and have noted minimal compromise. We select tissue with postmortem intervals of less than 12 hours and without confounding diseases such as tumors or traumatic brain injury. These and other strategies employed enhance the internal validity of our results derived from the human postmortem brain tissues.

5. CONCLUSION

In summary, we demonstrate that adipokines influence cerebrovascular pathology primarily via leptin rather than adiponectin. Together with epidemiological studies showing that diabetes and obesity both with insulin resistance may play a role in vascular and AD dementia [105], our studies including the current results [39], help elucidate underlying neuropathological mechanisms common to both vascular dementia and AD/ Alzheimer's Disease Related Dementias (ADRD). Further research on brain signaling and human clinical studies will inform on whether the leptin signaling pathway may offer potential targets for diagnosis and treatment of dementia. With increasing recognition that peripheral insulin resistance and cardiovascular disease increase the risk of dementia [106], future research is needed to examine the contribution of altered adipokine signaling in brain and the periphery, to cerebrovascular changes in AD and non-AD states, as well as in aging with and without diabetes.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest related to this study. Dr Amber Khan, Dr. Bouchra Taib, Dr. Frederick Anokye-Danso and Rexford S Ahima have nothing to declare. Dr. Wang has received grants in the past 36 months from NIH (R01 AG15819, R01 NS084965, R01 AG057658 and RF1 AG059621, R44 AG 060878, R01NS084965, R42AG057329, R01 MH116463-01 and AG065890) to his institution. He also serves as a consultant and a member of scientific advisory board for Cassava Sciences, an unpaid scientific advisor for Neuropharmalogic Inc. R01NS084965 and R01 AG057658 paid to him for attending meetings. He has two patents: US Patent No: 10363239 (7/30/2019) and US Patent No.: 10,222,368 (3/5/2019). Dr. Capuano has received grants from NIH (P30 AG10161, R01 AG15819, R01 NS084965, R01 AG057658 and RF1 AG059621). She has participated in data and safety board advisory board: Data and Safety Monitoring, Communication Bridge: A person-centered internet-based intervention for individuals with primary progressive aphasia, PI Emily J. Rogalski, Ph.D., Northwestern University and received consulting fee. She also function as an Unpaid elected Vice-chair, Executive Committee of the Design and Data Analytics, ISTAART, Alzheimer's Association from 2020-present and an invited Programs Chair, Executive Committee of the Design and Data Analytics, ISTAART, Alzheimer's Association (2018-2019). Dr. Arnold has received grants from NIH (R01 NS084965 and RF1 AG059621), Abbvie, Amylyx, Seer Biosciences, John Sperling Foundation Challenger Foundation, Alzheimer's Association Massachusetts Life Sciences Center, Janssen, EIP Pharma, vTv Athira and Alzheimer's Drug Discovery Foundation. He receives consulting fee from Biogen, Sage, Abbvie, EIP, Cassava sciences and Eisai. He also receives honoraria from Biogen and Abbvie. He received payment from Cortexyme. Dr. Schneider has received grants from NIH (P30 AG10161, R01 AG15819) and consulting fee from Alnylam, AVID radiopharmaceuticals and National Hockey League. She receives consulting fee for educational activities including lectures and grant reviews. She also provides expert testimony on personal injury case for local hospital/doctors. She receives

supports to attend meetings by academic Universities and non-governmental organizations. She serves in the advisory board of Framingham and Discovery OSMB. Dr. Bennett receives grants from NIH (P30 AG10161, R01 AG15819) and Neurovision. He receives consulting fee from AbbVie, DSMB, Takeda, adjudication comm. Origent and SBIR. He receives supports to attend meetings by academia and government. He is a member of AbbVie advisory board. Dr. Arvanitakis has received grants from NIH (P30 AG10161, R01 AG15819, R01 NS084965, and RF1 AG059621) and Spire Learning. She receives consulting fee from Spire Learning.

AUTHOR CONTRIBUTIONS

Z.A., S.E.A., R.S.A. developed the study concept.

Z.A., S.E.A., R.S.A., H-Y.W., A.W.C. designed the study.

Z.A., H-Y.W., R.S.A., S.E.A., A.W.C., J.A.S., D.A.B., A.K., B.T., F. A-D. contributed to data acquisition.

Z.A., A.W.C. analyzed the data, and drafted the manuscript and tables.

Z.A., R.S.A., S.E.A., H-Y.W., A.W.C., J.A.S., D.A.B. revised the manuscript.

COMPETING INTERESTS

H-Y.W.: Nothing to report.

A.W.C.: Nothing to report.

S.E.A.: Nothing to report.

A.K.: Nothing to report.

B.T.: Nothing to report.

F. A-D.: Nothing to report.

J.A.S.: Nothing to report.

D.A.B.: Nothing to report.

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Rosanne Barbra Hendriksen, Ellen José van der Gaag

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Nicholas A. Bianco, Patrick W. Franks, Jennifer L. Hicks, Scott L. Delp

Quantifying *Karenia brevis* bloom severity and respiratory irritation impact along the shoreline of Southwest Florida

Richard P. Stumpf, Yizhen Li, Barbara Kirkpatrick, R. Wayne Litaker, Katherine A. Hubbard, Robert D. Currier, Katherine Kohler Harrison, Michelle C. Tomlinson

User perspectives on critical factors for collaborative playlists

So Yeon Park, Blair Kaneshiro

Burrowing crabs and physical factors hasten marsh recovery at panne edges

Kathryn Beheshti, Charlie Endris, Peter Goodwin, Annabelle Pavlak, Kerstin Wasson

Happiness at work: A cross-cultural validation of happiness at work scale

Nina Fitriana, Fonny Dameaty Hutagalung, Zainudin Awang, Sumaia Mohammed Zaid

Are nitrogen and carbon cycle processes impacted by common stream antibiotics? A comparative assessment of single vs. mixture exposures

Austin D. Gray, Emily Bernhardt

A clinical trial to evaluate the dayzz smartphone app on employee sleep, health, and productivity at a large US employer

Rebecca Robbins, Matthew D. Weaver, Stuart F. Quan, Jason P. Sullivan, Mairav Cohen-Zion, Laura Glasner, Salim Qadri, Charles A. Czeisler, Laura K. Barger

Drought prediction based on an improved VMD-OS-QR-ELM model

Yang Liu, Li Hu Wang, Li Bo Yang, Xue Mei Liu

Analysis of coding variants in the human *FTO* gene from the gnomAD database

Mauro Lúcio Ferreira Souza Junior, Jaime Viana de Sousa, João Farias Guerreiro

Automated satellite remote sensing of giant kelp at the Falkland Islands (Islas Malvinas)

Henry F. Houskeeper, Isaac S. Rosenthal, Katherine C. Cavanaugh, Camille Pawlak, Laura Trouille, Jarrett E. K. Byrnes, Tom W. Bell, Kyle C. Cavanaugh

The social specificities of hostility toward vaccination against Covid-19 in France

Nathalie Bajos, Alexis Spire, Léna Silberzan, for the EPICOV study group

Pricing and assembly rate decisions for a prefabricated construction supply chain under subsidy policies

Wen Jiang, Xian Qi

Anemia and undernutrition in intestinally parasitized schoolchildren from Gakenke district, Northern Province of Rwanda

María José Irisarri-Gutiérrez, Lucrecia Acosta, Lucy Anne Parker, Rafael Toledo, Fernando Jorge Bornay-Llinares, José Guillermo Esteban, Carla Muñoz-Antolí

Depressive symptoms in non-alcoholic fatty liver disease are identified by perturbed lipid and lipoprotein metabolism

Daniel E. Radford-Smith, Preya J. Patel, Katharine M. Irvine, Anthony Russell, Dan Siskind, Daniel C. Anthony, Elizabeth E. Powell, Fay Probert

The lower airways microbiome and antimicrobial peptides in idiopathic pulmonary fibrosis differ from chronic obstructive pulmonary disease

Kristel S. Knudsen, Sverre Lehmann, Rune Nielsen, Solveig Tangedal, Ingvild Haaland, Pieter S. Hiemstra, Tomas M. Eagan

Pandemic-related declines in hospitalization for non-COVID-19-related illness in the United States from January through July 2020

Jennifer L. Nguyen, Michael Benigno, Deepa Malhotra, Farid Khan, Frederick J. Angulo, Jennifer Hammond, David L. Swerdlow, Maya Reimbaeva, Birol Emir, John M. McLaughlin

Global cervical cancer research: A scientometric density equalizing mapping and socioeconomic

analysis

Dörthe Brüggmann, Kathrin Quinkert-Schmolke, Jenny M. Jaque, David Quarcoo, Michael K. Bohlmann, Doris Klingelhöfer, David A. Groneberg

Small but visible: Predicting rare bryophyte distribution and richness patterns using remote sensing-based ensembles of small models

Carlos Cerrejón, Osvaldo Valeria, Jesús Muñoz, Nicole J. Fenton

Nutrition education incorporation into mainstream primary school curriculum in Ghana: Stakeholders' sources of nutrition information and perceived barriers

Esi Quaidoo, Agatha Ohemeng, Mawuli K. Kushitor, Janet Antwi

Investigating the incidence and risk factors of hypertension: A multicentre retrospective cohort study in Tabuk, Saudi Arabia

Umar Yagoub, Nasrin S. Saiyed, Bandar Al Qahtani, Attiya Mohammed Al Zahrani, Yassir Birema, Ibrahim Al Hariri

Unstructured clinical notes within the 24 hours since admission predict short, mid & long-term mortality in adult ICU patients

Maria Mahbub, Sudarshan Srinivasan, Ioana Danciu, Alina Peluso, Edmon Begoli, Suzanne Tamang, Gregory D. Peterson

The impact of COVID-19 on fertility behaviour and intentions in a middle income country

Tom Emery, Judith C. Koops

Association of circulating MR-proADM with all-cause and cardiovascular mortality in the general population: Results from the KORA F4 cohort study

Christina Gar, Barbara Thorand, Christian Herder, Chaterina Sujana, Margit Heier, Christa Meisinger, Annette Peters, Wolfgang Koenig, Wolfgang Rathmann, Michael Roden, Michael Stumvoll, Haifa Maalmi, Thomas Meitinger, Holger Then, Jochen Seissler, Cornelia Then

In search of autophagy biomarkers in breast cancer: Receptor status and drug agnostic transcriptional changes during autophagy flux in cell lines

Francesca Mascia, Ilya Mazo, Wei-Lun Alterovitz, Konstantinos Karagiannis, Wells W. Wu, Rong-Fong Shen, Julia A. Beaver, V. Ashutosh Rao

Association between being metabolically healthy/unhealthy and metabolic syndrome in Iranian adults

Ozra Tabatabaei-Malazy, Sahar Saeedi Moghaddam, Masoud Masinaei, Nazila Rezaei, Sahar Mohammadi Fateh, Arezou Dilmaghani-Marand, Elham Abdolhamidi, Farideh Razi, Patricia Khashayar, Alireza Mahdavihezaveh, Siamak Mirab Samiee, Bagher Larijani, Farshad Farzadfar

Mean platelet volume and mean platelet volume to platelet count ratio as predictors of severity and mortality in sepsis

Jorge Luis Vélez-Páez, Pedro Legua, Pablo Vélez-Páez, Estefanía Irigoyen, Henry Andrade, Andrea Jara, Fernanda López, Jorge Pérez-Galarza, Lucy Baldeón

Exploratory attitude survey of homeless persons regarding telecare services in shelters providing mid- and long-term accommodation: The importance of trust

Zsuzsa Györfy, Sándor Békási, Bence Döbrössi, Virág Katalin Bognár, Nóra Radó, Emília Morva, Szabolcs Zsigri, Péter Tari, Edmond Girasek

Performance of custom made videolaryngoscope for endotracheal intubation: A systematic review

Pawan Kumar Hamal, Rupesh Kumar Yadav, Pragya Malla

Engaging Female Community Health Volunteers (FCHVs) for cardiovascular diseases risk screening in Nepal

Lal B. Rawal, Yuewen Sun, Padam K. Dahal, Sushil C. Baral, Sudeepa Khanal, Abriti Arjyal, Shraddha Manandhar, Abu S. Abdullah

Regeneration of duckweed (*Lemna turonifera*) involves genetic molecular regulation and cyclohexane release

Lin Yang, Jinge Sun, Congyu Yan, Junyi Wu, Yaya Wang, Qiuting Ren, Shen Wang, Xu Ma, Ling Zhao, Jinsheng Sun

Heavy metal pollution and associated health risk assessment of urban dust in Riyadh, Saudi Arabia

Abdulaziz G. Alghamdi, Mohamed H. EL-Saeid, Abdulhakim J. Alzahrani, Hesham M. Ibrahim

Do empowered women receive better quality antenatal care in Pakistan? An analysis of demographic and health survey data

Muhammad Asim, Waqas Hameed, Sarah Saleem

Serum miR-34a-5p and miR-199a-3p as new biomarkers of neonatal sepsis

Omayma O. Abdelaleem, Shereen Rashad Mohammed, Hassan S. El Sayed, Sherin Khamis Hussein, Doaa Y. Ali, Mostafa Y. Abdelwahed, Sylvana N. Gaber, Nada F. Hemeda, Rehab G. Abd El-Hmid

Evaluation of virtual tour in an online museum: Exhibition of Architecture of the Forbidden City

Jia Li, Jin-Wei Nie, Jing Ye

Pharmacokinetics of a 503B outsourcing facility-produced theophylline in dogs

Jennifer M. Reinhart, Gabriela A. R. de Oliveira, Lauren Forsythe, Zhong Li

Gender sensitivity and stereotypes in medical university students: An Italian cross-sectional study

Fabrizio Bert, Edoardo Boietti, Stefano Rousset, Erika Pompili, Eleonora Franzini Tibaldeo, Marta Gea, Giacomo Scaioli, Roberta Siliquini

Empirical modeling of the percent depth dose for megavoltage photon beams

Xiao-Jun Li, Yan-Cheng Ye, Yan-Shan Zhang, Jia-Ming Wu

Attention based automated radiology report generation using CNN and LSTM

Mehreen Sirshar, Muhammad Faheem Khalil Paracha, Muhammad Usman Akram, Norah Saleh Alghamdi, Syeda Zainab Yousuf Zaidi, Tatheer Fatima

Reproducibility of knee extensor and flexor contraction velocity in healthy men and women assessed using tensiomyography: A study protocol

Georg Langen, Christine Lohr, Olaf Ueberschär, Michael Behringer

Cognitive cascades: How to model (and potentially counter) the spread of fake news

Nicholas Rabb, Lenore Cowen, Jan P. de Ruiter, Matthias Scheutz

Development of an artificial intelligence-based algorithm to classify images acquired with an intraoral scanner of individual molar teeth into three categories

Nozomi Eto, Junichi Yamazoe, Akiko Tsuji, Naohisa Wada, Noriaki Ikeda

Clinical efficacy of nivolumab is associated with tertiary lymphoid structures in surgically resected primary tumors of recurrent gastric cancer

Takuya Mori, Hiroaki Tanaka, Sota Deguchi, Yoshihito Yamakoshi, Yuichiro Miki, Mami Yoshii, Tatsuro Tamura, Takahiro Toyokawa, Shigeru Lee, Kazuya Muguruma, Masaichi Ohira

Improved log-Gaussian approximation for over-dispersed Poisson regression: Application to spatial analysis of COVID-19

Daisuke Murakami, Tomoko Matsui

Working memory guidance of visual attention to threat in offenders

Tamara S. Satmarean, Elizabeth Milne, Richard Rowe

Utilization of preconception care and associated factors in Hosanna Town, Southern Ethiopia

Meron Admasu Wegene, Negeso Gebeyehu Gejo, Daniel Yohannes Bedecha, Amene Abebe Kerbo, Shemsu Nuriye Hagisso, Solomon Abrha Damtew

Inclusion at universities: Psychometric properties of an inclusive management scale as perceived by students

María José Solis-Grant, Camila Espinoza-Parçet, Cristóbal Sepúlveda-Carrasco, Cristhian Pérez-Villalobos, Iván Rodríguez-Núñez, Cristian Pincheira-Martínez, Juan Pablo Gómez-Varela, Daniela Aránguiz-Ibarra

An evaluation of the diagnostic performance characteristics of the Yellow Fever IgM immunochromatographic rapid diagnostic test kit from SD Biosensor in Ghana

Lawrence Henry Ofosu-Appiah, Dodzi Kofi Amelor, Bright Ayensu, Ernest Akyereko, Nafisah Issah Rabiwu, David Opare, Godfred Owusu-Okyere, Dennis Odai Laryea, Franklin Asiedu-Bekoe, Julius Abraham Addo Mingle

The association between geriatric treatment and 30-day readmission risk among medical inpatients aged ≥ 75 years with multimorbidity

Marte Sofie Wang-Hansen, Hege Kersten, Jūratė Šaltytė Benth, Torgeir Bruun Wyller

Know your enemy: Application of ATR-FTIR spectroscopy to invasive species control

Claire Anne Holden, John Paul Bailey, Jane Elizabeth Taylor, Frank Martin, Paul Beckett, Martin McAinsh

Establishing laboratory-specific reference intervals for TSH and fT4 by use of the indirect Hoffman method

Sylvia Płaczowska, Małgorzata Terpińska, Agnieszka Piwowar

Mental health status of informal waste workers during the COVID-19 pandemic in Bangladesh

Md. Rajwanul Haque, Md. Mostaufed Ali Khan, Md. Mosfequr Rahman, M. Sajjadur Rahman, Shawkat A. Begum

Characteristics of severely malnourished under-five children immunized with Bacillus Calmette-Guérin following Expanded Programme on Immunization schedule and their outcomes during hospitalization at an urban diarrheal treatment centre, Bangladesh

Mst. Mahmuda Ackhter, Abu Sadat Mohammad Sayeem Bin Shahid, Tahmeed Ahmed, Parag Palit, Irin Parvin, Md. Zahidul Islam, Tahmina Alam, Shamsun Nahar Shaima, Lubaba Shahrin, Farzana Afroze, Monira Sarmin, Shoeb Bin Islam, Zubair Akhtar, Mohammad Jobayer Chisti, Fahmida Chowdhury

A deep hybrid learning pipeline for accurate diagnosis of ovarian cancer based on nuclear morphology

Duhita Sengupta, Sk Nishan Ali, Aditya Bhattacharya, Joy Mustafi, Asima Mukhopadhyay, Kaushik Sengupta

Communities' perceptions towards cervical cancer and its screening in Wolaita zone, southern Ethiopia: A qualitative study

Birhanu Wondimeneh Demissie, Gedion Asnake Azeze, Netsanet Abera Asseffa, Eyasu Alem Lake, Befekadu Bekele Besha, Kelemu Abebe Gelaw, Taklu Marama Mokonnen, Natnael Atnafu Gebeyehu, Mohammed Suleiman Obsa

Understanding the epidemiological HIV risk factors and underlying risk context for youth residing in or originating from the Middle East and North Africa (MENA) region: A scoping review of the literature

Roula Kteily-Hawa, Aceel Christina Hawa, David Gogolishvili, Mohammad Al Akel, Nicole Andruszkiewicz, Haran Vijayanathan, Mona Loutfy

Hypoattenuating periportal halo on CT in a patient population can occur in presence of a variety of diseases

Susann Dressel-Böhm, Henning Richter, Patrick R. Kircher, Francesca Del Chicca

The Australian living guidelines for the clinical care of people with COVID-19: What worked, what didn't and why, a mixed methods process evaluation

Tari Turner, Julian Elliott, Britta Tendal, Joshua P. Vogel, Sarah Norris, Rhiannon Tate, Sally Green, on behalf of the National COVID-19 Clinical Evidence Taskforce

Associations between infant and maternal characteristics measured at child age 5 months and maternal feeding styles and practices up to child age two years

Christine Helle, Elisabet R. Hillesund, Nina C. Øverby

Social jetlag and sleep debts are altered in different rosters of night shift work

Swaantje Casjens, Frank Brenscheidt, Anita Tisch, Beate Beermann, Thomas Brüning, Thomas Behrens, Sylvia Rabstein

Efficiency and bacterial diversity of an improved anaerobic baffled reactor for the remediation of wastewater from alkaline-surfactant-polymer (ASP) flooding technology

Dong Wei, Xinxin Zhang, Chunying Li, Min Zhao, Li Wei

Retrospective study of toxoplasmosis prevalence in pregnant women in Benin and its relation with malaria

Magalie Dambrun, Célia Dechavanne, Nicolas Guigue, Valérie Briand, Tristan Candau, Nadine Fievet, Murielle Lohezic, Saraniya Manoharan, Nawal Sare, Firmine Viwami, François Simon, Sandrine Houzé, Florence Migot-Nabias

Comparison between 20 and 30 meters in walkway length affecting the 6-minute walk test in patients with chronic obstructive pulmonary disease: A randomized crossover study

Narongkorn Saiphoklang, Apiwat Pugongchai, Kanyada Leelasittikul

The mediation of perceived risk's impact on destination image and travel intention: An empirical study of Chengdu, China during COVID-19

Xiufang Jiang, Jianxiong Qin, Jianguo Gao, Mollie G. Gossage

Association of genetic variations in *ACE2*, *TIRAP* and *factor X* with outcomes in COVID-19

Marissa J. M. Traets, Roel H. T. Nijhuis, Servaas A. Morré, Sander Ouburg, Jasper A. Remijn, Bastiaan A. Blok, Bas de Laat, Eefje Jong, Gerarda J. M. Herder, Aernoud T. L. Fiolet, Stephan P. Verweij

Combined application of zinc and iron-lysine and its effects on morpho-physiological traits, antioxidant capacity and chromium uptake in rapeseed (*Brassica napus* L.)

Ihsan Elahi Zaheer, Shafaqat Ali, Muhammad Hamzah Saleem, Hafiza Sana Yousaf, Afifa Malik, Zohaib Abbas, Muhammad Rizwan, Muyassar H. Abualreesh, Aishah Alatawi, Xiukang Wang

MARIDA: A benchmark for Marine Debris detection from Sentinel-2 remote sensing data

Katerina Kikaki, Ioannis Kakogeorgiou, Paraskevi Mikeli, Dionysios E. Raitsos, Konstantinos Karantzas

Facility and care provider emergency preparedness for neonatal resuscitation in Kano, Nigeria

Fatima Usman, Fatimah I. Tsiga-Ahmed, Mohammed Abdulsalam, Zubaida L. Farouk, Binta W. Jibir, Muktar H. Aliyu

Exogenous putrescine attenuates the negative impact of drought stress by modulating physio-biochemical traits and gene expression in sugar beet (*Beta vulgaris* L.)

Md Jahirul Islam, Md Jalal Uddin, Mohammad Anwar Hossain, Robert Henry, Mst. Kohinoor Begum, Md. Abu Taher Sohel, Masuma Akter Mou, Juhee Ahn, Eun Ju Cheong, Young-Seok Lim

CRISPR/Cas9-mediated Bag-1 knockout increased mesenchymal characteristics of MCF-7 cells via Akt hyperactivation-mediated actin cytoskeleton remodeling

Pelin Ozfiliz Kilbas, Nisan Denizce Can, Tugba Kizilboga, Fikret Ezberci, Hamdi Levent Doganay, Elif Damla Arisan, Gizem Dinler Doganay

Emotions and emotion up-regulation during the COVID-19 pandemic in Germany

Iris Schelhorn, Swantje Schlüter, Kerstin Paintner, Youssef Shiban, Ricardo Lugo, Marie Meyer, Stefan Sütterlin

Association of cognitive function with increased risk of cancer death and all-cause mortality: Longitudinal analysis, systematic review, and meta-analysis of prospective observational studies

Somayeh Rostamian, Saskia le. Cessie, Koen A. Marijt, J. Wouter Jukema, Simon P. Mooijaart, Mark A. van Buchem, Thorbald van Hall, Jacobijn Gussekloo, Stella Trompet

***Fusobacterium nucleatum* and *Bacteroides fragilis* detection in colorectal tumours: Optimal target site and correlation with total bacterial load**

Marie S. Rye, Kerry L. Garrett, Robert A. Holt, Cameron F. Platell, Melanie J. McCoy

Baseline clinical features of COVID-19 patients, delay of hospital admission and clinical outcome: A complex relationship

Cédric Dananché, Christelle Elias, Laetitia Hénaff, Sélilah Amour, Elisabetta Kuczewski, Marie-Paule Gustin, Vanessa Escuret, Mitra Saadatian-Elahi, Philippe Vanhems

Characterization of cassava ORANGE proteins and their capability to increase provitamin A carotenoids accumulation

Angélica M. Jaramillo, Santiago Sierra, Paul Chavarriaga-Aguirre, Diana Katherine Castillo, Anestis Gkanogiannis, Luis Augusto Becerra López-Lavalle, Juan Pablo Arciniegas, Tianhu Sun, Li Li, Ralf Welsch, Erick Boy, Daniel Álvarez

Lack of authentic atrial fibrillation in commonly used murine atrial fibrillation models

Fumin Fu, Michael Pietropaolo, Lei Cui, Shilpa Pandit, Weiyan Li, Oleg Tarnavski, Suraj S. Shetty, Jing Liu, Jennifer M. Lussier, Yutaka Murakami, Prabhjit K. Grewal, Galina Deyneko, Gordon M. Turner, Andrew K. P. Taggart, M. Gerard Waters, Shaun Coughlin, Yuichiro Adachi

Transgenic overexpression of CTRP3 does not prevent alcohol induced hepatic steatosis in female mice

Kristy L. Thomas, Callie L. Root, Jonathan M. Peterson

Reference centiles based on year-to-year changes for a longitudinal evaluation of motor performance in children and adolescents

Sven Wessela, Christof Meigen, Tanja Poulain, Carolin Sobek, Mandy Vogel, Siegfried Möller, Wieland Kiess

Intention and practice on breastfeeding among pregnant mothers in Malaysia and factors associated with practice of exclusive breastfeeding: A cohort study

Nurul Mursyidah Shohaimi, Majidah Mazelan, Kanesh Ramanathan, Mai Shahira Meor Hazizi, Yan Ning Leong, Xiang Bin Cheong, Subashini Ambigapathy, Ai Theng Cheong

Fibrolytic rumen bacteria of camel and sheep and their applications in the bioconversion of barley straw to soluble sugars for biofuel production

Alaa Emara Rabee, Amr A. Sayed Alahl, Mebarek Lamara, Suzanne L. Ishaq

Assessment of soil quality for guided fertilization in 7 barley agro-ecological areas of China

Yu Zhou, Yingcheng Fan, Guang Lu, Anyong Zhang, Ting Zhao, Genlou Sun, Daokun Sun, Qi Yu, Xifeng Ren

Scalable *in vitro* production of defined mouse erythroblasts

Helena S. Francis, Caroline L. Harold, Robert A. Beagrie, Andrew J. King, Matthew E. Gosden, Joseph W. Blayney, Danuta M. Jeziorska, Christian Babbs, Douglas R. Higgs, Mira T. Kassouf

Influence of slope incline on the ejection of two-phase soil splashed material

Michał Beczek, Magdalena Ryżak, Rafał Mazur, Agata Sochan, Cezary Polakowski, Andrzej Bieganski

Exploratory content analysis of direct-to-consumer pet genomics: What is being marketed and what are consumers saying?

Nikki E. Bennett, Silvio Ernesto Mirabal Torres, Peter B. Gray

A deep neural network model for multi-view human activity recognition

Prasetia Utama Putra, Keisuke Shima, Koji Shimatani

COVID-19 outbreaks in nursing homes: A strong link with the coronavirus spread in the surrounding population, France, March to July 2020

Muriel Rabilloud, Benjamin Riche, Jean François Etard, Mad-Hélénie Elsensohn, Nicolas Voirin, Thomas Bénet, Jean Iwaz, René Ecochard, Philippe Vanhems

Can open-defecation free (ODF) communities be sustained? A cross-sectional study in rural Ghana

Caroline Delaire, Joyce Kisiangani, Kara Stuart, Prince Antwi-Agyei, Ranjiv Khush, Rachel Peletz

BITES study: A qualitative analysis among emergency medicine physicians on snake envenomation management practices

Anna Tupetz, Loren K. Barcenas, Ashley J. Phillips, Joao Ricardo Nickenig

Vissoci, Charles J. Gerardo

An approximation of one-dimensional nonlinear Kortweg de Vries equation of order nine

Sidra Saleem, Malik Zawwar Hussain, Imran Aziz

Identification of an early-stage Parkinson's disease neuromarker using event-related potentials, brain network analytics and machine-learning

Sharon Hassin-Baer, Oren S. Cohen, Simon Israeli-Korn, Gilad Yahalom, Sandra Benizri, Daniel Sand, Gil Issachar, Amir B. Geva, Revital Shani-Hershkovich, Ziv Peremen

Quantile-specific heritability of plasma fibrinogen concentrations

Paul T. Williams

***Thainema* gen. nov. (Leptolyngbyaceae, Synechococcales): A new genus of simple trichal cyanobacteria isolated from a solar saltern environment in Thailand**

Somayeh Rasouli-Dogaheh, Jiří Komárek, Thomrat Chatchawan, Tomáš Hauer

A 3-D groundwater isoscape of the contiguous USA for forensic and water resource science

Gabriel J. Bowen, Jessica S. Guo, Scott T. Allen

Queen triggerfish *Balistes vetula*: Validation of otolith-based age, growth, and longevity estimates via application of bomb radiocarbon

Virginia R. Shervette, Jesús M. Rivera Hernández

Effects of mild-to-moderate sensorineural hearing loss and signal amplification on vocal emotion recognition in middle-aged–older individuals

Mattias Ekberg, Josefine Andin, Stefan Stenfelt, Örjan Dahlström

Functional MRI-based study of emotional experience in patients with psychogenic non-epileptic seizures: Protocol for an observational case-control study–EMOCRISES study

Pierre Fauvé, Louise Tyvaert, Cyril Husson, Emmanuelle Hologne, Xiaoqing Gao, Louis Maillard, Raymund Schwan, Claire Banasiak, Wissam El-Hage, Gabriela Hossu, Coraline Hingray

Assessing the efficacy of an integrated intervention to create demand for fishermen's schistosomiasis and HIV services (FISH) in Mangochi, Malawi: Study protocol for a cluster randomized control trial

Donaldson F. Conserve, Sekeleghe Kayuni, Moses K. Kumwenda, Kathryn L. Dovel, Augustine Talumba Choko

A multi-center, international, randomized, 2-year, parallel-group study to assess the superiority of IVUS-guided PCI versus qualitative angio-guided PCI in unprotected left main coronary artery (ULMCA) disease: Study protocol for OPTIMAL trial

Giovanni Luigi De Maria, Luca Testa, Jose M. de la Torre Hernandez, Dimitrios Terentes-Printzios, Maria Emfietzoglou, Roberto Scarsini, Francesco Bedogni, Ernest Spitzer, Adrian Banning

Changing antibiotic prescribing practices in outpatient primary care settings in China: Study protocol for a health information system-based cluster-randomised crossover controlled trial

Yue Chang, Yuanfan Yao, Zhezhe Cui, Guanghong Yang, Duan Li, Lei Wang, Lei Tang

From: Hoau-yan Wang
Sent time: 01/11/2022 09:55:28 AM
To: [REDACTED]@gmail.com
Cc: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: Concerns with publication in Alzheimer's Research & Therapy (MS ID AZRT-D-17-00036/ DOI 10.1186/s13195-017-0280-8)
Attachments: whole blots -ART -Fig1A-Fig1C-Fig5A-Fig6A.pdf 39371501-v2-ART follow-up clean (1).pdf Wang Letter to ART Publisher (2).docx

Dear Dr. Vellas,

Please find the following message from the publisher of *Alzheimer's Research and Therapy* regarding our 2017 paper. I'm not sure this reached you. I obtained your email address from Dr. Burns so I could forward it. I had submitted annotated whole blot images for this paper to the editors and publisher. Despite no evidence of manipulation, the publisher indicated that they concluded my arguments and evidence provided (the whole blot images) were "insufficient". Enclosed please find my response to the publisher's email requesting my explanation. Please note the publisher requested individual responses from all authors to **either agree or disagree** to retract the manuscript by 1/14/2022, and to provide reasoning. I am working on reaching any of my Servier co-authors, but as this manuscript was the culmination of 8 years of work, other than Dr. Pueyo none of them are still at Servier. One is deceased.

I strongly disagree with retracting for the following reasons:

1. There was no manipulation, and even COPE guidelines require **evidence** of manipulation. There is none.
2. Importantly, I ran these Western blots **blind** to treatment and APOE status, then forwarded the data to my Servier co-authors. I am still blind. If there were any manipulation in favor of treatment effects, it would therefore have to be on the part of Servier. I find this equally implausible.

Thank you for responding to this journal as a co-author. Please respond to Rebecca. If you would like to copy the editors-in-chief, their email addresses are dgalasko@health.ucsd.edu and p.scheltens@amsterdamumc.nl. As you know, I have been inundated with requests to prove an absence of manipulation in multiple papers. I appreciate your time.

Best regards,
Hoau-Yan

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

From: Rebecca Pearce <rebecca.pearce@biomedcentral.com>
Sent: Tuesday, January 4, 2022 10:16 AM dgalasko@health.ucsd.edu
To: PUEYO Maria IRIS; [REDACTED] thibierge@gmail.com; Isabelle.guignot@servier.com; [REDACTED]@yahoo.fr; karine.deschet@orange.fr; [REDACTED]@gmail.com; [REDACTED]@yahoo.fr; ousset.pj@chu-toulouse.fr; vellas.b@chu-toulouse.fr; Hoau-yan Wang
Subject: [EXTERNAL] Concerns with publication in Alzheimer's Research & Therapy (MS ID AZRT-D-17-00036/ DOI 10.1186/s13195-017-0280-8)

Wang, HY., Trocmé-Thibierge, C., Stucky, A. *et al.* Increased A β ₄₂- α 7-like nicotinic acetylcholine receptor complex level in lymphocytes is associated with apolipoprotein E4-driven Alzheimer's disease pathogenesis. *Alz Res Therapy* 9, 54 (2017). <https://doi.org/10.1186/s13195-017-0280-8>

Dear Prof Wang et al,

After further careful consideration, the journal has taken the decision to retract the article in line with COPE guidelines. Our investigation has concluded that explanation provided for the inconsistencies in the Western blots were insufficient and therefore confidence in the integrity of the data presented in article is compromised.

In line with our protocols for retracting articles, we will be publishing a Retraction Notice which will be bi-directionally linked to your article. The proposed wording can be found below:

Retraction for: [10.1186/s13195-017-0280-8](https://doi.org/10.1186/s13195-017-0280-8)

The Editors-in-Chief have retracted this article. Following publication, concerns have been raised regarding the western blot images presented in Figs. 1, 5 and 6. The authors have provided the raw data, which have been assessed by independent experts and deemed insufficient to address the concerns. The Editors-in-Chief therefore no longer have confidence in the integrity of the data in this article.

We would appreciate it if each author could **individually respond** in writing with whether they agree or disagree with the retraction and the retraction wording. Individual agreement will be logged in the retraction notice, but please note that while we give dissenting authors space to explain why they dissent, those reasons would not be included in the notice. We will

include in the notification that Prof Morain has passed.

We look forward to hearing from you by January 14, 2022.

With best wishes,

Rebecca

Rebecca Pearce

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T + 1 (212) 451-8733

rebecca.pearce@springernature.com

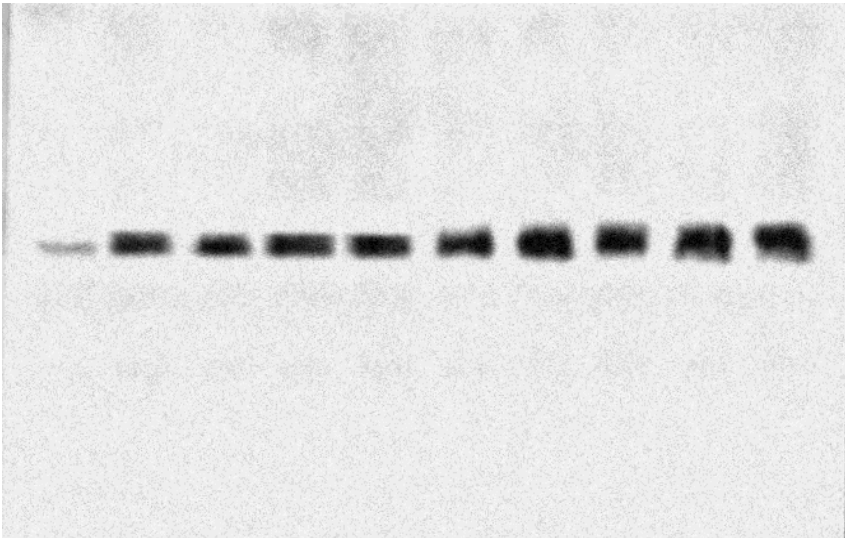
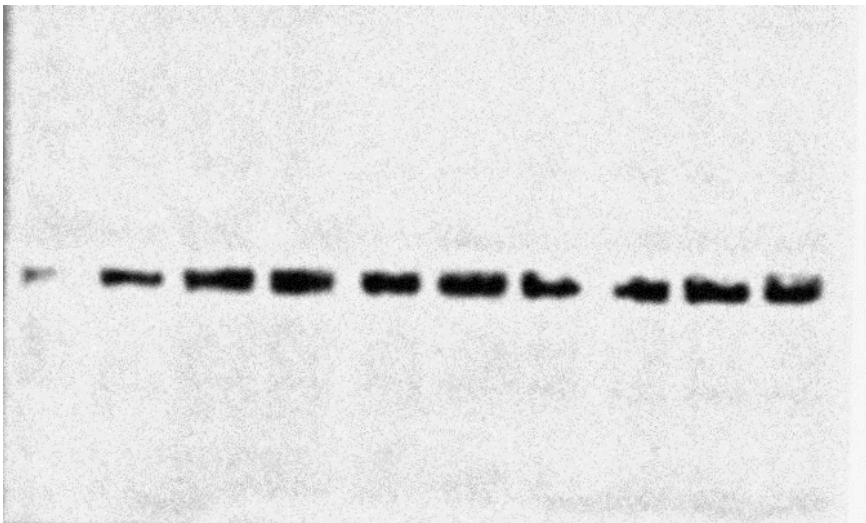
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Fig 1A

ApoE133-149

ApoE133-149(K→E)

α7nAChR



β-Actin

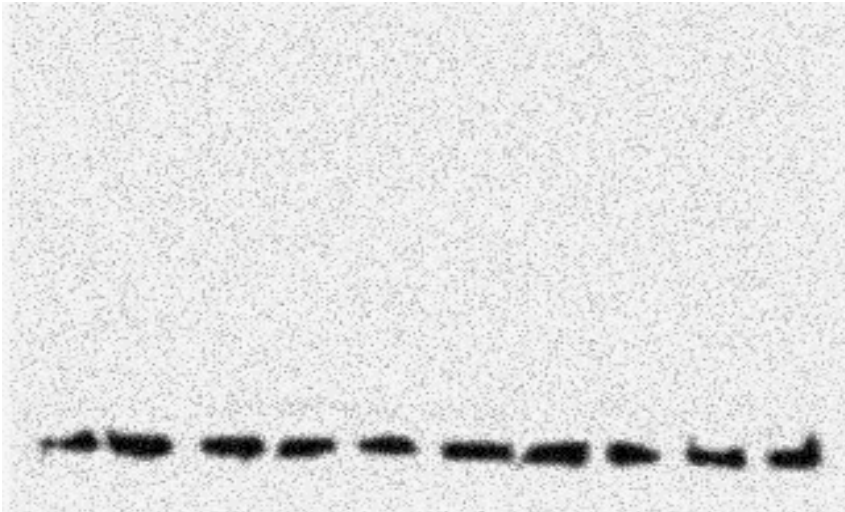
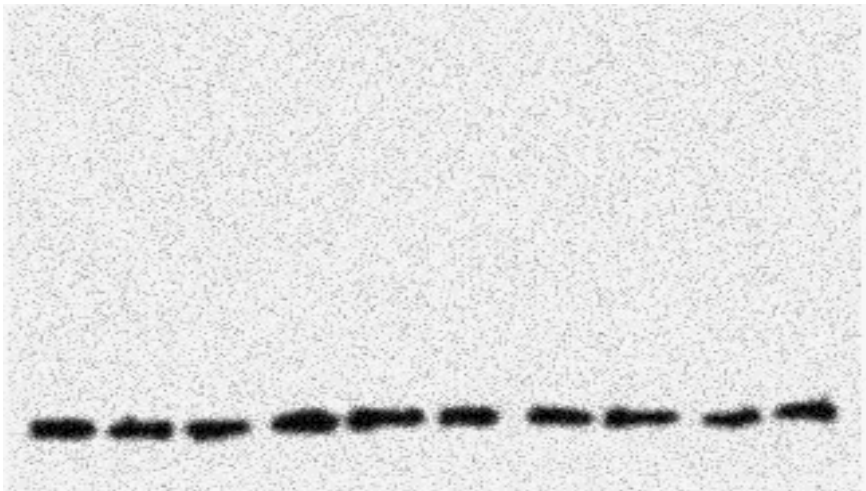
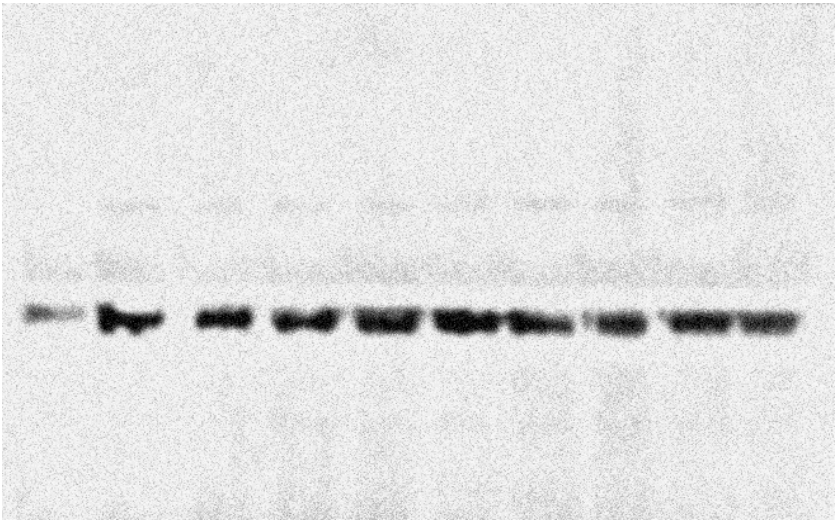
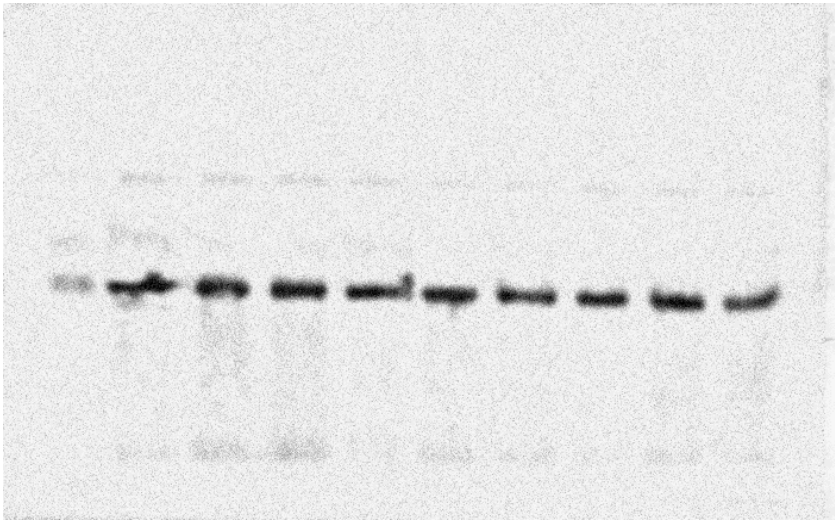


Fig 1A

ApoE141-148 Scrambled

ApoE133-140

$\alpha 7$ nAChR



β -Actin

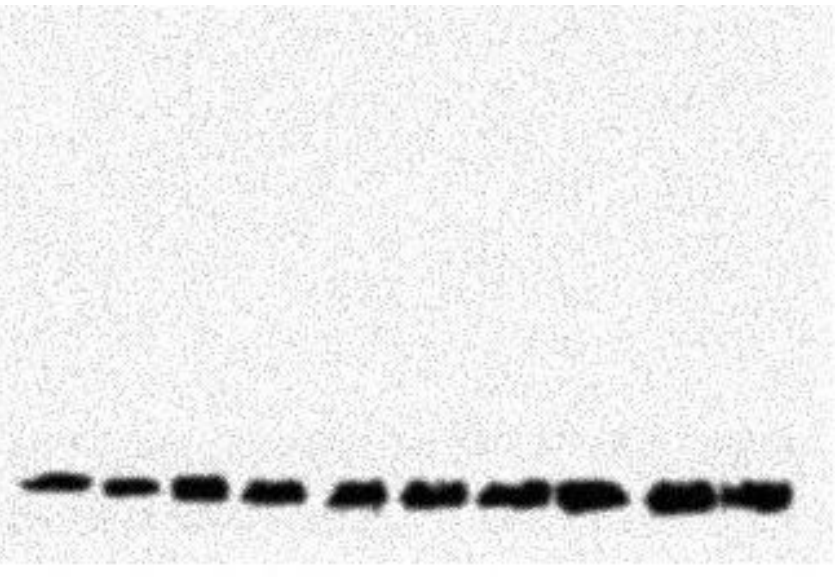
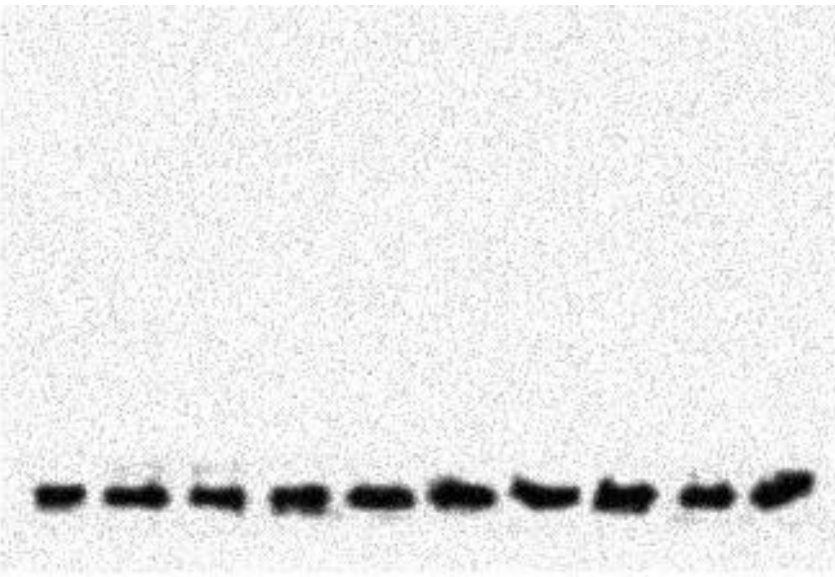
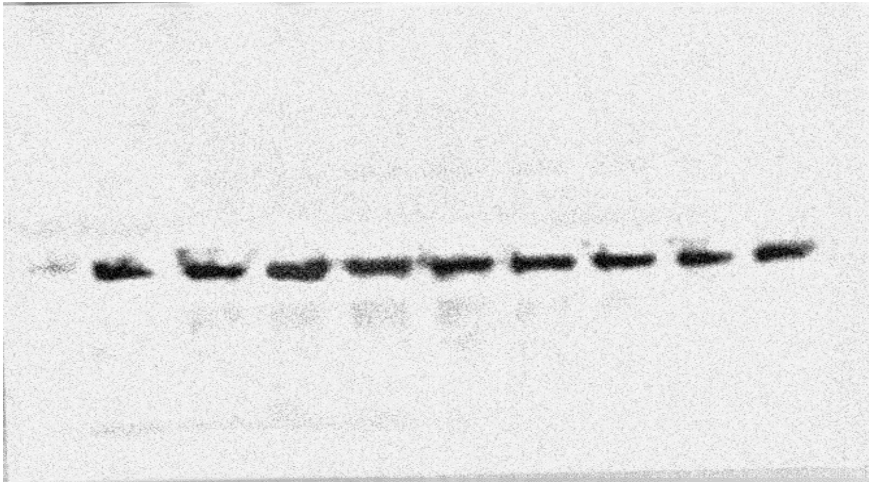
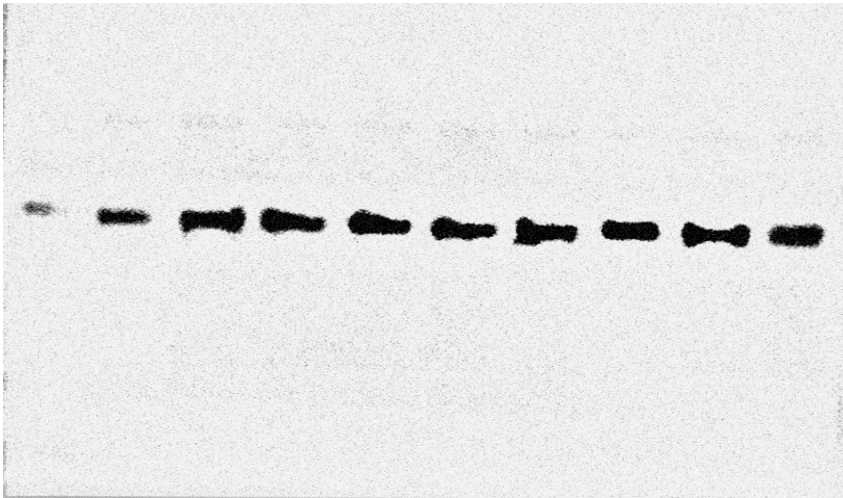


Fig 1A

ApoE141-148

ApoE141-148(K→E)

α7nAChR



β-Actin

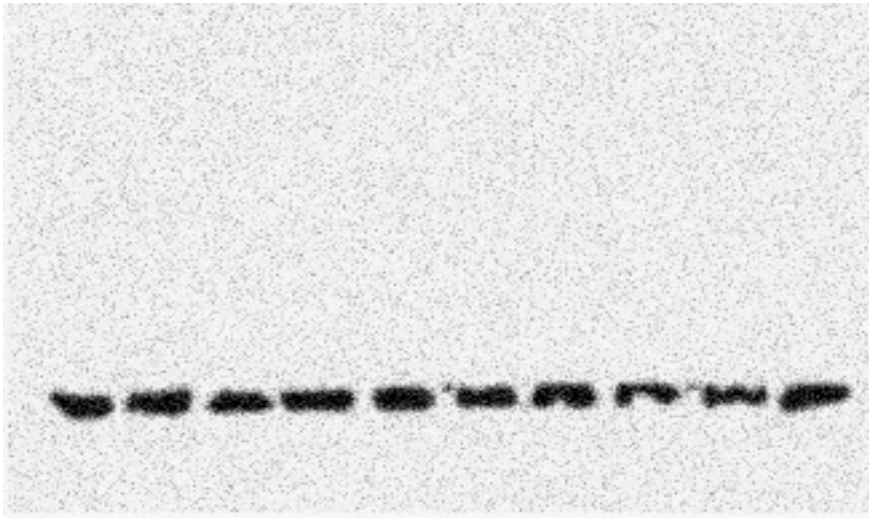
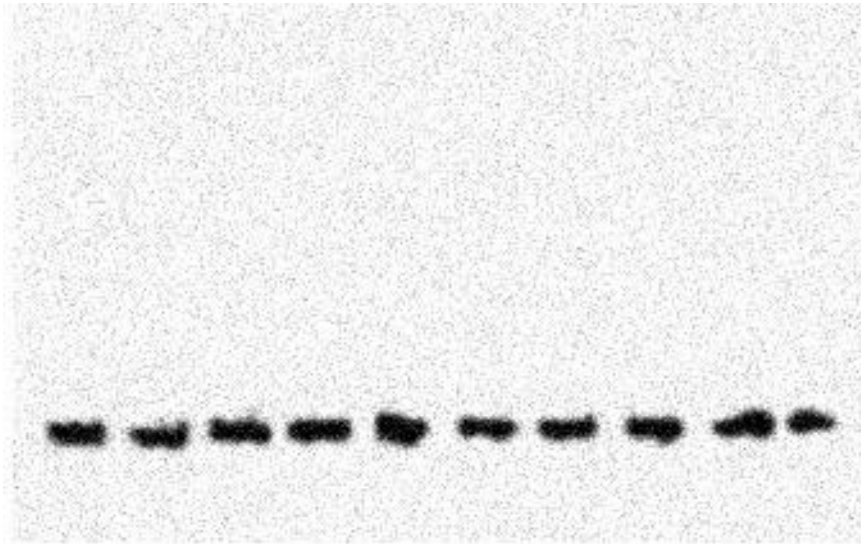
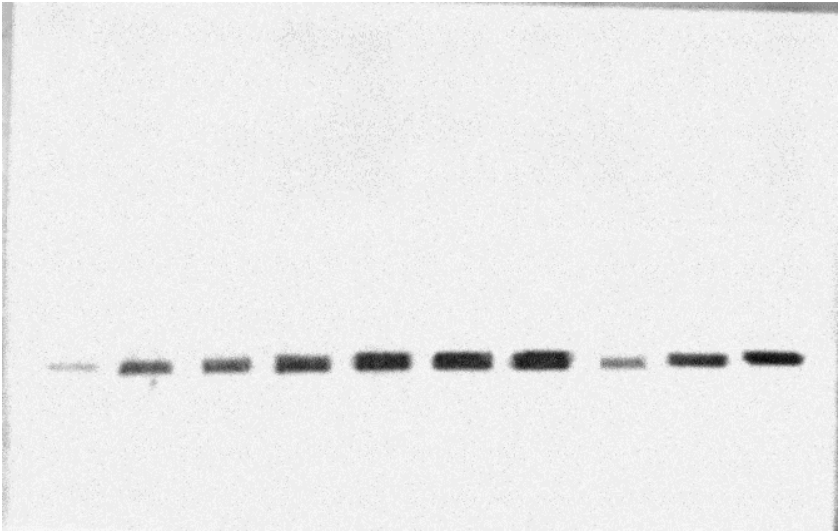


Fig 1C

ApoE133-149

ApoE141-148

α7nAChR



β-Actin

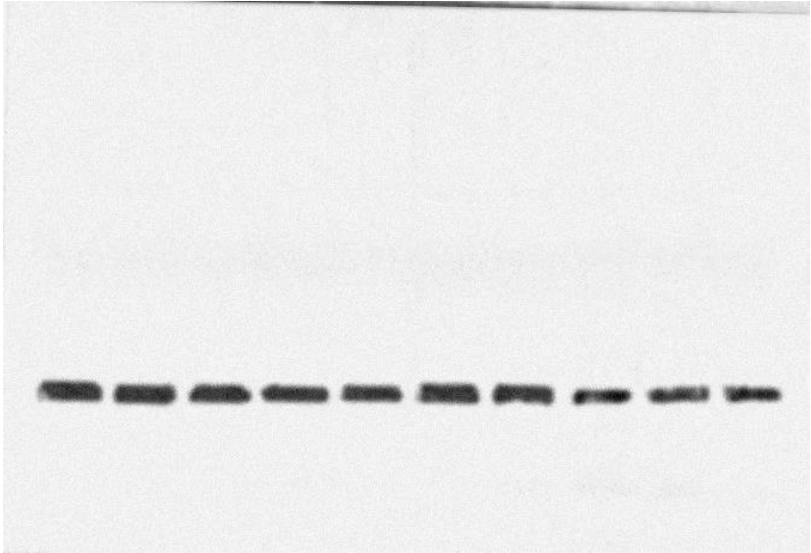
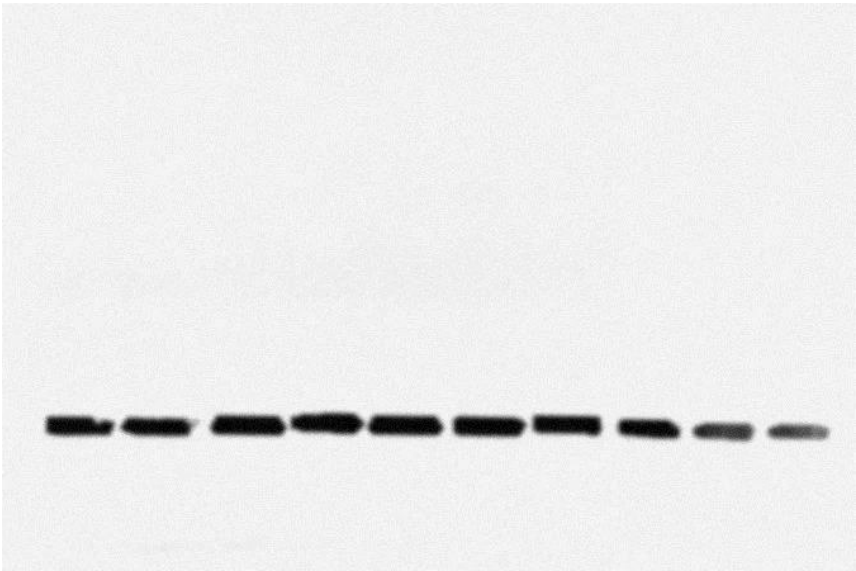


Fig 5A **pS202 Tau**

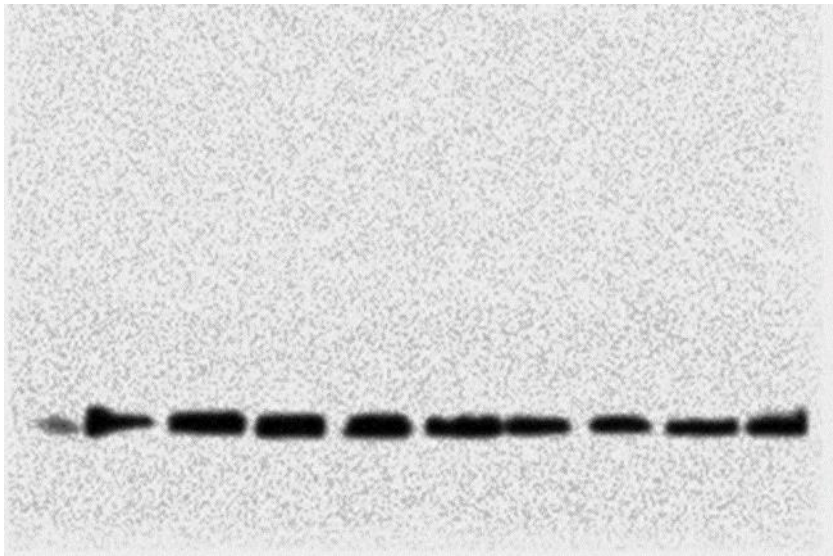
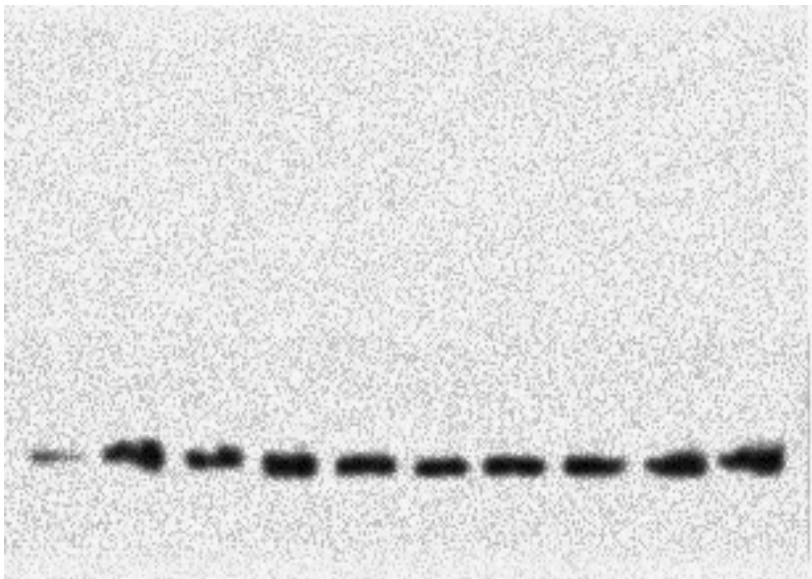
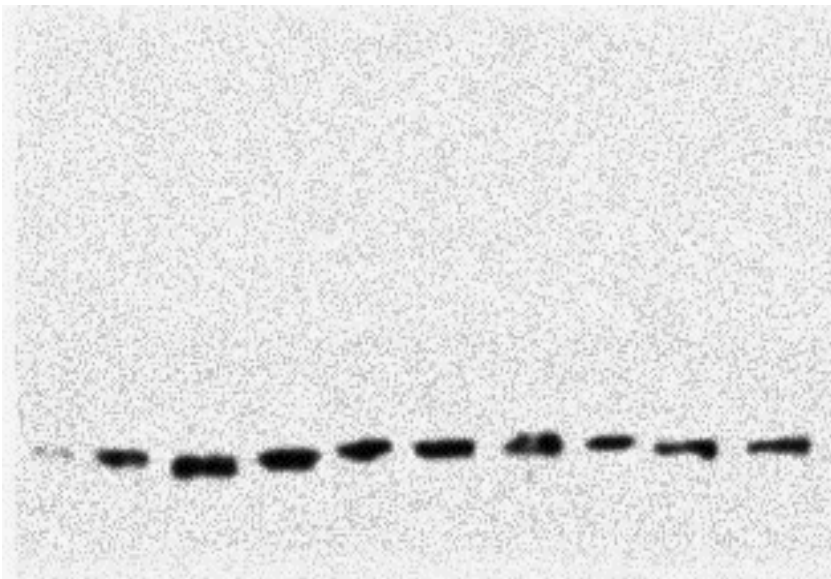


Fig 5A **pT231 Tau**

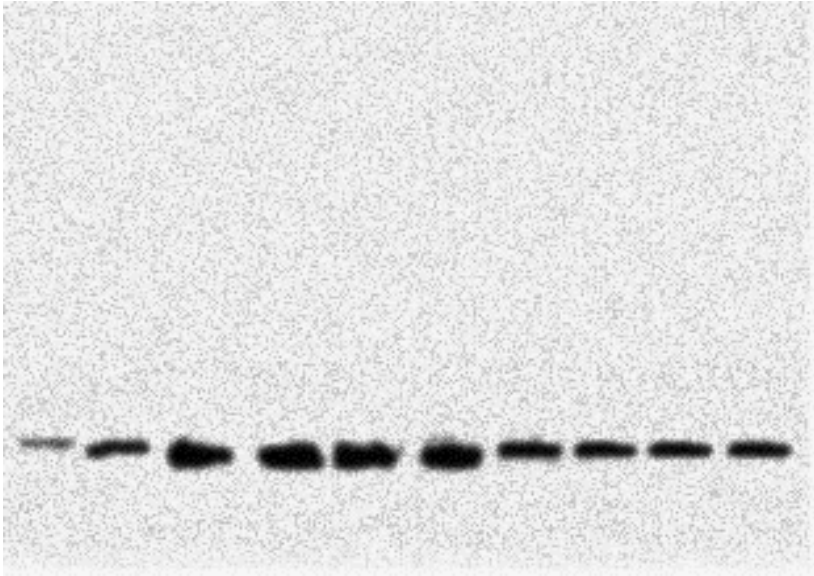
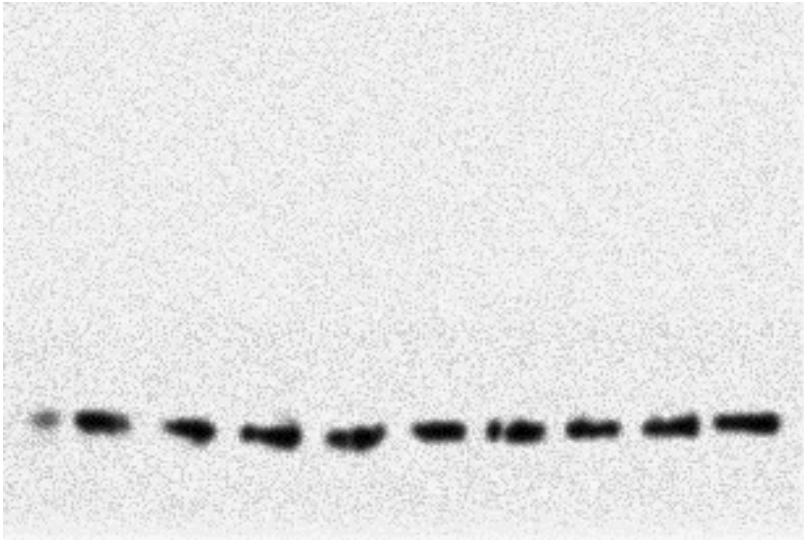
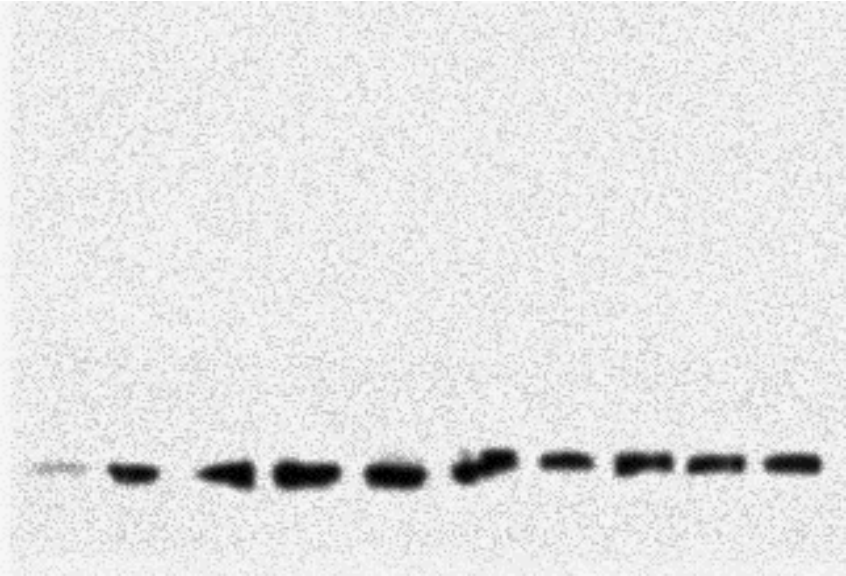


Fig 5A **pT181 Tau**

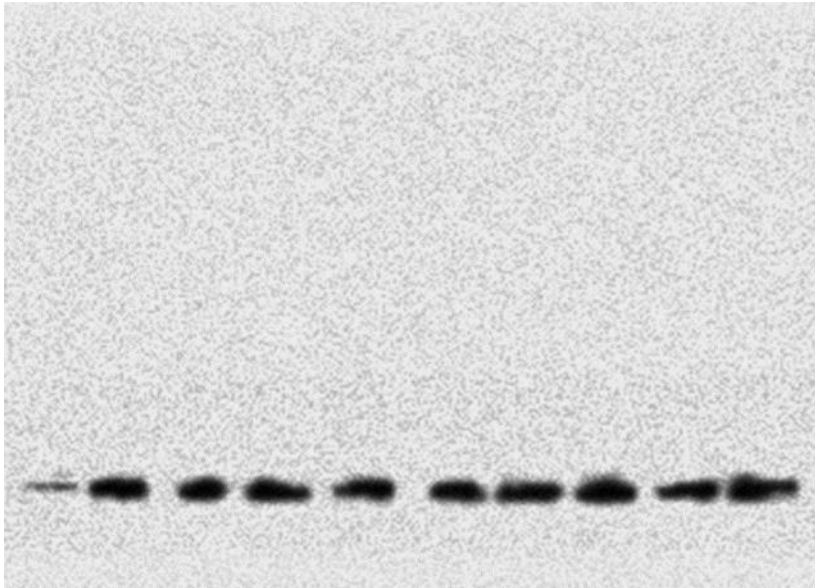
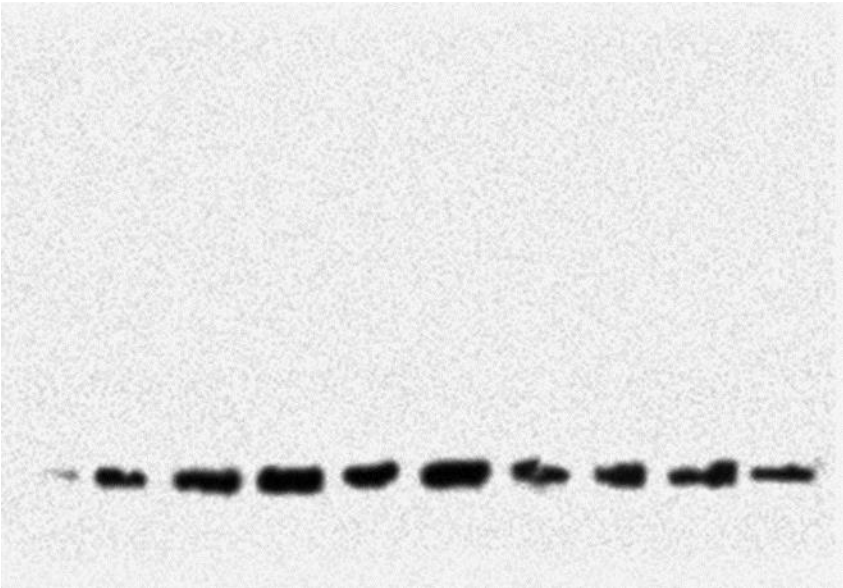


Fig 5A **Tau (Tau-5)**

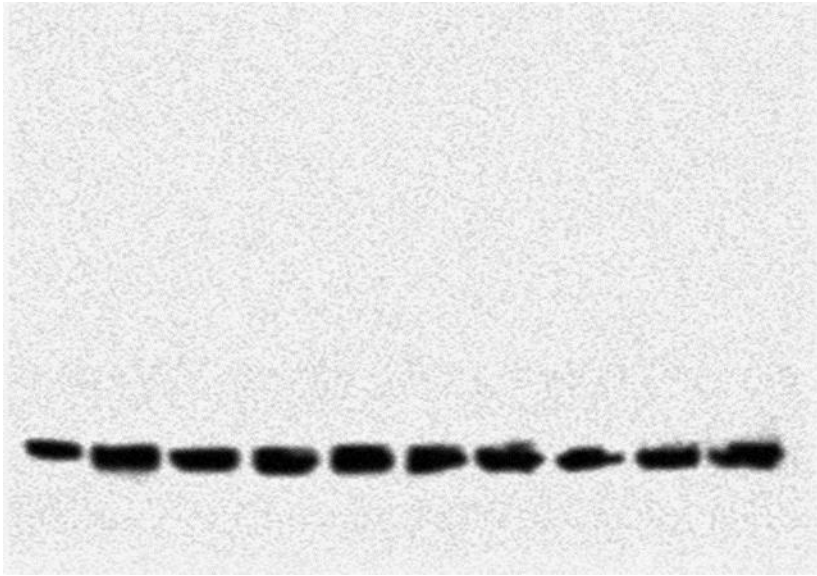
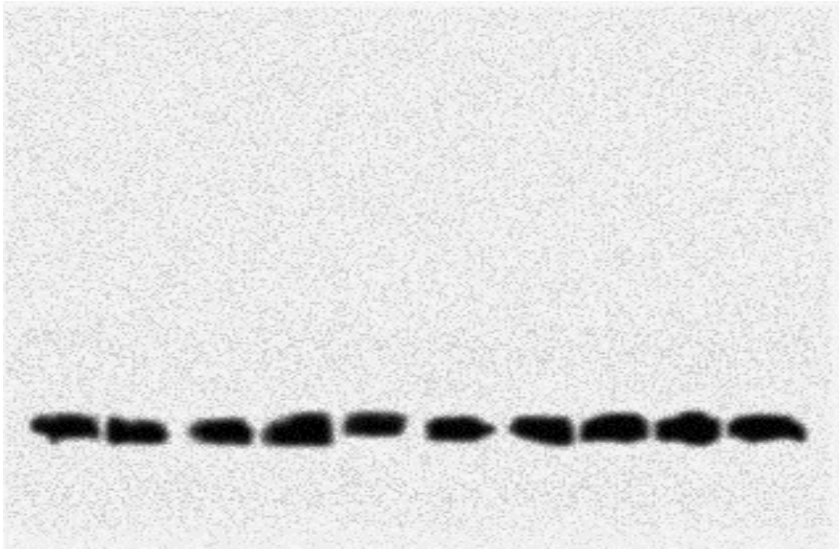
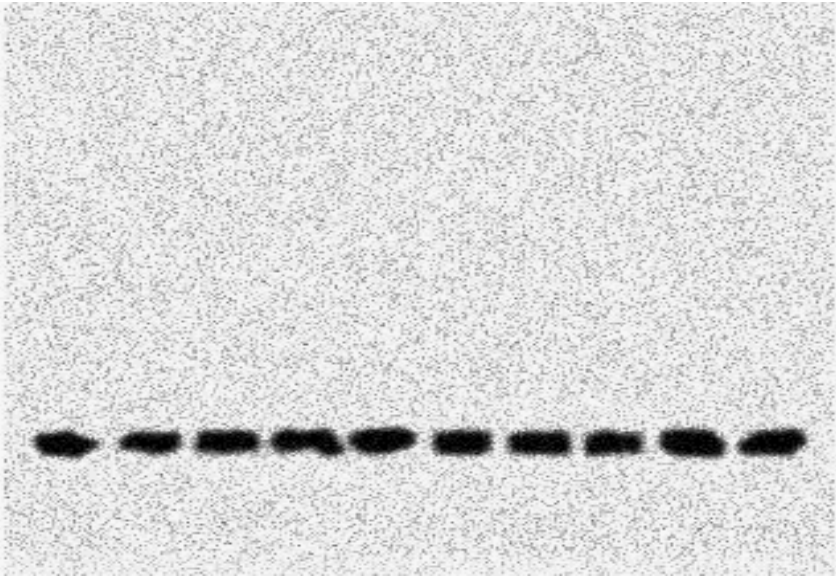
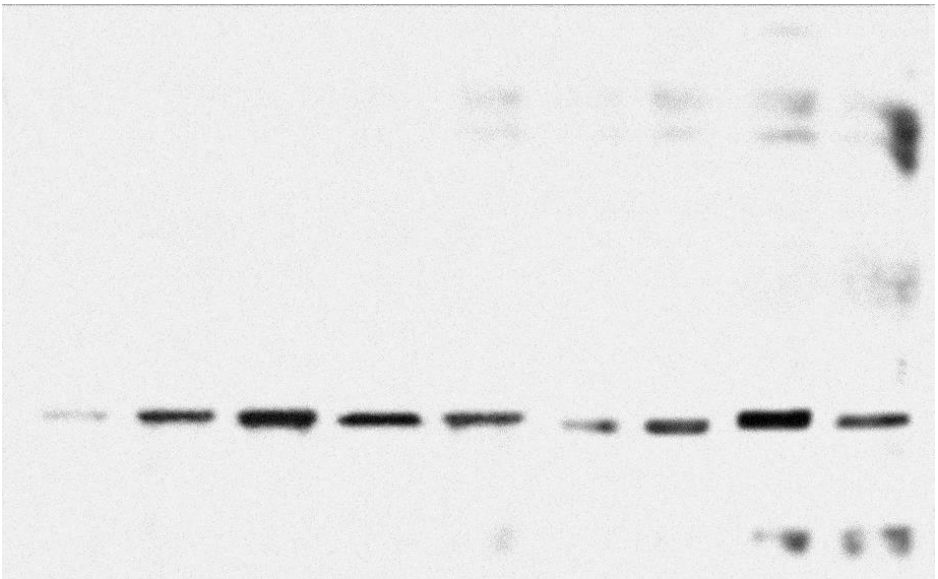
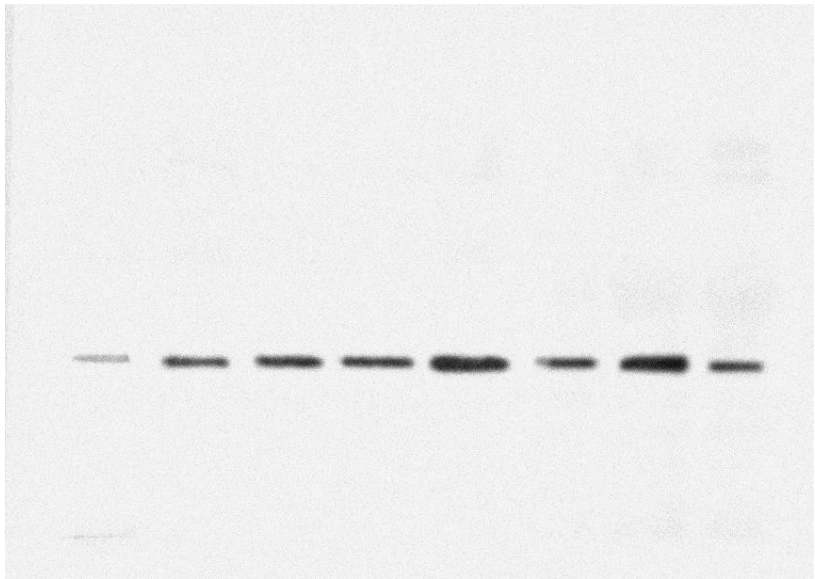


Fig 6A

ApoE2/ApoE3

ApoE3/ApoE3

α 7nAChR



β -Actin

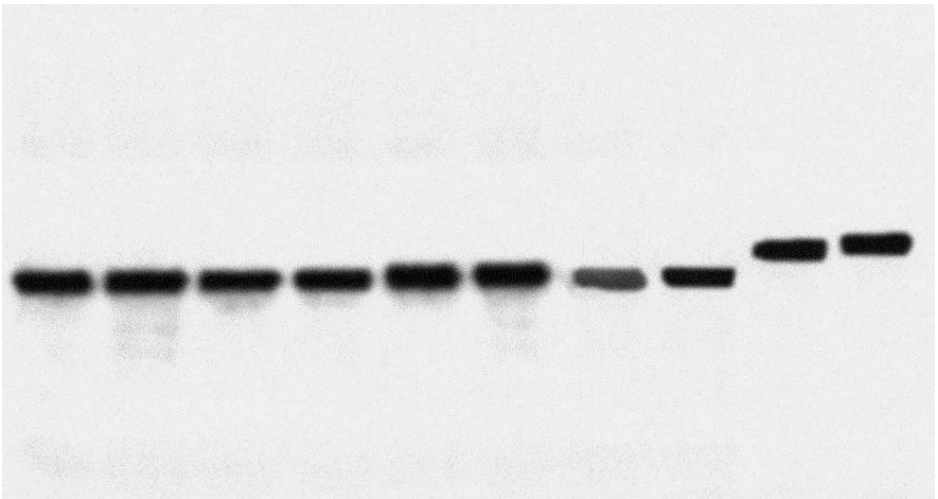
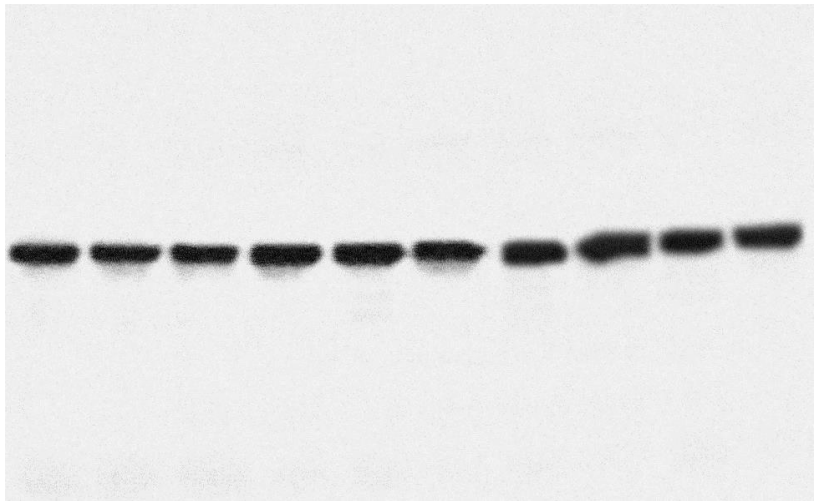
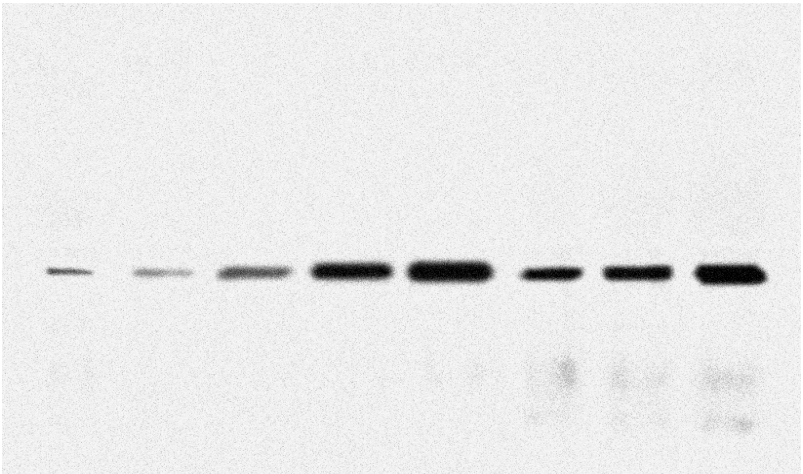
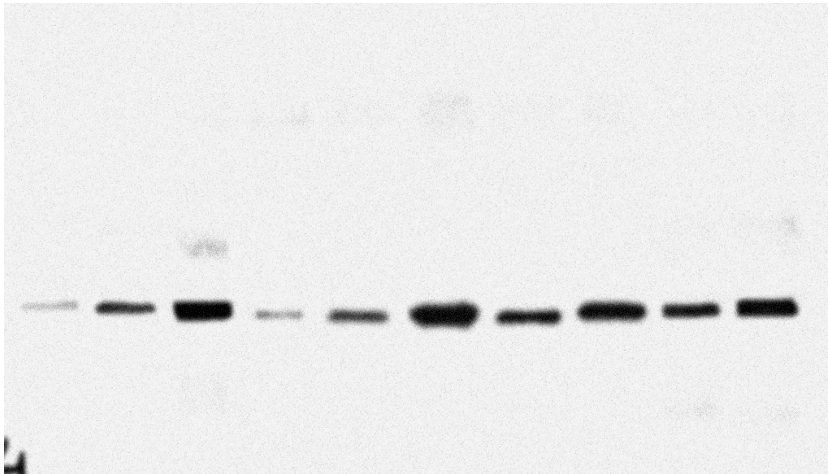


Fig 6A

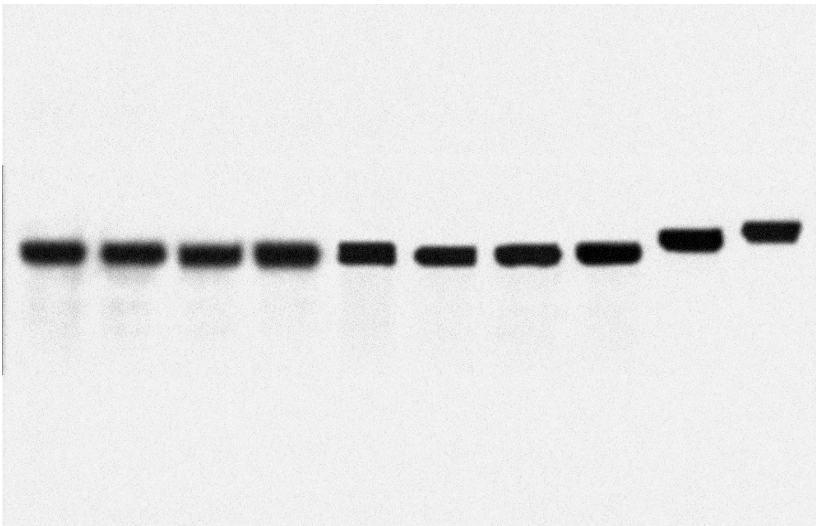
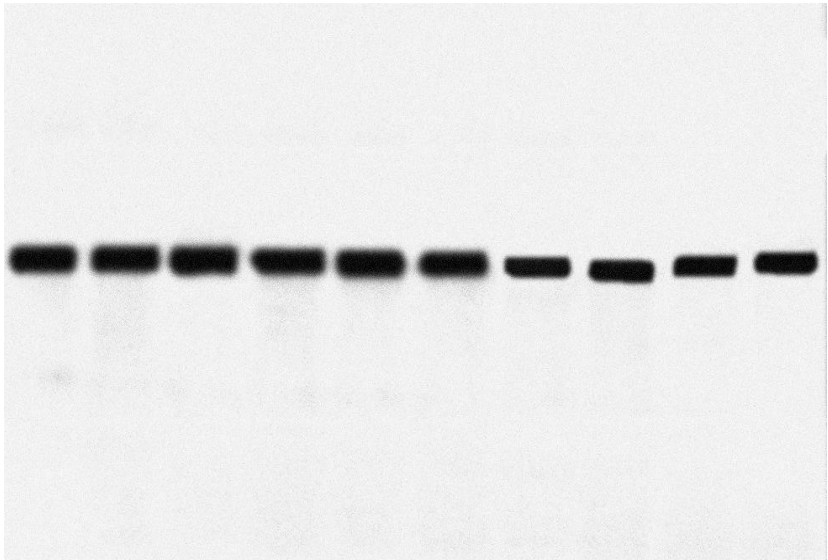
ApoE3/ApoE4

ApoE4/ApoE4

α 7nAChR



β -Actin



December 9, 2021

Douglas Galasko, PhD, and Philip Scheltens, PhD
Editors-in-Chief
Alzheimer's Research & Therapy

RE: Concerns on Wang et al. (2017) Increased A β ₄₂- α 7-like nicotinic acetylcholine receptor complex level in lymphocytes is associated with apolipoprotein E4-driven Alzheimer's disease pathogenesis *Alzheimer's Research & Therapy* 9:54.

Dear Drs. Glasko and Schelten:

This letter is in response to publisher Rebecca Pearce asking for a retraction due to allegations around my publication in *Alzheimer's Research and Therapy* (MS ID AZRT-D-17-00036/ DOI 10.1186/s13195-017-0280-8). With this letter response I explain why the allegations are false.

I previously emailed 10 attachments of original uncropped blots; none show evidence of image manipulation. Ms. Pearce stated in her email that the reasons for retraction are "in line with COPE guidelines." I respectfully disagree. The stated reason for retraction is: "*Our investigation has concluded that explanation provided for the inconsistencies in the Western blots were insufficient and therefore confidence in the integrity of the data presented in article is compromised.*" It appears that the explanations in my letter were examined, but the original blots provided in the other 10 attachments were not examined during the investigation. Critically, COPE guidelines for retraction require "**clear evidence** [*emphasis added*] that the findings are unreliable, either as a result of major error (eg, miscalculation or experimental error), or as a result of fabrication (eg, of data) or falsification (eg, image manipulation)." These basic elements of retraction are lacking in the proposed retraction. And in fact, the high-resolution TIFF image files of the original uncropped blots sent in 10 separate attachments provide clear evidence of an **absence** of manipulation.

It is alleged that by creating the right mix of contrast and/or darkness to the entire image, one protein band, or set of bands, has a very slightly different background.

But, as is apparent in the original whole blots, herewith provided once more for your consideration, background inconsistencies are not created unless and until extreme high contrast (+ 100%) and darkness (- 48%) settings are applied. Applying such extreme settings is itself manipulation and does not support that the allegations are true. Further, the continuity of the surrounding background of the protein bands in each original blot image shows evidence that these protein bands were not, and cannot have been, transplanted from a different source. There is no apparent manipulation of the protein band or blot.

In general, a practiced Western blot researcher knows that image backgrounds can vary slightly for many reasons, including use of hand-poured gels; x-ray film condition; streaks produced by the film processor; wrinkles and folds of the plastic wrap that covers the membrane to prevent drying from influencing the background (and uneven drying of the membrane); air bubbles; trace amounts of chemiluminescent reagents; patches intrinsic to the nitrocellulose membranes; scotch tape or other markings remaining on the underlying, previously exposed film to which the smaller film (cut to fit the size of the gel) is taped so that it more easily fits through the processor; and so on. Cutting film to fit the size of gel is a practice of many academic labs conducting high volumes of Western blots and using x-ray film rather than digital imaging.

(Digital imaging does avoid many of these visual artifacts, which is one reason, along with cost of film, that labs have been transitioning to digital imaging for immunoblotting, but my lab did not have the resources to convert to digital imaging although we are working toward digital imaging.) Any one or a combination of these things can influence an image background on x-ray film and result in a minor visual imprint. None of these things are evidence of data manipulation.

I urge you to consider the profit motive that is admittedly at the base of these allegations. Starting in August 2021, my entire academic research career was suddenly subjected to intense public scrutiny when Wall Street investors and their collaborators started to relentlessly attack my reputation and scientific integrity, with unfounded claims of data manipulation that are published on social media for maximum effect. The goal of these objectors was to depress the stock price of Cassava Sciences, for which I have led research collaborations for over a decade. The objectors had an admitted short position in Cassava stock and stood to benefit financially from a reduction in stock price, even if prompted by spreading false information.

Please note that the editors of *Journal of Neuroscience* (Marina Picciotto, PhD) and *Neuroscience* (Prof. Juan Lerma, PhD) both recently agreed that I had not engaged in data manipulation following a thorough examination of raw data in three papers. For all three papers, the editors-in-chief found “*no evidence of data manipulation.*”

An independent expert on Western blots, Dr. Charles Spruck, has also examined and refuted the allegations of manipulation of my Western blot images across many papers, as shown in the attached letter by Dr. Spruck. Dr. Spruck is a molecular biologist whose academic lab runs ~1,000 Western blots each year. He is not being paid by CUNY, Cassava, or me. Dr. Spruck has agreed to speak with journal editors, but he wants to remain anonymous on social media sites. Dr. Spruck’s bio and blog posts are available at the below links:

<https://ad-science.org/2021/10/21/notes-from-a-molecular-biologist/>
<https://ad-science.org/2021/10/21/of-shorts-and-blots/>
<https://www.sbpdiscovery.org/our-scientists/charles-spruck-phd>

This letter response, along with the original blots, shows by clear evidence that the allegations concerning *Alzheimer’s Research & Therapy* 9: 54 are meritless. There is no evidence of data manipulation. For these reasons, I believe there is no basis for a retraction.

Thank you for your time and the opportunity to respond.

Sincerely yours,

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY School of Medicine

Attachment: Letter from Dr. Spruck refuting allegations of WB image manipulation.

Dear Ms. Pearce,

Enclosed are the requested whole blot images used in Figures 1A, 1C, 5A, and 6A arranged according to the format presented in the published article. It should be noted that the data included in this article were collected over 9 years (2008-2016) with most of it collected before 2012. All plasma and blood cell samples were processed blind to the subjects' identities and conditions. Analysis of the raw data was performed by Servier's statistical team, not by me or my team. We received permission to publish the results in late 2016.

As you can see from attached TIFF files, the images in the published article derived from the respective 300 dpi whole blot images without any manipulation. The images retrieved from the online article by the PubPeer are probably even lower resolution. The alleged inconsistencies and breaks could simply be artefacts of making extreme adjustments of contrast and brightness to the low-resolution images in the published article. Many factors could alter and break continuity among background pixels of low-resolution images, including streaks of a film produced by the film processor, wrinkles and folds of the plastic wrap that cover the membrane to prevent drying from influencing the background of the figure, air bubbles, trace amounts of chemiluminescent reagents and/or patches intrinsic to the nitrocellulose membranes. Such changes in background may be exaggerated during processing of the images for publication.

Regardless of the reasons for the alleged inconsistencies and breaks in our published figures, the attached whole blot images for these figures verify that the original images were not manipulated or misrepresented in any way in the published article. Indeed, no such concern was mentioned in the three rounds of peer review of the manuscript or by readers after publication.

Thank you.

Best regards,

Hoau-Yan Wang

From: Hoau-yan Wang
Sent time: 01/12/2022 08:53:03 AM
To: Beidel, Jennifer L. <jennifer.beidel@saui.com>
Subject: Fw: [EXTERNAL] New Yorker magazine fact checking inquiry

From: Feldman Emison, Linnea <linnea_feldmanemison@newyorker.com>
Sent: Tuesday, January 11, 2022 2:02 PM
To: mediarelations@cuny.edu
Cc: Hoau-yan Wang
Subject: [EXTERNAL] New Yorker magazine fact checking inquiry

Hello,

I'm a fact checker at The New Yorker magazine working with the writer Patrick Radden Keefe on an upcoming piece about the attorney Jordan Thomas and Cassava Sciences, including Dr. Wang's work with the company. I have some questions, listed below. Please let me know if I can clarify anything or provide further information. My deadline is this Thursday (January 13th) at 10am EST.

Thanks very much.

All best,
Linnea

- Is it correct that Dr. Wang is an associate medical professor at CUNY?
- Is it correct that Dr. Wang is an author of all of the biotech company Cassava's publications on the drug Simufilam?
- Is it correct that Dr. Wang conducted a retrial of Simufilam over the summer after disappointing results from the second trial of the drug, and that Dr. Wang's retrial indicated a significant reduction in biomarkers for Alzheimer's compared with the placebo?
- Would CUNY or Dr. Wang like to comment on the challenges to the claims made by other scientists to papers authored by Dr. Wang?
- Would CUNY or Dr. Wang like to comment on the methodological issues identified by scientists in roughly 30 of his papers?
- Would CUNY or Dr. Wang like to comment on the claim that there is no evidence of a connection between Filamin A and Alzheimer's?
- Would CUNY or Dr. Wang like to comment on Dr. Wang's participation in Cassava's compensation scheme tied to stock price?
- Would CUNY or Dr. Wang like to comment on the allegation that some of Cassava's Western blot tests, including those used at a conference presentation last summer in Denver, appear to have been manipulated with Photoshop or similar software, possibly by copying portions of images onto others?
- The piece states that the image manipulation expert Elisabeth Bik asked Cassava and Dr. Wang's lab for higher resolution versions of its Western blots, which were not provided to her. Would you like to comment?

- Would CUNY or Dr. Wang like to comment on statements of concern issued by journals that have published his work?
- Would CUNY or Dr. Wang like to comment on the claim that Dr. Wang's practice of freezing brains for months or years before thawing them makes it unlikely that the tissue is still usable for testing?
- Does Dr. Wang view Dr. David Bredt as an academic competitor?
- Has the FDA been in touch with Dr. Wang's lab since the filing of the petition?
- Would CUNY or Dr. Wang like to comment on the Quintessential Capital report on Simufilam?

--

Linnea Feldman Emison
The New Yorker
(212) 286-7362

From: Bruno Vellas <[REDACTED]@gmail.com>
Sent time: 01/13/2022 10:39:31 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Concerns with publication in *Alzheimer's Research & Therapy* (MS ID AZRT-D-17-00036/ DOI 10.1186/s13195-017-0280-8)
Attachments: 39371501-v2-ART follow-up clean (1).pdf ATT00001.htm Wang Letter to ART Publisher (2).docx ATT00002.htm

Thank you to let me know

Envoyé de mon iPhone

Le 11 janv. 2022 à 15:55, Hoau-yan Wang <hywang@med.cuny.edu> a écrit :

Dear Dr. Vellas,

Please find the following message from the publisher of *Alzheimer's Research and Therapy* regarding our 2017 paper. I'm not sure this reached you. I obtained your email address from Dr. Burns so I could forward it. I had submitted annotated whole blot images for this paper to the editors and publisher. Despite no evidence of manipulation, the publisher indicated that they concluded my arguments and evidence provided (the whole blot images) were "insufficient". Enclosed please find my response to the publisher's email requesting my explanation. Please note the publisher requested individual responses from all authors to **either agree or disagree** to retract the manuscript by 1/14/2022, and to provide reasoning. I am working on reaching any of my Servier co-authors, but as this manuscript was the culmination of 8 years of work, other than Dr. Pueyo none of them are still at Servier. One is deceased.

I strongly disagree with retracting for the following reasons:

1. There was no manipulation, and even COPE guidelines require **evidence** of manipulation. There is none.
2. Importantly, I ran these Western blots **blind** to treatment and APOE status, then forwarded the data to my Servier co-authors. I am still blind. If there were any manipulation in favor of treatment effects, it would therefore have to be on the part of Servier. I find this equally implausible.

Thank you for responding to this journal as a co-author. Please respond to Rebecca. If you would like to copy the editors-in-chief, their email addresses are dgalasko@health.ucsd.edu and p.scheltens@amsterdamumc.nl. As you know, I have been inundated with requests to prove an absence of manipulation in multiple papers. I appreciate your time.

Best regards,

Hoau-Yan

Hoau-Yan Wang, Ph.D.

Medical Professor

CUNY SOM

From: Rebecca Pearce <rebecca.pearce@biomedcentral.com>
Sent: Tuesday, January 4, 2022 10:16 AM dgalasko@health.ucsd.edu
To: PUEYO Maria IRIS; [REDACTED]@gmail.com; Isabelle.guignot@servier.com; [REDACTED]@yahoo.fr;

karine.deschet@orange.fr; [REDACTED]@gmail.com; [REDACTED]@yahoo.fr; ousset.pj@chu-toulouse.fr; vellas.b@chu-toulouse.fr; Hoau-yan Wang

Subject: [EXTERNAL] Concerns with publication in Alzheimer's Research & Therapy (MS ID AZRT-D-17-00036/ DOI 10.1186/s13195-017-0280-8)

Wang, HY., Trocmé-Thibierge, C., Stucky, A. *et al.* Increased A β_{42} - α 7-like nicotinic acetylcholine receptor complex level in lymphocytes is associated with apolipoprotein E4-driven Alzheimer's disease pathogenesis. *Alz Res Therapy* 9, 54 (2017). <https://doi.org/10.1186/s13195-017-0280-8>

Dear Prof Wang et al,

After further careful consideration, the journal has taken the decision to retract the article in line with COPE guidelines. Our investigation has concluded that explanation provided for the inconsistencies in the Western blots were insufficient and therefore confidence in the integrity of the data presented in article is compromised.

In line with our protocols for retracting articles, we will be publishing a Retraction Notice which will be bi-directionally linked to your article. The proposed wording can be found below:

Retraction for: [10.1186/s13195-017-0280-8](https://doi.org/10.1186/s13195-017-0280-8)

The Editors-in-Chief have retracted this article. Following publication, concerns have been raised regarding the western blot images presented in Figs. 1, 5 and 6. The authors have provided the raw data, which have been assessed by independent experts and deemed insufficient to address the concerns. The Editors-in-Chief therefore no longer have confidence in the integrity of the data in this article.

We would appreciate it if each author could **individually respond** in writing with whether they agree or disagree with the retraction and the retraction wording. Individual agreement will be logged in the retraction notice, but please note that while we give dissenting authors space to explain why they dissent, those reasons would not be included in the notice. We will include in the notification that Prof Morain has passed.

We look forward to hearing from you by January 14, 2022.

With best wishes,

Rebecca

Rebecca Pearce

Publisher

Springer Nature

One New York Plaza, Suite 4600, NY, NY 10004-1562

T +1 (212) 451-8733

rebecca.pearce@springernature.com

www.springernature.com

December 9, 2021

Douglas Galasko, PhD, and Philip Scheltens, PhD
 Editors-in-Chief
 Alzheimer's Research & Therapy

RE: Concerns on Wang et al. (2017) Increased A β ₄₂- α 7-like nicotinic acetylcholine receptor complex level in lymphocytes is associated with apolipoprotein E4-driven Alzheimer's disease pathogenesis *Alzheimer's Research & Therapy* 9:54.

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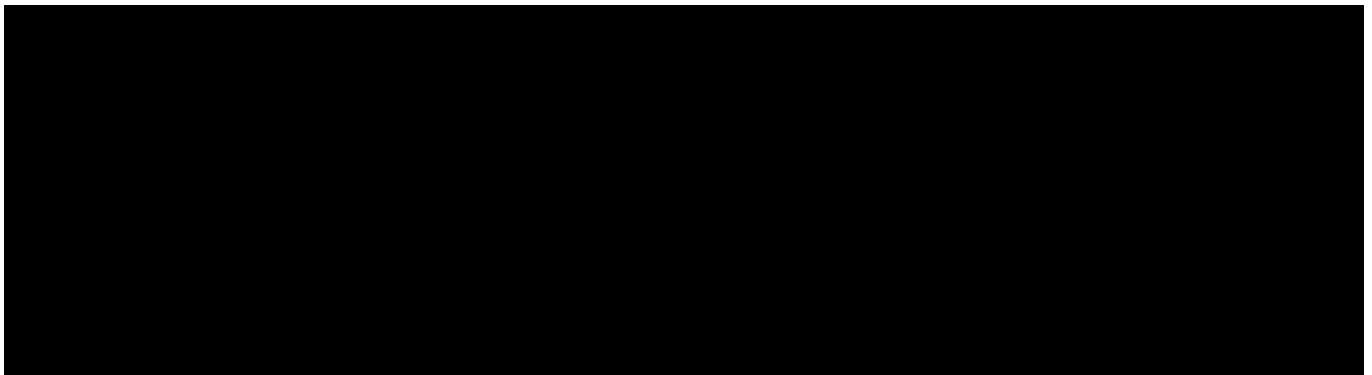
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Thank you for your time and the opportunity to respond.

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Medical Professor
CUNY School of Medicine

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Dear Ms. Pearce,

Enclosed are the requested whole blot images used in Figures 1A, 1C, 5A, and 6A arranged according to the format presented in the published article. It should be noted that the data included in this article were collected over 9 years (2008-2016) with most of it collected before 2012. All plasma and blood cell samples were processed blind to the subjects' identities and conditions. Analysis of the raw data was performed by Servier's statistical team, not by me or my team. We received permission to publish the results in late 2016.

As you can see from attached TIFF files, the images in the published article derived from the respective 300 dpi whole blot images without any manipulation. The images retrieved from the online article by the PubPeer are probably even lower resolution. The alleged inconsistencies and breaks could simply be artefacts of making extreme adjustments of contrast and brightness to the low-resolution images in the published article. Many factors could alter and break continuity among background pixels of low-resolution images, including streaks of a film produced by the film processor, wrinkles and folds of the plastic wrap that cover the membrane to prevent drying from influencing the background of the figure, air bubbles, trace amounts of chemiluminescent reagents and/or patches intrinsic to the nitrocellulose membranes. Such changes in background may be exaggerated during processing of the images for publication.

Regardless of the reasons for the alleged inconsistencies and breaks in our published figures, the attached whole blot images for these figures verify that the original images were not manipulated or misrepresented in any way in the published article. Indeed, no such concern was mentioned in the three rounds of peer review of the manuscript or by readers after publication.

Thank you.

Best regards,

Hoau-Yan Wang

From: Mat <[REDACTED]@gmail.com>
Sent time: 01/18/2022 07:10:31 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Quick question

Dr Wang,

It is my privilege to write you. My name is Mathew and I represent an investment group who is most excited about your work regarding PTI-125 and how it applies to the clinical trials Simufilam.

To be clear, we don't believe the hedgefunds who are trying to smear your name for the purpose of profits and we have been trying to help anyway we can (petitions, public articles...etc).

That being said, we have been digging and it seems the best we can find is that CUNY has to clear you after a maximum of 150 days from the start of their investigation Remi asked for for the purpose of clearing you.

What we can't find is proof that that investigation started and if so when?

I sure hope this ok to ask! Could you be able to give us any information on those dates?

For what it's worth, I am so sorry you have had to go through this. I am not a research scientist myself but I can appreciate the awful situation you've been placed in.

Hope all is well.

Your fan,

Mathew

From: Hoau-yan Wang
Sent time: 01/18/2022 12:21:09 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Cc: [REDACTED]@gmail.com
Subject: Fw: [EXTERNAL] Quick question

POL 87(2)(a)

[REDACTED]

Hoau

From: Mat <[REDACTED]@gmail.com>
Sent: Tuesday, January 18, 2022 7:10 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Quick question

Dr Wang,

It is my privilege to write you. My name is Mathew and I represent an investment group who is most excited about your work regarding PTI-125 and how it applies to the clinical trials Simufilam.

To be clear, we don't believe the hedgefunds who are trying to smear your name for the purpose of profits and we have been trying to help anyway we can (petitions, public articles...etc).

That being said, we have been digging and it seems the best we can find is that CUNY has to clear you after a maximum of 150 days from the start of their investigation Remi asked for for the purpose of clearing you.

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For what it's worth, I am so sorry you have had to go through this. I am not a research scientist myself but I can appreciate the awful situation you've been placed in.

Hope all is well.

Your fan,

Mathew

From: Editor - Pathology <editor@respubmail.biz>
Sent time: 01/18/2022 01:49:28 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Allied Medicine: Publicize your Scholarly Work

Dear Dr. HoauYan Wang,

Journal of Pathology & Allied Medicine aims to facilitate the exchange of ideas in the forum of research related to the areas of **Pathology** and **Allied Medicine**.

In appreciation to your previous work entitled "**PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis**", we would like to invite you to publish your upcoming eminent research works towards the journal.

Authors can submit their manuscripts using following option
<http://advanceoj.biz/paper-submission.php?journal=95>

The journal strictly rejects the paper if it contains plagiarized, copied, or any unprofessional content. It strictly follows the publication ethics in publishing the articles online.

We hope to have your collaboration with the journal.

Sincerely,
George Williams
Journal of Pathology & Allied Medicine

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From: Ana Carrillo
Sent time: 01/19/2022 09 34 26 AM
To: Hoau-yan Wang
Subject: Hi Prof. Wang---Reminder to certify Fall 2021 Released Time Effort Certification Now Available Online

Hi Prof. Wang,

I hope that all is going well. The Research Foundation Academic Effort Certification system is open to certify the Fall 2021. Below is a message from RF CUNY. Kindly when you have some time, please certify the fall 2021. Please use the link provided: <https://www.rfcuny.org/effortreporting/certification/>. Kindly be reminded to complete the other categories as you deem appropriate (Instruction, Department Administration, Other Institutional Activity, and University Research), and take into consideration that the grand total effort must not surpass 100 percent.


If you have questions, please contact me.

Emp Name	Semester Code	Project	Project Department	Project Name	Start Date	End Date	Certification Status	Grant Effort %	PI Name	PI Email
Wang, Hoau-yan	FALL2021	72598-00 04	Molecular, Cellular Sciences	TREAT ALZHEIMER'S DISEASE-REDUCE INSULIN	09/01/2021	01/15/2022	Not Done	10.14	Wang, Hoau-Yan	hywang@med.cuny.edu
Wang, Hoau-yan	FALL2021	72639-00 04	Molecular, Cellular Sciences	LINKING PERIPHERAL AND BRAIN INSULIN	09/01/2021	01/15/2022	Not Done	10.20	Wang, Hoau-Yan	hywang@med.cuny.edu
Wang, Hoau-yan	FALL2021	72587-00 02	Molecular, Cellular Sciences	OPEN-LABEL EXTENSION STUDY OF PTI-125	09/01/2021	12/31/2021	Not Done	7.00	Wang, Hoau-Yan	hywang@med.cuny.edu
Wang, Hoau-yan	FALL2021	72762-00 02	Molecular, Cellular Sciences	HYPOACTIVITY IS INTEGRAL TO GLUTAMATERGI	09/01/2021	11/30/2021	Not Done	7.01	Wang, Hoau-Yan	hywang@med.cuny.edu

Thank you!!

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: FinanceAlerts1 <FinanceAlerts1@rfcuny.org>
Sent: Tuesday, January 18, 2022 10:19 AM
To: Candice Baptiste-Sexton <cs Sexton@ccny.cuny.edu>
Subject: [EXTERNAL] Fall 2021 Released Time Effort Certification Now Available Online

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Fall 2021 Released Time Effort Certification Now Available Online

The online Fall 2021 released time certification module is now available. After the fact effort certification is a sponsor requirement and must be completed by you as part of the award process. As in the past, principal investigators must certify effort for any faculty members who received released time on their award(s).

Fall 2021 released time effort certification (labeled [Effort Reporting](#)) module can be located under *Electronic Tools* on the RFCUNY homepage www.rfcuny.org (three-digit ID required to login). Detailed instructions can be found under the help icon located on the right hand corner of the each of the modules.

For questions related to released time effort certification, please contact Tatyana Gun at Tatyana_Gun@rfcuny.org.

Thank you.
Finance Department
Research Foundation, CUNY

Our mailing address is:
Research Foundation of The City University of New York
20 West 41st St. 7th Floor, New York, NY 10036-7207
212-417-8300 | www.rfcuny.org

From: Hoau-yan Wang
Sent time: 01/19/2022 09:38:23 AM
To: Ana Carrillo
Subject: Re: Hi Prof. Wang---Reminder to certify Fall 2021 Released Time Effort Certification Now Available Online

DONE. Thanks

Hoau

From: Ana Carrillo
Sent: Wednesday, January 19, 2022 9:34 AM
To: Hoau-yan Wang
Subject: Hi Prof. Wang---Reminder to certify Fall 2021 Released Time Effort Certification Now Available Online

Hi Prof. Wang,

I hope that all is going well. The Research Foundation Academic Effort Certification system is open to certify the Fall 2021. Below is a message from RF CUNY. Kindly when you have some time, please certify the fall 2021. Please use the link provided: <https://www.rfcuny.org/effortreporting/certification/>. Kindly be reminded to complete the other categories as you deem appropriate (Instruction, Department Administration, Other Institutional Activity, and University Research), and take into consideration that the grand total effort must not surpass 100 percent.


If you have questions, please contact me.

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Wang, Hoau-yan	FALL2021	72639-00 04	Molecular, Cellular Sciences	LINKING PERIPHERAL AND BRAIN INSULIN	09/01/2021	01/15/2022	Not Done	10.20	Wang, Hoau-Yan	hywang@med.cuny.edu
Wang, Hoau-yan	FALL2021	72587-00 02	Molecular, Cellular Sciences	OPEN-LABEL EXTENSION STUDY OF PTI-125	09/01/2021	12/31/2021	Not Done	7.00	Wang, Hoau-Yan	hywang@med.cuny.edu
Wang, Hoau-yan	FALL2021	72762-00 02	Molecular, Cellular Sciences	HYPOACTIVITY IS INTEGRAL TO GLUTAMATERGI	09/01/2021	11/30/2021	Not Done	7.01	Wang, Hoau-Yan	hywang@med.cuny.edu

Thank you!!

Ana Carrillo
Grants Administrator
acarrillo@ccny.cuny.edu

From: FinanceAlerts1 <FinanceAlerts1@rfcuny.org>
Sent: Tuesday, January 18, 2022 10:19 AM
To: Candice Baptiste-Sexton <csexton@ccny.cuny.edu>
Subject: [EXTERNAL] Fall 2021 Released Time Effort Certification Now Available Online

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Finance

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For questions related to released time effort certification, please contact Tatyana Gun at Tatyana_Gun@rfcuny.org.

Thank you.
Finance Department
Research Foundation, CUNY

Our mailing address is:
Research Foundation of The City University of New York
20 West 41st St., 7th Floor, New York, NY 10036-7207
212-417-8300 | www.rfcuny.org

From: Yiming Jeng <[REDACTED]@gmail.com>
Sent time: 01/20/2022 10:23:12 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: FW: Correlation of oxidative stress and Filamin A (Revised)

Dear Hoau-Yan :

Nice to see your application of patent for "Alzheimer's Disease Assay in a Living Patient" which determines an amount which is significantly greater than the value presented in the standard body sample preparation indicated the presence of AD pathology. This is a step closer to your search for savaDx's test of early AD symptoms from FLNA. These efforts show your determination to find specificity and sensitivity of blood test. I am curious how much is quantified as "significantly greater" or how sensitive this test would be.

Recently, there was a published story
https://urldefense.proofpoint.com/v2/url?u=https-3A__www.newyorker.com_magazine_2022_01_24_jordan-2Dthomas-2Darmy-2Ddof-2Dwhistle-2Dblowers&d=DwIFaQ&c=4NmamNZG3KTnUCoC6InoLJ6KV1tbVKrkZXHRwtIMGmo&r=YAnDdIh9IEWHiy_3lavbTLajOSlrKTXLS4AccHSzT3c&m=cymau252Sxt9rTEDTuNglEDwZwZrg5tRtqKrFF5BqMw&s=b5VhCpsepSggrea5rD0VAkdItgnYc9Up0Re4wovZYTg&e=
in which Dr. Thomas Südhof along with Mr. Geoffrey Pitt and Mr. David Bredt showed skepticisms against PTI-125. It seemed to me this story and related comments have tried to tarnish hard works from you and colleagues. But these information will not last forever as time will tell. As said before, victims of AD deserve a better remedy compared to current treatments even that this is a tough challenge. BTW, I will work for a Singapore company starting from February and retire from CDIB. This is why I am sending email from my personal account instead of corporate account.

Hope that you have a happier and wonderful Chinese New Year !

Best Regards,
宜明

鄭宜明 Eddy Jeng - CDIB 於 2021年1月28日 週四 上午10:19寫道:

>
> FYI
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Tuesday, September 29, 2020 4:35 AM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: Correlation of oxidative stress and Filamin A (Revised)
>
> Dear 宜明,
>
> Sorry for my later reply. I simply got too much to do. In general, directly affect kinases and terminal targets such as many receptors are NOT good targets for treatment. This is because these kinases are needed for normal physiology and function. PTI-125 reduces abnormal activation from upstream but still keeping the activity of these kinases (in other word, their activities remain intact). Reduced K-RAS oncogenic properties is a necessary to reduce tumor progression (very long story).
>
> SV2A expressed ubiquitously are the target of many anti-epileptic drugs such as anti-epileptic drugs (anticonvulsants) such as levetiracetam and brivaracetam. These modulators do not have enough selectivity so that it blocks abnormal excitability. Amyloid toxicity causes neuron destruction so that the surrounding healthy neurons increase their synaptic activities to compensate for the lost neurons. Using SV2A modulators such as GB101 actually reduces neurotransmitter release therefore causes toxicity. I predict the patients on GB101 will be sedated and cognitive impairment become more severe.
>
> Modulating neuroinflammation is a double-edge sword. our bodies use inflammatory processes to recruit immune cells, monitor cell including neurons and remove debris. Hence, anti-inflammatory drugs use too early brains with Alzheimer's disease will be full of debris. If anti-inflammatory drugs use too late it won't be effective (too late). When is appropriate time, hard to say. Regarding modulating immunity using tyrosine kinase inhibitors, this will not only ineffective but also have intolerable adverse effects. (see above)
>
> As for methods we used to identify compounds such as PTI-125, all the traditional and modern methods had been used.
>

> Hope my comments to your questions helpful.
>
> Best,
>
> Hoau-Yan
>
>
> _____
> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Saturday, September 26, 2020 12:45 AM
> To: Hoau-yan Wang
> Subject: [EXTERNAL] RE: Correlation of oxidative stress and Filamin A (Revised)
>
> Dear Hoau-Yan :
>
> Please disregard my previous email regarding to brain AKT phosphorylation. After some readings of your patent entitled "Method for inhibiting growth of cancer cell", I found that PTI-125 inhibited the phosphorylation at site serine2152 and FLNA knockout mice showed reduced oncogenic properties of K-RAS , including the downstream activation of ERK and Akt . These clues should be related to the answer of my question.
>
> Since you mentioned that upstream molecular targets causing destructions of neurons should be much more effective, how about other approaches intended to preserve neuron functionality and reduce amyloid protein/ tau phosphorylation as follows :
> 1) enhance synaptic plasticity and neuroprotection by SV2A modulator which tends to reduce amyloid-induced neuronal hyperactivity and improve synaptic function, such as GB101 from AgeneBio ;
> 2) target Inflammation/immunity by tyrosine kinase inhibitor which tends to modulate mast cell-related inflammatory processes and reduce amyloid protein and tau phosphorylation, such as Masitinib from AB Science .
>
> Last but not the least, you mentioned that it was not easy as it seems to select compounds restoring normal shapes of FLNA in the brain. I am curious by which method, such as gene/cellular analysis, assistance from computational model, selection by trial and error, etc., current chemical compound was selected. Is it likely that another chemical compound will be more optimal to produce desirable effects of restoration ?
>
> Thanks again for your consideration of my follow-up questions.
>
> Best Regards,
> 宜明
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Wednesday, September 23, 2020 5:49 AM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: Correlation of oxidative stress and Filamin A
>
> Dear 宜明,
>
> I am delighted that you are truly putting efforts into neuroscience of the neurodegenerative disease. I don't mind at all to answer any questions when I have time.
>
> Regarding your questions:
> Alzheimer's disease is a complex disease that have numerous pathogenic drives causing the particular (obviously critical) neurons to die. Hence, identifying and treating upstream molecular targets that cause destruction of neurons should be much more effective than targeting terminal events such as receptors. However, the upstream pathogenic events have to be treatable (meaning that it is an identifiable cause). Oxidative stress refers to destruction of the mitochondria but its relationship with hyper-phosphorylation and neurofibrillary lesions is complex. Obviously, preservation of mitochondrial function keeps the neuron functioning. Hence, simply using antioxidants to prevent oxidative stress just didn't work.
>
> Filamin A is a vital scaffolding proteins that coordinate many proteins that are interacting with each other and many yet to be identified molecules. It is the pathological processes that affect filamin A and its interaction with all these proteins. It took some times (years) to sort out which filamin A-mediated events are related to Alzheimer's disease pathogenesis and how to make this work that followed by selecting compounds. NOT AS EASY AS IT SEEMS. Again, the inter-relationship between pathogenic events such as oxidative stress and abnormalities in filamin A are chicken and egg questions. We still don't know for sure who comes first but we do know if we make the filamin A healthier the neurons function better and survive though wounded. We should get better treatment result if we can identify Alzheimer's disease earlier although I am sure there are many causes of the disease that most likely to interact with each other.
>
> Thanks.
>
> Best,

>
> Hoau-Yan
>
> -----
> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Tuesday, September 22, 2020 6:31 AM
> To: Hoau-yan Wang
> Subject: [EXTERNAL] Correlation of oxidative stress and Filamin A
>
> Dear Hoau-Yan :
>
> Sorry to bother you again during your busy hours. After numerous emails asking premature questions, I felt deeply obliged to your time-consuming answers and suddenly realized there are plenty of dots and lines left for me to be connected together in this complicated field of neuro sciences. Please forgive me for taking too much of your precious time.
>
> From many investigated clinical trials, more indications show that upstream treatment of Alzheimer disease is warranted to be explored with. However, my lack of correlated understandings between oxidative stress and Filamin A seemed to bother me. From referenced literatures, it showed the following hypothesis and observation :
> 1) Oxidative stress might be a driving force for tau hyperphosphorylation and synapse dysfunction. Thus, understanding the oxidative stress mechanism and degenerating synapses is crucial for the development of therapeutics strategies designed to prevent AD pathogenesis.
> 2) Filamin A binds over 30 proteins with intracellular signaling intermediates, including the Rho GTPases and Rho GTPase regulating proteins implicated in actin remodeling. Normal Filamin A expression is a prerequisite for mammalian cellular locomotion.
>
> From my searches, there seems to be many lipid/proteins associated with oxidative stress. Is it true that Filamin A play a central role is in this cell-damaging process ? Is it true that Oxidative stress might be a possible cause for abnormal Filamin A ? Thanks for your consider my question at your conveniences.
>
> Best Regards,
> 宜明
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Wednesday, September 16, 2020 8:14 PM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: Cogratulation !
>
> Dear 宜明,
>
> I still think your mother's memory problem is reversible by increasing social contacts and physical exercise. Caring for patients with dementia for long-term is physically and mentally draining.
>
> Regarding your concerns:
> 1). p-tau181 in fact all phosphorylated tau species are very difficult to reduce and we don't know for sure the magnitude of reduction is truly reflect the degree of cognitive improvement. We think the reduction in p-tau181 is due to reduction in neuronal destruction but we can't quantitatively assign the number of pT-181 tau to the improvement in damaged neurons. Obviously, the earlier we can detect the disease, the reduction in p-tau181 should be greater. A greater reduction in 2b than 2a may be related to the subjects (perhaps earlier in Alzheimer's disease course) but not the drug.
> 2) We like to think improvement in biomarkers reflect cognitive improvement. However, we still can't quantitatively say this much reduction in p-tau181 is enough to show cognitive improvement. This is because we can't know for certain how much damages had been done and to what degree such damages are recoverable. Given that Alzheimer's disease is a progressive in nature, if we can stop neurons from degeneration (many causes as well and not all related to tau), we should retain what is left. Again, if we can stop the progression earlier we can better save the memory. I am working on diagnosis to detect it earlier.
>
> My life time commitment is to help solving this terrible disease. To see less suffering in Alzheimer's disease is my reward.
>
> All the best,
>
> Hoau-Yan
>
>
>
> -----
> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Tuesday, September 15, 2020 10:58 PM
> To: Hoau-yan Wang
> Subject: [EXTERNAL] RE: Cogratulation !
>

> Dear Hoau-Yan :
>
> Thanks a lot for your taking time to answer my questions. After your suggestions, my great concern for my mom's memory problem has been relieved a little bit. I do appreciate your reminding me to have more contacts with my mom. This is very helpful to me. I wish that this will be more positive in the future.
>
> After more thoughts of phase2b and phase2a results, I found that concerns arise as follows :
>
> 1) Biomarkers, which exclude P-tau181, perform parallelly well in both studies. Since cognitive improvements correlates mostly with decreases in CSF P tau181, I am wondering if 11% improvement of P-tau181 in phase2b compared with 34% in phase2a will affect cognitive improvements in phase2b. Which factors contribute to these differences in P-tau181 ? Attributes of participants or drug substances ?
> 2) With other biomarkers set to be equal, will good biomarker improvements of disease pathology be a prerequisite for cognitive restoration ? Then, does the issue to improve P-tau181 play an important role ?
>
> If these issues get in a better shape, the chance to nominate you as a Noble prize candidate is not too far. This always has in my mind.
>
> Best Regards,
> 宜明
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Wednesday, September 16, 2020 10:22 AM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: Cogratulation !
>
> Dear 宜明,
>
> Thanks for your well wishes and encouragement. Yes, PTI-125 phase 2b data indicate that PTI-125 appears to be effective in slowing AD progression. Clearly, more work need to be done though we are encouraged.
>
> Your mother's memory problem is not unique since it has been well-recognized in the caregivers because they sustained a protracted stress both mentally and physically. We know memory problem do associate with depression although such memory problem is more reversible (unlike AD) if treated with appropriate antidepressants if no other organic problems. Make sure your mother do exercise (walking is actually a good idea) and have social interactions (someone to talk to). The memory problem in elderly also has an age component.
>
> Regarding p3 PTI-125 study, both biomarkers and cognitive assessments (MMSE is not sufficient) will be used. In p3, we aim to have AD subjects with mild or moderate dementia. I would expect the data from 2b will hold true in P3 given that in p3 the treatment duration is increased.
>
> Hope I answer your questions.
>
> All the best,
>
> Hoau-Yan
>
> -----
> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Monday, September 14, 2020 8:41 PM
> To: Hoau-yan Wang
> Subject: [EXTERNAL] Cogratulation !
>
> Dear Hoau-Yan :
>
> Congratulations to the good P2b results of PTI-125 as my email should be one among many compliments. As you pointed out earlier, published results showed total Tau and phosphorylated Tau reductions coupling with the increase of CSF A β 42. These findings indicated that PTI-125 is heading to a right direction. As many earlier trials failed in the clinical, your research finally has enlightened hopes to help many in needs. More jobs need to be done and I truly wish there will be positive impacts in the future.
>
> My mom has memory problems with emotional distress after caring with my father. I am wondering if my mom is an appropriate person to participate in PTI-125 trials which should be suitable for certain targets. Besides, what are standard models of bioanalysis and MMSE which would be incorporated into Phase 3 ? I am wondering if analysis results of P2b would be consistent and compatible in future studies. Thanks again for your consideration.
>
> Best Regards,
> 宜明
>

> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Friday, August 21, 2020 11:14 PM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear 宜明,
>
> Tau (including phosphorylated) is released from degenerated (dead) neurons, hence reduction in total and phosphorylated Tau can be taken as the sign of less neuronal destruction (perhaps some healthier neurons). Simultaneously, increase in CSF Abeta42 is presumably indicating less plaque formation (although this is much less clear whether this is necessarily true- long story that needs to have a long explanation and many Alzheimer's disease researchers don't buy into this). Another big factor is the inflammatory components.
>
> I would say reduction in total and phosphorylated tau is probably necessary. When coupled with reduction in inflammation in the brain as indicated in phase 2a results, PTI-125 is heading to a right direction. Whether these are enough and how long the treatment is effective that is what everyone trying to investigated.
>
> Thanks.
>
> Have a good weekend.
>
> Best,
>
> Hoau
>
>
>

> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Thursday, August 20, 2020 9:21 PM
> To: Hoau-yan Wang
> Subject: RE: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> After some thoughts about needs of total Tau and phosphorylated Tau reduction coupling with the increase of CSF Abeta42, I am wondering if the chemical structure of PTI-125 need to be modified with this important property ? Does PTI-125 have medical meanings in this regard ? Is a combination therapy with PTI-125 necessary ? Thanks again for your consideration of my trivial question.
>
> Best Regards,
> 宜明
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Tuesday, August 18, 2020 1:44 AM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear 宜明,
>
> Sorry for my late reply. NY area is indeed much better than previous months and other metro areas. However, people should not let the guard down so that the chance of resurgence is reduced to minimum.
>
> Regarding your questions:
> 1. It is really not my place to agree or disagree with company's assessment of the results obtained. Obviously, the best way to address the issue is to get a second assessment with hope the data are consistent. The process is ongoing. I am sure they will make announcement when appropriate.
> 2. There had been multiple attempts to target Abeta42 in CSF. Since we know CSF Abeta42 decreases as Alzheimer's disease worsen (Abeta42 molecules are trapped in amyloid plaques therefore soluble Abeta42 decreases). Hence, increase in Abeta42 in CSF is viewed as a good sign, especially coupled with reduced total tau and pT181Tau (and other phosphorylated Tau). As for how much increases needed to support treatment is effective, we don't know. In the phase 2a, PTI-125 only marginally increased CSF Abeta42 but that was not compared to placebo. This phase 2b trial should tell us more whether the increase after treatment reaches statistic significance. Again even if PTI-125 is the only one that increase CSF Abeta42, the increase in CSF Abeta42 has to couple with reduction of total and phosphorylated Tau to be properly interpreted as beneficial.
>
> Hope I have answered your questions.
>
> Best,

>
> Hoau
>
> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Thursday, August 13, 2020 4:54 AM
> To: Hoau-yan Wang
> Subject: RE: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> How's going recently ? Are you having a summer vacation now ? From my observation, NY area in recent days seems to be much safer compared to previous month and other area in terms of Covid-19 infections. That's a good sign.
>
> Regarding to Cassava's press release yesterday, it mentioned that the data set from that initial bioanalysis showed unnaturally high variability and other problems, such as no correlation among changes in levels of biomarkers over 28 days, even in the placebo group, and different biomarkers of disease moving in opposite directions in the same patient.
>
> My two questions are as below :
> 1) The press release seems to imply that an outside lab generated an initial bioanalysis made apparent mistakes in the assay process. Is a redo of new bioanalysis based on the similar approach as in Phase 2a to derive a more consistent set of data ?
> 2) Is PTI-125 the only available drug to increases AB42 in CSF ? Any other alternative available now ?
>
> Thanks in advance for your assistance.
>
> Best Regards,
> 宜明
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Thursday, July 30, 2020 10:49 PM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear 宜明,
>
> Thanks for the link you have provided. Yes, pTau-217 in plasma is the talk in town. Yes, it shows some promises and appears to be a better biomarker than p-Tau-181 (most used) in term of differential diagnosis between Alzheimer's disease and other degenerative disorders but both fall into a territory how early this change can be detected. If it is detected when a patient is well into dementia (meaning no treatments can reverse it). Actually, our problem is that we don't have any useful treatments for Alzheimer's disease.
>
> As for PTI-125 blood test, it is different and offer a different look of the Alzheimer's disease.
>
> Thanks again for your continue interests in Alzheimer's disease research.
>
> Best,
>
> Hoau-Yan
>
>
> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Thursday, July 30, 2020 3:47 AM
> To: Hoau-yan Wang
> Subject: RE: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> Here comes a report which indicated that levels of p-tau-217 are elevated during the early stages of Alzheimer's disease and could lead to a simple blood test. The related links are as below :
>
> https://urldefense.proofpoint.com/v2/url?u=https-3A__medicalxpress.com_news_2020-2D07-2Dsignificant-2Dblood-2DAlzheimer-2Ddisease.html&d=DwIGog&c=4NmamNZG3KTnUCoC6InoLJ6KV1tbVKrkZXHRwtIMGmo&r=YAnDdIh9IEWHiy_3lavsTLajOS1rKTXLS4AccHSzT3c&m=e1_NVW4NqqzMvqZ8ccqxJ6JVYzeFonytpBrYhyo_RvI&s=_w14Nihm0tiuLX2aX1bbP_Vbdlm1EVbb5xlrnMiP8z3M&e=
> https://urldefense.proofpoint.com/v2/url?u=https-3A__jamanetwork.com_journals_jama_fullarticle_2768841&d=DwIGog&c=4NmamNZG3KTnUCoC6InoLJ6KV1tbVKrkZXHRwtIMGmo&r=YAnDdIh9IEWHiy_3lavsTLajOS1rKTXLS4AccHSzT3c&m=e1_NVW4NqqzMvqZ8ccqxJ6JVYzeFonytpBrYhyo_RvI&s=rva7M6wAYTDj6ArkD4jXC5QRAOnW4mRYqluBB40fS0&e=

>
> I am wondering how the accuracy of P-tau-217 approach differs from that of PTI-125 blood test.
Hope that this information is relevant for your research.
>
> Best Regards,
> 宜明
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Wednesday, July 8, 2020 2:19 AM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear 宜明,
>
> Thanks for your email. Actually not much of the break for me because there are many projects
(yes, in addition to the clinical trials I have to deal with) but I am OK with my busy schedule.
>
> Regarding your questions, indeed half a year had past after conclusion of the phase 2b.
However, the extension study was just approved to proceed around mid May. We need to get the
patients back on and I am still blind to the subjects and treatments. Biomarker reassessment and
cognitive assessment had been addressed. I am not sure what do you mean by explaining in a
reasonable manner but they must be re-evaluated. Since I am blind to the treatment and subjects,
I can't say anything. I am sure there will be some announcement in the future hopefully soon.
>
> Sorry I don't have enough information to answer your questions fully so that it is better for me
to keep quiet.
>
> Best regards,
>
> Hoau-Yan
>
>

> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Monday, July 6, 2020 3:28 AM
> To: Hoau-yan Wang
> Subject: RE: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> Hope that you have a nice holiday weekend of independent day with a relief of hard works in
laboratories. Regarding to the extension study of PTI-125 in Phase 2b, I assume that a half year
has passed for certain patients in this trial. Are there any indications of cognitive
improvements among these observable subjects ? This should be more clarified if safety issues do
not surface during this study.
>
> Furthermore, any difference between a reassessment of overall results for Phase 2b and an
earlier automated Digital ELISA1 evaluation has been reported ? From the perspective of outsider,
this serious drawback is needed to be explained in a reasonable manner. Your clarification of my
questions is deeply appreciated in advance.
>
> Best Regards,
> Yiming
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Monday, June 29, 2020 9:36 PM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear 宜明,
>
> Thanks for keeping in touch. Indeed, I am busy with lots of current projects. Thanks for well
wishes. Nice to know students had recognized the efforts I put in to educate new front line
physicians and care. This is a reminder to me that I need to push all I can. I do my best to
give lectures but my main responsibilities are in the laboratories (i love bench work).
>
> All the best,
>
> Hoau
>
>

> From: 鄭宜明 Eddy Jeng - CDIB
> Sent: Monday, June 29, 2020 4:06 AM
> To: Hoau-yan Wang

> Subject: RE: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> It's been for a while since your recent email was received. Lots of concurrent projects must make you busy at these days. Nice to know that you were chosen for the faculty of the Year award at the 2020 PA Graduation. This must be a plus to your memorable moments. Congratulations !
>
> Best Regards,
> Yiming
>
> -----Original Message-----
> From: Hoau-yan Wang
> Sent: Tuesday, June 16, 2020 5:53 AM
> To: 鄭宜明 Eddy Jeng - CDIB
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear 宜明,
>
> Sorry for my late reply. I am just trying hard to keep up with the demands of running multiple projects.
>
> I always maintain the same attitude to projects. We collectively need to do better by using sound scientific rationales and rigorous preclinical and clinical evaluation processes to move candidates forward. If the scientific rationale is weak, the compound will fail eventually. The most unfortunate thing is that these types of projects use up the resources and move into phase 3 but fail miserably. We can not move forward just because we desperately need a treatment.
>
> I am sorry that your mother show cognitive decline. There are few questions I have for you regarding your mother (you don't need to tell me if you don't want to). How long has your mother shown cognitive decline? age? Was the cognitive decline shown after taking care of your father?
>
> It has been shown the stress of caring for Alzheimer's disease patients causes higher incidence of depression and cognitive impairment. Cognitive impairments do come with depression and people with stressful life have higher incidence of dementia. . I am not suggest your mother is depressed but you may want to have a medical evaluation to rule it out.
>
> Hope this helps.
>
> Thanks for your vote of confidence in my research efforts. I will do my best.
>
> Best regards,
>
> Hoau-Yan
>
> -----
> From: 鄭宜明/CDB
> Sent: Sunday, June 7, 2020 10:33 PM
> To: Hoau-yan Wang
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> Appreciate your insights regarding to NDX-1017 which closed \$85 Million Series B Financing on June 4th and will continue to Phase 2/3 studies. I am not familiar with their MOA and related Phase 1B results. From this event of fund-raising in NDX-1017, medical community in need of new treatments of Alzheimer disease is for sure.
>
> The reason why I am interested in this neurodegenerative filed is that my mother now has a serious memory problem after taking care of my father with Alzheimer disease for many years. If there is an improvement to cognitive decline, it will help lots of suffered persons and surrounding people
> without doubts. After so many communications, I do admire your
> dedications and have serious expectations in your research efforts. Your taking care of my questions is very much appreciated.
>
> Best Regards,
> Yiming
>
>
>
> 寄件者: Hoau-yan Wang
> 收件者: 鄭宜明/CDB ,
> 日期: 2020/06/05 下午 10:33
> 主旨: Re: [EXTERNAL] Are you in the office ?
>
>

>
> Dear 宜明,
>
> Thanks for your note and continuous interest and supports. I am aware of Athira Pharma's NDX-1017. While it is encouraging to see Athira can raise
> \$85 millions to fund their Phase II/III trial (there is a hope!), I am more concerned about the investors pouring money into something scientifically may not be sound. HGF is a growth factors that predominantly express in glia, microglia, white matters (nerve fibers in deeper part of the brain) and blood vessels. Although HGF receptor, c-MET is found in neurons and shown to improve neuronal activities, the destruction of the neurons will reduce any chance for HGF to help holding the progression of cognitive decline. Dead neurons can't be revived. More importantly, treatment with growth factors carries a risk of brain tumor development.
>
> I can certainly use some positive news and clearly believe we have an effective agent in hand and wish to continue to the clinical development.
> I think confidence of the investors should be based on sound scientific rationales but not blind faith based on animal studies. This is clearly not the case in Alzheimer's disease field which resulted in all the failed phase III clinical trials (the most expensive phase).
>
> Anyway, thanks again for your continuous supports and encouragement. You too have a good weekend.
>
> All the best,
>
> Hoau-Yan
>
>
>
> _____
> From: 鄭宜明/CDB
> Sent: Friday, June 5, 2020 6:18 AM
> To: Hoau-yan Wang
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> There is a recent news regarding to a Seattle-based Athira Pharma which announces an \$85 million round to fund their Phase II/III Alzheimer drug NDX-1017. NDX-1017 is a small molecule designed to target hepatocyte growth factor (HGF) and its receptor, MET, to regenerate afflicted tissue for cognitive improvement. I am surprised that Athira Pharma could raise such amounts of capital and wondering if this approach is similar to PTI-125. If PTI-125 could have contributions to patient's confidence of life, Athira Pharma could be a good example for PTI-125 to advance its clinical trials. Hope that this news would have positive impacts to your studies. Have a nice weekend.
>
> Best Regards,
> Yiming
>
>
> 寄件者: Hoau-yan Wang
> 收件者: 鄭宜明/CDB ,
> 日期: 2020/05/19 上午 12:10
> 主旨: Re: [EXTERNAL] Are you in the office ?
>
>
>
> Dear 宜明,
>
> I can't comment on the results of phase 2b since these are NOT from my laboratory collected using very different assay platforms each with its own variations. Moreover, I am NOT the manager of the program. The first thing they need to do is to have a good look of the source of problem.
> Since I am blind to the treatment I can't even speculate. I am sorry that I can't be helpful to illuminate the future development of the program but the reflex type of responses as how should be proceed should not be the way to move forward. Instead, I would think to use other parameters to assess the effects is probably the right way to go although this will take time to sort out in light of the pandemics.
>
> Thanks for letting me know of your opinion. I truly appreciate your thoughts.
>
> Best,
>
> Hoau-Yan
>
> _____
> From: 鄭宜明/CDB
> Sent: Sunday, May 17, 2020 10:26 PM
> To: Hoau-yan Wang
> Subject: Re: [EXTERNAL] Are you in the office ?

>
> Dear Hoau-Yan :
>
> After last Friday's disappointed announcement, what is your take about placebo effect which might be result of window-dressing effects of PTI-125 in phase 2a or mismanagement of independent biomarker analysis conducted by outside lab ? Some experienced medical expert even commented that a main takeaway?that the program should be terminated?does not require a lot of reflection.
>
> What bothers me now is management did not elaborate accurate results of phase 2b which might cause legitimate concerns of PTI-125 and investigations of previous phase 2a data. Without merits of consistent biomarker data between phase 2a and 2b without placebo groups, this future development of PTI-125 is in real jeopardy. Future funding of PTI-125 in further clinical trials would be difficult under such circumstances. Sorry for my personal expression.
>
> Best Regards,
> Yiming
>
>
>
>
>
> 寄件者: Hoau-yan Wang
> 收件者: 鄭宜明/CDB ,
> 日期: 2020/05/12 上午 06:02
> 主旨: Re: [EXTERNAL] Are you in the office ?
>
>
>
> Dear 宜明,
>
> Sorry for my late reply. Even though I am not in the lab, there are plenty of work to do. Just like you, we are all surprised by the severity and dimension of spread in New York state (NYC in particular). The recent numbers had been a bit better but it is still a far cry from under control.
>
>
> Regarding the PTI-125 clinical trial, yes Cassava is set to release the top-line data sooner than expected. We (I at least) want to take conservative steps in interpreting data even though we are confident (cautiously). The overall function changes such as cognition are much more difficult to achieve in short duration (in fact that may not be a good thing as our brain needs time to make adjustments. We are fortunate to have NIH support to further extend our trial to full year. This will allow us to see a much clear cut and hopefully uniform effects of PTI-125. We just has to be a bit more patient since there are more data forth coming to help us understand PTI-125 and the Alzheimer's disease better. We are obviously keeping FDA informed and surely will take the best step if
> PTI-125 meet or exceed our expectations. Stay tuned for further information.
>
> Thanks.
>
> I wish you well.
>
> All the best,
>
> Hoau-Yan
>

> From: 鄭宜明/CDB
> Sent: Thursday, May 7, 2020 10:06 PM
> To: Hoau-yan Wang
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> How's going recently ? From related covid-19 reports, I am kind of surprised that NY and other major states have incurred lots of infected
> patients after weeks of experiences to deal with such matters, Even
> people stayed at home have been infected recently. These situations are
> out of my personal expectations. Be cautious to meet with such challenges
> and stay safe.
>
> Regarding to PTI-125, Cassava Sciences (abbreviated as Sava hereafter) have provided their PTI-125 update in which top-line results of Phase 2b study would be disclosed earlier than mid-2020. From my understandings, most people seems to be conservative about cognitive data of learning test
> while expectation of biomarker data is positive. Sava seems to prepare
> for secondary offering to raise fund for later developments of PTI-125.
> BTW, congratulation to your teams wining NIH grant of \$2.5 Million supporting further clinical studies. A long-awaited journey of scientific verification is just about to start.
>

> Open-label study of PTI-125 at 100 mg twice-daily for 12 months have 20% of targeted patients enrolled which seemed to be delayed by Covid-19 pandemic.
> I am not sure if there are further cognitive improvements among patients in
> extended studies up to now with supposed no safety issues. Furthermore,
> is there any PTI-125 application of breakthrough therapy designation with FDA in process if this therapy meets original expectation ? Thanks again for your taking time to consider my trivial questions.
>
> Be safe and have a nice weekend.
>
> Best Regards,
> Eddy
>
>
>
> 寄件者: Hoau-yan Wang
> 收件者: 鄭宜明/CDB ,
> 日期: 2020/04/08 下午 11:06
> 主旨: Re: [EXTERNAL] Are you in the office ?
>
>
>
> Dear 宜明,
>
> We can try Thursday night around 8:45 PM. Here is my number: [REDACTED].
> It is a landline so that it should be more stable.
>
> Look forward to talking with you.
>
> All the best,
>
> Hoau-Yan
>

> From: 鄭宜明/CDB
> Sent: Monday, April 6, 2020 8:38 PM
> To: Hoau-yan Wang
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear Haou-Yan :
>
> Nice to know your recent status. Sorry to bother you at this moment when
> you are busy with various jobs. Would it be fine for me to call you on
> Thursday night at your local time around 8:45pm or Friday morning at
> 9:00pm ? BTW, what is your number to call at ? Thanks for your
> consideration.
>
> Best Regards,
> Yiming
>
>
>
> 寄件者: Hoau-yan Wang
> 收件者: 鄭宜明/CDB ,
> 日期: 2020/04/07 上午 02:36
> 主旨: Re: [EXTERNAL] Are you in the office ?
>
>
>
> Dear 宜明,
>
> Sorry for my late/lack of response. I am overwhelmed by various work required for transition to online instruction (teaching) and myriad of other work related to my research projects. PTI-125 is not my only work.
> At the moment, we are not permitted to be in the laboratories.
>
> We are making progress (slowly) in analyzing the samples. Since I am
> blind (and will remain blind) to the study population and the treatment. I can't tell you much other than what was released in public. I am fine with a personal phone call (toward the end of the week is better).
>
> Thanks.
>
> Hoau-Yan
>

> From: 鄭宜明/CDB
> Sent: Monday, April 6, 2020 1:46 AM

> To: Hoau-yan Wang
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-Yan :
>
> Hope that you are safe when NYC is under pressure with virus pandemic.
> Are you fine with a personal telephone call this week ? I am curious with
> the latest development of PTI-125. Thanks in advance.
>
> Best Regards,
> Yiming
>
>
>
> 寄件者: Hoau-yan Wang
> 收件者: 鄭宜明/CDB ,
> 日期: 2020/03/26 下午 11:10
> 主旨: Re: [EXTERNAL] Are you in the office ?
>
>
>
> Dear 宜明,
>
> Thanks for your concerns. My days were consumed by many online teaching sessions and
conferences. Since we are ordered to be sheltered in place and close our labs for the duration, I
had stopped commuting by public transportation since beginning of last week. I live far away from
NYC. It is truly horrifying to see the COVID-19 pandemic unfolds in NYC. I expect this will
reach peak in the coming days and sincerely hope NYC medical facility would not be overwhelmed as
did Italy and Spain...
>
> I know Taiwan is much safer than most and the Tsai government is doing all the right things to
keep Taiwan safe.
>
> Thanks again for your concerns and I wish you and your family safe and well in this crazy time.
>
> Best,
>
> Hoau-Yan
>

> From: 鄭宜明/CDB
> Sent: Wednesday, March 25, 2020 11:38 PM
> To: Hoau-yan Wang
> Subject: Re: [EXTERNAL] Are you in the office ?
>
> Dear Hoau-yen :
>
> Regarding the percent of NYC population which will be ultimately Covid-19 positive projected
from NY major in a recent news conference, I am astonished by this number and underestimated the
impact of virus pandemic.
> Infected persons with covid-19 might be jammed into subways even they are no
> longer in schools or bars. Are you still relied on public transportation
> including subways ? If that is the case, my suggestion is to avoid taking subways and stay at
home or safer places with trusted vehicles. Hope that you are fine with all things considered.
>
> Best Regards,
> Yiming
>
>
>
>
>
> 寄件者: Hoau-yan Wang
> 收件者: 鄭宜明/CDB ,
> 日期: 2020/03/18 上午 01:33
> 主旨: Re: [EXTERNAL] Are you in the office ?
>
>
>
> Dear 宜明,
>
> Thanks for your concerns. I am very sorry for my lack of response to your earlier email. As I
am overwhelmed by all the work required to efficiently safe guard all my research lab and
transition our teaching activities to online courses.
>
> Part of NYC is clearly one of the hard-hit areas, I actually live far away (from NYC) and depend
on public transportation. I am clearly quite vulnerable. I know Taiwan had done a highly

admirable job in keeping 23.5 Ms people safe.

>

> Regarding the PTI-125 phase 2b trial, although we had wrapped up the trial and collected the samples. I have to remain blind to the treatment because I run many analyses. With the complications from COVID-19 we will have to wait further.

>

> Be safe and thanks again for your concerns.

>

> Best,

>

> Hoau-Yan

>

> From: 鄭宜明/CDB

> Sent: Monday, March 16, 2020 8:38 PM

> To: Hoau-yan Wang

> Subject: [EXTERNAL] Are you in the office ?

>

> Dear Hoau-Yan :

>

> Are you still in school in both academic and research areas ? From recent news, many schools including universities have taken measures to protect

> persons with facilities of remote learning. How's going in NY Area

> regarding to the covid-19 problem ? Relatively speaking, Taiwan might be a safer place to stay away from this infectious epidemics. You might consider to be in Taiwan for a period of time for personal safety issue.

> Just my trivial suggestion for your consideration. Be safe,

>

> Best Regards,

> Yiming

>

>

>

>

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From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent time: 01/20/2022 11:45:20 AM
To: Hoau-yan Wang
Cc: Bollinger, Andrew E. <Andrew.Bollinger@saul.com>; Helmerhorst, Eva J. <eva.helmerhorst@saul.com>
Subject: RE: [EXTERNAL] New Yorker magazine fact checking inquiry

POL 87(2)(a)

Jennifer L. Beidel | 215.972.7850 | jennifer.beidel@saul.com

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 12, 2022 8:53 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] New Yorker magazine fact checking inquiry

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From: Feldman Emison, Linnea <linnea_feldmanemison@newyorker.com>
Sent: Tuesday, January 11, 2022 2:02 PM
To: mediarelations@cuny.edu
Cc: Hoau-yan Wang
Subject: [EXTERNAL] New Yorker magazine fact checking inquiry

Hello,

I'm a fact checker at The New Yorker magazine working with the writer Patrick Radden Keefe on an upcoming piece about the attorney Jordan Thomas and Cassava Sciences, including Dr. Wang's work with the company. I have some questions, listed below. Please let me know if I can clarify anything or provide further information. My deadline is this Thursday (January 13th) at 10am EST.

Thanks very much.

All best,
Linnea

- Is it correct that Dr. Wang is an associate medical professor at CUNY?
-
- Is it correct that Dr. Wang is an author of all of the biotech company Cassava's publications on the drug Simufilam?
-
-
- Is it correct that Dr. Wang conducted a retrial of Simufilam over the summer
- after disappointing results from the second trial of the drug, and that Dr. Wang's retrial
- indicated a significant reduction in biomarkers for Alzheimer's compared with the placebo?
-
-
- Would CUNY or Dr. Wang like to comment on the challenges to the claims made by other scientists to papers authored by Dr. Wang?
-
-
- Would CUNY or Dr. Wang like to comment on the methodological issues identified by scientists in roughly 30 of his papers?
-
-
- Would CUNY or Dr. Wang like to comment on the claim that
- there is no evidence of a connection between Filamin A and Alzheimer's?

-
-
- Would CUNY or Dr. Wang like to comment on Dr. Wang's participation in Cassava's compensation scheme tied to stock price?
-
- Would CUNY or Dr. Wang like to comment on the allegation that some of Cassava's Western blot tests, including those used at a conference presentation last summer in Denver, appear to have been manipulated with Photoshop or similar software, possibly by copying portions of images onto others?
-
- The piece states that the image manipulation expert Elisabeth Bik asked Cassava
- and Dr. Wang's lab for higher resolution versions of its Western blots, which were not provided to her. Would you like to comment?
-
-
- Would CUNY or Dr. Wang like to comment on statements of concern issued by
- journals that have published his work?
-
-
- Would CUNY or Dr. Wang like to comment on the claim that Dr. Wang's practice
- of freezing brains for months or years before thawing them makes it unlikely that the tissue is still usable for testing?
-
-
- Does Dr. Wang view Dr. David Bredt as an academic competitor?
-
-
-
- Has the FDA been in touch with Dr. Wang's lab since the filing of the petition?
-
- Would CUNY or Dr. Wang like to comment on the Quintessential Capital report on Simufilam?

--

Linnea Feldman Emison
The New Yorker
(212) 286-7362

"Saul Ewing Arnstein & Lehr LLP (saul.com)" has made the following annotations:

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From: Editor-Clinical Cytology and Pathology <editor@scimailmanuscript.biz>
Sent time: 01/21/2022 04:36:32 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Gain the Chance to Announce your Study

Dear Dr. HoauYan Wang,

Archives of Clinical Cytology and Pathology is an open access journal in which, Articles/Manuscripts are run through a detailed review by our eminent panel of Editorial Board who spend their valuable time to review these articles.

Recently we have gone through your publications, where we found "**PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis**" as a pioneering publication. So, we thought it would be the right time to take a chance to invite you for the submission of your article for our upcoming issue.

-Online Submission link [Click here to submit your manuscript](#)

As the journal is not funded by any funding resources we will charge the minimum publication fee (based on the economic standards of the country which is given by World Bank) to maintain its standards online.

We hope to have your collaboration with the journal.

Sincerely,
Editor-Clinical Cytology and Pathology
Archives of Clinical Cytology and Pathology

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From: Max C. <[REDACTED]@outlook.fr>
Sent time: 01/23/2022 07:51:13 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] 3 Questions for a Belgian investigative journal

Hello Dr Wang,

Before saying anything, I just want to tell you that I help a journalist cover the Simufilam story for a Belgian paper. We are totally unbiased and we just thought that it would do a great investigative article.

I only have three questions that are absolutely not controversial and it would be terrific if you could answer.

1. How do you feel about the CUNY's investigation? (Angry? Relaxed? Anxious? ...)
2. Do you feel you are a victim of short sellers and that the investigation tarnished your reputation?
3. When do you expect an answer from CUNY?

Even if you don't reply, I'd like to thank you for your precious time.

Best regard.

BAUDUIN Simon

From: Hoau-yan Wang
Sent time: 01/23/2022 05:12:28 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: 3 Questions for a Belgian investigative journal

From: Max C. <[REDACTED]@outlook.fr>
Sent: Sunday, January 23, 2022 7:51 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] 3 Questions for a Belgian investigative journal

Hello Dr Wang,

Before saying anything, I just want to tell you that I help a journalist cover the Simufilam story for a Belgian paper. We are totally unbiased and we just thought that it would do a great investigative article.

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Best regard.

BAUDUIN Simon

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent time: 01/24/2022 12:41:03 PM
To: Hoau-yan Wang
Cc: Bollinger, Andrew E. <Andrew.Bollinger@saul.com>; Helmerhorst, Eva J. <eva.helmerhorst@saul.com>
Subject: [EXTERNAL] RE: 3 Questions for a Belgian investigative journal

POL 87(2)(a)

[REDACTED]

Jennifer L. Beidel | 215.972.7850 | jennifer.beidel@saul.com

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Sunday, January 23, 2022 5:12 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: 3 Questions for a Belgian investigative journal

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From: Max C. <[REDACTED]@outlook.fr>
Sent: Sunday, January 23, 2022 7:51 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] 3 Questions for a Belgian investigative journal

Hello Dr Wang,

Before saying anything, I just want to tell you that I help a journalist cover the Simufilam story for a Belgian paper. We are totally unbiased and we just thought that it would do a great investigative article.

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Best regard.

BAUDUIN Simon

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From: PLOS ONE <alerts@e.plos.org>
Sent time: 01/24/2022 05:26:44 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] PLOS ONE New Articles Published

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A platform of assays for the discovery of anti-Zika small-molecules with activity in a 3D-bioprinted outer-blood-retina model

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Sooje Cho, Soyun Hwang, Jae Yun Jung, Young Ho Kwak, Do Kyun Kim, Jin Hee Lee, Jin Hee Jung, Joong Wan Park, Hyuksool Kwon, Dongbum Suh

Evolution of the quality of prenatal care in the primary network of Brazil from 2012 to 2018: What can (and should) improve?

Elaine Tomasi, Thales Moura de Assis, Paulo Guilherme Muller, Denise Silva da Silveira, Rosália Garcia Neves, Everton Fantinel, Elaine Thumé, Luiz Augusto Facchini

Quality of life of patients with rheumatic diseases

during the COVID-19 pandemic: The biopsychosocial path

Guillermo A. Guaracha-Basáñez, Irazú Contreras-Yáñez, Gabriela Hernández-Molina, Viviana A. Estrada-González, Lexli D. Pacheco-Santiago, Salvador S. Valverde-Hernández, José Roberto Galindo-Donaire, Ingris Peláez-Ballestas, Virginia Pascual-Ramos

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Lisa Katharina Maurer, Heiko Maurer, Mathias Hegele, Hermann Müller

Cost-effective synthesis of 2D molybdenum disulfide (MoS₂) nanocrystals: An exploration of the influence on cellular uptake, cytotoxicity, and bio-imaging

Dhirendra Sahoo, Sushreesangita P. Behera, Jyoti Shakya, Bhaskar Kaviraj

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Lisa M. Powell, Julien Leider

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Costs of polish county hospitals—A behavioral panel function

Agata Sielska

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Differences in cortical processing of facial emotions in broader autism phenotype

Patricia Soto-Icaza, Brice Beffara-Bret, Lorena Vargas, Francisco Aboitiz, Pablo Billeke

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Phillippa M. Cumberland, Vasiliki Bountziouka, Christopher J. Hammond, Pirro G. Hysi, Jugnoo S. Rahi, on behalf of the UK Biobank Eye and Vision Consortium

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Isolation of the side population from neurogenic niches enriches for endothelial cells

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Yan Wang, Eric Zhu, Erin R. Hager, Maureen M. Black

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Large-scale decrease in the social salience of climate change during the COVID-19 pandemic

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Effect of adverse events on non-adherence and study non-completion in malaria chemoprevention during pregnancy trial: A nested case control study

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Muhammad Noman, Shanshan Tu, Shahab Ahmad, Fahad Ullah Zafar, Haseeb Ahmad Khan, Sadaqat Ur Rehman, Muhammad Waqas, Adnan Daud Khan, Obaid ur Rehman

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Sophia Day, Emanuela Acquafredda, Jill Humphrey, Martha Johnson, Maria Fitzpatrick, Jasmina Spasojevic, Kevin Konty

Skin aging risk factors: A nationwide population study in Mongolia risk factors of skin aging

Tuya Nanzadsuren, Tuul Myatav, Amgalanbaatar Dorjkhuu, Mandukhai Ganbat, Chuluunbileg Batbold, Baljinnyam Batsuuri, Khandsuren Byamba

Hospitalization and ambulatory costs related to breast cancer due to physical inactivity in the Brazilian state capitals

Diego Augusto Santos Silva

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Tarun Walia, Gauri Kalra, Vijay Prakash Mathur, Jatinder Kaur Dhillon

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Identification of hub genes associated with COVID-19 and idiopathic pulmonary fibrosis by integrated bioinformatics analysis

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Human unintentional and intentional interpersonal coordination in interaction with a humanoid robot

Ghiles Mostafaoui, R. C. Schmidt, Syed Khursheed Hasnain, Robin Salesse, Ludovic Marin

Behavioral economic methods to inform infectious disease response: Prevention, testing, and vaccination in the COVID-19 pandemic

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Retraction: MicroRNA-20b (miR-20b) Promotes the Proliferation, Migration, Invasion, and Tumorigenicity in Esophageal Cancer Cells via the Regulation of

Phosphatase and Tensin Homologue Expression

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Correction: Exogenous application of moringa leaf extract improves growth, biochemical attributes, and productivity of late-sown quinoa

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Correction: Effects of nurse-led transitional care interventions for patients with heart failure on healthcare utilization: A meta-analysis of randomized controlled trials

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Comparison of ready-to-eat “organic” antimicrobials, sodium bisulfate, and sodium lactate, on *Listeria monocytogenes* and the indigenous microbiome of organic uncured beef frankfurters stored under refrigeration for three weeks

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Complexity and variability analyses of motor activity distinguish mood states in bipolar disorder

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Clinical-like cryotherapy in acute knee arthritis of the knee improves inflammation signs, pain, joint swelling, and motor performance in mice

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***Helicobacter pylori* infection is not associated with portal hypertension-related gastrointestinal complications: A meta-analysis**

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A 1 bp deletion in *HACE1* causes ataxia in Norwegian elkhound, black

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Isolation and characterization of *Streptomyces* bacteriophages and *Streptomyces* strains encoding biosynthetic arsenals

Elizabeth T. Montaña, Jason F. Nideffer, Lauren Brumage, Marcella Erb, Julia Busch, Lynley Fernandez, Alan I. Derman, John Paul Davis, Elena Estrada, Sharon Fu, Danielle Le, Aishwarya Vuppala, Cassidy Tran, Elaine Luterstein, Shivani Lakkaraju, Sriya Panchagnula, Caroline Ren, Jennifer Doan, Sharon Tran, Jamielyn Soriano, Yuya Fujita, Pranathi Gutala, Quinn Fujii, Minda Lee, Anthony Bui, Carleen Villarreal, Samuel R. Shing, Sean Kim, Danielle Freeman, Vipula Racha, Alicia Ho, Prianka Kumar, Kian Falah, Thomas Dawson, Eray Enustun, Amy Prichard, Ana Gomez, Kanika Khanna, Shelly Trigg, Kit Pogliano, Joe Pogliano

Wading through Molasses: A qualitative examination of the experiences, perceptions, attitudes, and knowledge of Australian medical practitioners regarding medical billing

Margaret Faux, Jon Adams, Simran Dahiya, Jon Wardle

Uterine prolapse and associated factors among reproductive-age women in south-west Ethiopia: A community-based cross-sectional study

Abebe Sorsa Badacho, Mengistu Auro Lelu, Zegeye Gelan, Deginesh Dawit Woltamo

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Saif Ullah, Nizami Moazzam Syed, Tian Gang, Rana Shahzad Noor, Sarir Ahmad, Muhammad Mohsin Waqas, Adnan Noor Shah, Sami Ullah

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Frits van Griensven, Nittaya Phanuphak, Chomnad Manopaiboon, Eileen F. Dunne, Donn J. Colby, Pannee Chaiphosri, Reshmie Ramautarsing, Philip A. Mock, Thomas E. Guadamuz, Ram Rangsin, Kanya Benjamineepairoj, Panus Na Nakorn, Ravipa Vannakit, Jan Willem de Lind van Wijngaarden, Matthew Avery, Stephen Mills

Investigating public support for biosecurity measures to mitigate pathogen transmission through the herpetological trade

Elizabeth F. Pienaar, Diane J. Episcopio-Sturgeon, Zachary T. Steele

Pro-active monitoring and social interventions at community level mitigate the impact of coronavirus (COVID-19) epidemic on older adults' mortality in Italy: A retrospective cohort analysis

Giuseppe Liotta, Leonardo Emberti Gialloreti, Maria Cristina Marazzi, Olga Madaro, Maria Chiara Inzerilli, Margherita D'Amico, Stefano Orlando, Paola Scarcella, Elisa Terracciano, Susanna Gentili, Leonardo Palombi

Microbial reductions and physical characterization of chitosan flocs when using chitosan acetate as a cloth filter aid in water treatment

Hemali H. Oza, Eleanor B. Holmes, Emily S. Bailey, Collin K. Coleman, Mark D. Sobsey

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Samantha S. R. Crossfield, Kieran Zucker, Paul Baxter, Penny Wright, Jon Fistein, Alex F. Markham, Mark Birkin, Adam W. Glaser, Geoff Hall

A nationwide survey of the association between nonalcoholic fatty liver disease and the incidence of asthma in Korean adults

Jae-Hyung Roh, Hanbyul Lee, Bae Yun-Jeong, Chan Sun Park, Hyo-Jung Kim, Sun-Young Yoon

“Sarcopenia and risk of osteoporosis, falls and bone fractures in patients with chronic kidney disease: A systematic review”

Anahita Rashid, Sabina Chaudhary Hauge, Charlotte Suetta, Ditte Hansen

Application of the Taguchi method to explore a robust

condition of tumor-treating field treatment

Kosaku Kurata, Kazuki Shimada, Hiroshi Takamatsu

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Alina Kirichenko, Dmitry Kireev, Alexey Lopatukhin, Anastasia Murzakova, Ilya Lapovok, Daria Saleeva, Natalya Ladnaya, Agigat Gadirova, Sabina Ibrahimova, Aygun Safarova, Trdat Grigoryan, Arshak Petrosyan, Tatevik Sarhatyan, Elena Gasich, Anastasia Bunas, Iryna Glinskaya, Pavel Yurovsky, Rustam Nurov, Alijon Soliev, Laylo Ismatova, Erkin Musabaev, Evgeniya Kazakova, Visola Rakhimova, Vadim Pokrovsky

Stress, non-restorative sleep, and physical inactivity as risk factors for chronic pain in young adults: A cohort study

Maja Lindell, Anna Grimby-Ekman

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Henry Querfurth, John Marshall, Keykavous Parang, Mengia S. Rioult-Pedotti, Rakesh Tiwari, Bumsup Kwon, Steve Reisinger, Han-Kyu Lee

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Alicia M. Paul, Shraddha Nepal, Kamana Upreti, Jeevan Lohani, Rajiv N. Rimal

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Steven Kwasi Korang, Elena von Rohden, Areti Angeliki Veroniki, Giok Ong, Owen Ngalamika, Faiza Siddiqui, Sophie Juul, Emil Eik Nielsen, Joshua Buron Feinberg, Johanne Juul Petersen, Christian Legart, Afoke Kokogho, Mathias Maagaard, Sarah Klingenberg, Lehana Thabane, Ariel Bardach, Agustín Ciapponi, Allan Randrup Thomsen, Janus C. Jakobsen, Christian Gluud

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Cristina Lavilla Olleros, Cristina Ausín García, Alejandro David Bendala Estrada, Ana Muñoz, Philip Erick Wikman Jogersen, Ana Fernández Cruz, Vicente Giner Galvañ, Juan Antonio Vargas, José Miguel Seguí Ripoll, Manuel Rubio-Rivas, Rodrigo Miranda Godoy, Luis Mérida Rodrigo, Eva Fonseca Aizpuru, Francisco Arnalich Fernández, Arturo Artero, Jose Loureiro Amigo, Gema María García García, Luis Corral Gudino, Jose Jiménez Torres, José-Manuel Casas-Rojo, Jesús Millán Núñez-Cortés, On behalf of the SEMI-COVID-19 Network

Multi-channel convolutional neural network

architectures for thyroid cancer detection

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Effects of long-term and high-dose administration of glucocorticoids on the cranial cruciate ligament in healthy beagle dogs

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Napa Sae-Bae, Nasir Memon

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Prospective observational study investigating the effectiveness, safety, women's experiences and quality of life at 3 months regarding cervical ripening methods for induction of labor at term—The MATUCOL study protocol

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Understanding the interplay between lifestyle factors and emotional distress for hemorrhagic stroke survivors and their informal caregivers: Protocol for a mixed methods dyadic natural history study

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Carol Chunfeng Wang, Lisa Whitehead, Travis Cruickshank, Johnny Lo, Jianhong (Cecilia) Xia, Jun Wen

Retraction: MiRNA-107 enhances the malignant progression of pancreatic cancer by targeting TGFBR3

The PLOS ONE Editors

Correction: Characterization of cassava ORANGE proteins and their capability to increase provitamin A carotenoids accumulation

The PLOS ONE Staff

Correction: Politicization of COVID-19 health-protective behaviors in the United States:

Longitudinal and cross-national evidence

Wolfgang Stroebe, Michelle R. vanDellen, Georgios Abakoumkin, Edward P. Lemay Jr, William M Schiavone, Maximilian Agostini, Jocelyn J. Bélanger, Ben Gützkow, Jannis Kreienkamp, Anne Margit Reitsema, Jamilah Hanum Abdul Khaiyom, Vjolica Ahmedi, Handan Akkas, Carlos A. Almenara, Mohsin Atta, Sabahat Cigdem Bagci, Sima Basel, Edona Berisha Kida, Allan B. I. Bernardo, Nicholas R. Buttrick, Phatthanakit Chobthamkit, Hoon-Seok Choi, Mioara Cristea, Sára Csaba, Kaja Damjanović, Ivan Danyliuk, Arobindu Dash, Daniela Di Santo, Karen M Douglas, Violeta Enea, Daiane Gracieli Faller, Gavan Fitzsimons, Alexandra Gheorghiu, Ángel Gómez, Ali Hamaidia, Qing Han, Mai Helmy, Joevarian Hudiyan, Bertus F. Jeronimus, Ding-Yu Jiang, Veljko Jovanović, Željka Kamenov, Anna Kende, Shian-Ling Keng, Tra Thi Thanh Kieu, Yasin Koc, Kamila Kovyazina, Inna Kozytska, Joshua Krause, Arie W. Kruglanski, Anton Kurapov, Maja Kutlaca, Nóra Anna Lantos, Cokorda Bagus Jaya Lemsmana, Winnifred R. Louis, Adrian Lueders, Najma Iqbal Malik, Anton Martinez, Kira O. McCabe, Jasmina Mehulić, Mirra Noor Milla, Idris Mohammed, Erica Molinario, Manuel Moyano, Hayat Muhammad, Silvana Mula, Hamdi Muluk, Solomiia Myroniuk, Reza Najafi, Claudia F. Nisa, Boglárka Nyú, Paul A. O'Keefe, Jose Javier Olivas Osuna, Evgeny N. Osin, Joonha Park, Gennaro Pica, Antonio Pierro, Jonas Rees, Elena Resta, Marika Rullo, Michelle K. Ryan, Adil Samekin, Pekka Santtila, Edyta Sasin, Birga M. Schumpe, Heyla A. Selim, Michael Vicente Stanton, Samiah Sultana, Robbie M. Sutton, Eleftheria Tseliou, Akira Utsugi, Jolien Anne van Breen, Caspar J. Van Lissa, Kees Van Veen, Alexandra Vázquez, Robin Wollast, Victoria Wai-Lan Yeung, Somayeh Zand, Iris Lav Žeželj, Bang Zheng, Andreas Zick, Claudia Zúñiga, N. Pontus Leander

Correction: Transcript Analysis and Regulative Events during Flower Development in Olive (*Olea europaea* L.)

Fiammetta Alagna, Marco Cirilli, Giulio Galla, Fabrizio Carbone, Loretta Daddiego, Paolo Facella, Loredana Lopez, Chiara Colao, Roberto Mariotti, Nicolò Cultrera, Martina Rossi, Gianni Barcaccia, Luciana Baldoni, Rosario Muleo, Gaetano Perrotta

Correction: Chromosomal variants accumulate in genomes of the spontaneous aborted fetuses revealed by chromosomal microarray analysis

Sen Li, Lei-Ning Chen, Xing-Hua Wang, Hai-Jing Zhu, Xiao-Long Li, Xie Feng, Lei Guo, Xiang-Hong Ou, Jun-Yu Ma

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Cc: Bollinger, Andrew E. <Andrew.Bollinger@saul.com>; Helmerhorst, Eva J. <eva.helmerhorst@saul.com>
Subject: Re: 3 Questions for a Belgian investigative journal

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From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent: Monday, January 24, 2022 12:41 PM
To: Hoau-yan Wang
Cc: Bollinger, Andrew E.; Helmerhorst, Eva J.
Subject: [EXTERNAL] RE: 3 Questions for a Belgian investigative journal

Jennifer L. Beidel | 215.972.7850 | jennifer.beidel@saul.com

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Sunday, January 23, 2022 5:12 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: 3 Questions for a Belgian investigative journal

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From: Max C. <[REDACTED]@outlook.fr>
Sent: Sunday, January 23, 2022 7:51 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] 3 Questions for a Belgian investigative journal

Hello Dr Wang,

Before saying anything, I just want to tell you that I help a journalist cover the Simufilam story for a Belgian paper. We are totally unbiased and we just thought that it would do a great investigative article.

I only have three questions that are absolutely not controversial and it would be terrific if you could answer.

1. How do you feel about the CUNY's investigation? (Angry? Relaxed? Anxious? ...)
2. Do you feel you are a victim of short sellers and that the investigation tarnished your reputation?
3. When do you expect an answer from CUNY?

Even if you don't reply, I'd like to thank you for your precious time.

Best regard.

BAUDUIN Simon

"Saul Ewing Arnstein & Lehr LLP (saul.com)" has made the following annotations:

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Katsuhiko Hayashi, Takashi Misawa, Chihiro Goto, Yosuke Demizu, Yukiko Hara-Kudo, Yutaka Kikuchi

Multilocus sequence based identification and adaptational strategies of *Pseudomonas* sp. from the supraglacial site of Sikkim Himalaya

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Michael J. Harvey, Yi Zhong, Eric Morris, Jacob N. Beverage, Robert S. Epstein, Anita J. Chawla

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Colleen Blue, Mara Buchbinder, Mercedes E. Brown, Steve Bradley-Bull, David L. Rosen

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Giorgio Ciminata, Claudia Geue, Olivia Wu, Manuela Deidda, Noemi Kreif, Peter Langhorne

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Johnson Matowo, David Weetman, Patricia Pignatelli, Alexandra Wright, Jacques D. Charlwood, Robert Kaaya, Boniface Shirima, Oliva Moshi, Eliud Lukole, Jacklin Mosha, Alphaxard Manjurano, Franklin Mosha, Mark Rowland, Natacha Protopopoff

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Kazuma Ogiso, Sigfrid Casmir Shayo, Shigeru Kawade, Hiroshi Hashiguchi, Takahisa Deguchi, Yoshihiko Nishio

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Pegah Abed-Esfahani, Benjamin C. Darwin, Derek Howard, Nick Wang, Ethan Kim, Jason Lerch, Leon French

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Ting Wu, Yi Wang, Rebecca Ruan, Jianzhuang Zheng

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Nan-Chieh Chen, Yu-Tang Chang, Po-Chih Chang, Cheng-Sheng Chen, Chung-Sheng Lai

CardiOvascular examination in awake Orangutans (*Pongo pygmaeus pygmaeus*): Low-stress

Echocardiography including Speckle Tracking imaging (the COOLEST method)

Valérie Chetboul, Didier Concordet, Renaud Tissier, Irène Vonfeld, Camille Poissonnier, Maria Paz Alvarado, Peggy Passavin, Mathilde Gluntz, Solène Lefort, Aude Bourgeois, Dylan Duby, Christelle Hano, Norin Chai

Associations between anxiety and the willingness to be exposed to COVID-19 risk among French young adults during the first pandemic wave

Fabrice Etilé, Pierre-Yves Geoffard

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Khashayar Afshari, Erin D. Ozturk, Brandon Yates, Glen Picard, J. Andrew Taylor

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How can the education sector support children's mental health? Views of Australian healthcare clinicians

Kate Paton, Lynn Gillam, Hayley Warren, Melissa Mulraney, David Coghill, Daryl Efron, Michael Sawyer, Harriet Hiscock

COVID-19 infection prevention practices among a sample of food handlers of food and drink establishments in Ethiopia

Atsedemariam Andualem, Belachew Tegegne, Sewunet Ademe, Tarikuwa Natnael, Gete Berihun, Masresha Abebe, Yeshiwork Alemnew, Alemebante Mulu, Yordanos Mezemir, Abayneh Melaku, Taffere Addis, Emaway Belay, Zebader Walle, Lake Kumlachew, Abraham Teym, Metadel Adane

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Lauren Jodi Van Scoy, Bethany Snyder, Erin L. Miller, Olubukola Toyobo, Ashmita Grewal, Giang Ha, Sarah Gillespie, Megha Patel, Aleksandra E. Zgierska, Robert P. Lennon

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Faisal Alsayegh, Moh A. Alkhamis, Fatima Ali, Sreeja Attur, Nicholas M. Fountain-Jones, Mohammad Zubaid

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Alícia Zem Fraga, Luciano Hauschild, Paulo Henrique Reis Furtado Campos, Marcio Valk, Débora Zava Bello, Marcos Kipper, Ines Andretta

Review of guidance papers on regression modeling in statistical series of medical journals

Christine Wallisch, Paul Bach, Lorena Hafermann, Nadja Klein, Willi Sauerbrei, Ewout W. Steyerberg, Georg Heinze, Geraldine Rauch, on behalf of topic group 2 of the STRATOS initiative

***In silico* analysis of potential off-target sites to gene**

editing for Mucopolysaccharidosis type I using the CRISPR/Cas9 system: Implications for population-specific treatments

Paola Carneiro, Martiela Vaz de Freitas, Ursula Matte

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Ae-Young Her, Youngjune Bhak, Eun Jung Jun, Song Lin Yuan, Scot Garg, Semin Lee, Jong Bhak, Eun-Seok Shin

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Daniel Penados, José P. Pineda, Elisa Laparra-Ruiz, Manuel F. Galván, Anna M. Schmoker, Bryan A. Ballif, M. Carlota Monroy, Lori Stevens

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**and neurodevelopmental impairment at 2 year of age:
A post hoc analysis of the SafeBoosC II trial**

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Linh-Aurore Le Bras, Anatolie Timercan, Marie Llido, Yvan Petit, Bernard Seguin, Bertrand Lussier, Vladimir Brailovski

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Nguyen Phuoc Long, Da Young Heo, Seongoh Park, Nguyen Thi Hai Yen, Yong-Soon Cho, Jae-Gook Shin, Jee Youn Oh, Dong-Hyun Kim

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Laure Dayet, Francesco d'Errico, Marcos García Díez, João Zilhão

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Matthew J. Major, Julia Quinlan, Andrew H. Hansen, Elizabeth Russell Esposito

Anticancer activity of *Zingiber ottensii* essential oil and its nanoformulations

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Chunlin Zeng, Yuejin Zhou, Leiming Zhang, Donggui Mao, Kexin Bai

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Marion Schoof, Maureen O'Callaghan, Campbell R. Sheen, Travis R. Glare, Mark R. H. Hurst

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Masashi Sakuma, Shigeru Toyoda, Takuo Arikawa, Yota Koyabu, Toru Kato, Taichi Adachi, Hideaki Suwa, Jun-ichi Narita, Koetsu Anraku, Kimihiko Ishimura, Fumitake Yamauchi, Yasunori Sato, Teruo Inoue

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P63 targeted deletion under the FOXP1 promoter disrupts pre-and post-natal thymus development, function and maintenance as well as induces severe hair loss

Heather E. Stefanski, Yan Xing, Jemma Nicholls, Leslie Jonart, Emily Goren, Patricia A. Taylor, Alea A. Mills, Megan Riddle, John McGrath, Jakub Tolar, Georg A. Hollander, Bruce R. Blazar

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Bilema Mwambenu, Vundli Ramoloko, Ria Laubscher, Ute Feucht

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Mitsunori Miyazaki, Michito Shimozuru, Toshio Tsubota

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Sabrina Sebbane, Sophie Bailly, Wayne-Corentin Lambert, Stéphane Sanchez, Coraline Hingray, Wissam El-Hage

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Wakshum Shiferaw, Sebsebe Demissew, Tamrat Bekele, Ermias Aynekulu

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Theis Christian Tønnessen, Arne Olav Melleby, Ida Marie Hauge-Iversen, Emil Knut Stenersen Espe, Mohammed Shakil Ahmed, Thor Ueland, Espen Andre Haavardsholm, Sara Marie Atkinson, Espen Melum, Håvard Attramadal, Ivar Sjaastad, Leif Erik Vinge

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Jana Stallmann, Caroline A. A. Pons, Rabea Schweiger, Caroline Müller

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Kevin Till, Rhodri S. Lloyd, Sam McCormack, Graham Williams, Joseph Baker, Joey C. Eisenmann

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Keiko Nakanishi, Kyohei Higashi, Toshihiko Toida, Masato Asai

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Matthew T. Siuba, Divyajot Sadana, Shruti Gadre, David Bruckman, Abhijit Duggal

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Ashraf Direkvand-Moghadam, Nasrin Roshan, Mona Bahmani, Safoura Taheri

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Jaime Carmona-Fonseca, Jaiberth Antonio Cardona-Arias

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Mateja Ozanic, Valentina Marecic, Masa Knezevic, Ina Kelava, Pavla Stojková, Lena Lindgren, Jeanette E. Bröms, Anders Sjöstedt, Yousef Abu Kwaik, Marina Santic

An account of *Colletotrichum* species associated with anthracnose of *Atractylodes ovata* in South Korea based on morphology and molecular data

Oliul Hassan, Ju Sung Kim, Bekale Be Ndong Dimitri Romain, Taehyun Chang

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Toshihiko Ogura

***CKMT1A* is a novel potential prognostic biomarker in patients with endometrial cancer**

Yaping Wang, Shujun Zhao, Qiaohong Qin, Xiang Gao, Xinlu Zhang, Min Zhang, Yi Jiang, Xiaorong Ji, Hai Zhu, Xin Zhao, Hongyu Li

The effects of gastrointestinal disturbances on the onset of depression and anxiety

David Cantarero-Prieto, Patricia Moreno-Mencia

Pharmacogenetic inhibition of lumbosacral sensory neurons alleviates visceral hypersensitivity in a mouse model of chronic pelvic pain

Alison Xiaoqiao Xie, Nao Iguchi, Taylor C. Clarkson, Anna P. Malykhina

Stopover use of a large estuarine wetland by dunlins during spring and autumn migrations: Linking local refuelling conditions to migratory strategies

Teresa Catry, José Pedro Granadeiro, Jorge Sánchez Gutiérrez, Edna Correia

An intercomparison study of ELISAs for the detection of porcine reproductive and respiratory syndrome virus – evaluating six conditionally dependent tests

Clara Schoneberg, Jens Böttcher, Britta Janowetz, Anja Rostalski, Lothar Kreienbrock, Amely Campe

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Yigezu Atnafe Yigezu, M. Wakilur Rahman, Tamer El-Shater, Arega D. Alene, Ashutosh Sarker, Shiv Kumar, Aymen Frija

COVID-19 vaccine hesitancy among medical and health science students attending Wolkite University in Ethiopia

Ayenew Mose, Kassahun Haile, Abebe Timerga

Multidimensional assessment of anxiety through the State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA): From dimensionality to response prediction across emotional contexts

Filipa Barros, Cláudia Figueiredo, Susana Brás, João M. Carvalho, Sandra C. Soares

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Diana Laila Ramatillah, Siew Hua Gan, Ika Pratiwy, Syed Azhar Syed Sulaiman, Ammar Ali Saleh Jaber, Nina Jusnita, Stefanus Lukas, Usman Abu Bakar

Modeling toes contributes to realistic stance knee mechanics in three-dimensional predictive simulations of walking

Antoine Falisse, Maarten Afschrift, Friedl De Groote

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João Paulo Silva de Paiva, Mônica Avelar Figueiredo Mafra Magalhães, Thiago Cavalcanti Leal, Leonardo Feitosa da Silva, Lucas Gomes da Silva, Rodrigo Feliciano do Carmo, Carlos Dornels Freire de Souza

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Is subject-specific musculoskeletal modelling worth the extra effort or is generic modelling worth the

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Riad Akhundov, David J. Saxby, Laura E. Diamond, Suzi Edwards, Phil Clausen, Katherine Dooley, Sarah Blyton, Suzanne J. Snodgrass

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Auction mechanism on construction land quota with selection on land location

Yang Deng, Weidong Meng, Bo Huang, Jingyu Liu

“The research assistants kept coming to follow me up; I counted myself as a lucky person”: Social support arising from a longitudinal HIV cohort study in Uganda

Jeffrey I. Campbell, Angella Musiimenta, Sylvia Natukunda, Nir Eyal, Jessica E. Haberer

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Prevalence of common carbapenemase genes and multidrug resistance among uropathogenic

Escherichia coli phylogroup B2 isolates from outpatients in Wasit Province/ Iraq

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Alteration of ankle proprioceptive threshold during gait in the presence of acute experimental pain

Michaël Bertrand-Charette, Miorie Le Quang, Jean-Sébastien Roy, Laurent J. Bouyer

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A hybrid neural network for driving behavior risk prediction based on distracted driving behavior data

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Assessment of the use of computed tomography colonography in early detection of peritoneal metastasis in patients with gastric cancer: A prospective cohort study

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Fikre Bojola, Wondimagegn Taye, Habtamu Samuel, Bahiru Mulatu, Aknew Kawza, Aleme Mekuria

Pooling saliva samples as an excellent option to increase the surveillance for SARS-CoV-2 when re-opening community settings

Joaquín Moreno-Contreras, Marco A. Espinoza, Carlos Sandoval-Jaime, Marco A. Cantú-Cuevas, Daniel A. Madrid-González, Héctor Barón-Olivares, Oscar D. Ortiz-

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Shohei Inui, Soon Ho Yoon, Ozkan Doganay, Fergus V. Gleeson, Minsuok Kim

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The possibility of sports industry business model innovation based on blockchain technology: Evaluation of the innovation efficiency of listed sports companies

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Correction: Evaluation of auditory perception development in neonates by quantitative electroencephalography and auditory event-related potentials

Qinfen Zhang, Qirui Cheng, Hongxin Li, Xuan Dong, Wenjuan Tu

Correction: Healthy volunteers in US phase I clinical trials: Sociodemographic characteristics and participation over time

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Internet use and pro-environmental behavior: Evidence from China

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The involvement of type IV pili and the phytochrome CphA in gliding motility, lateral motility and photophobotaxis of the cyanobacterium *Phormidium lacuna*

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The magnitude of failed induction and associated factors among women admitted to Adama hospital medical college: A cross-sectional study

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Impact of acute decompensation on the prognosis of patients with hepatocellular carcinoma

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Validation of a quantitative web-based food frequency questionnaire to assess dietary intake in the adult Emirati population

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Can big data increase our knowledge of local rental markets? A dataset on the rental sector in France

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How minimizing conflicts could lead to polarization on social media: An agent-based model investigation

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Adult schistosomes have an epithelial bacterial population distinct from the surrounding mammalian host blood

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From communities to protein complexes: A local community detection algorithm on PPI networks

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Factors associated with baseline smoking self-efficacy among male Qatari residents enrolled in a quit smoking study

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Different temporal weight-bearing tendencies of persons with right and left hemiplegia while sitting in a wheelchair

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Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: A placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients

Laurence M. Moss, Marijke Hyke Algera, Robert Dobbins, Frank Gray, Stephanie Strafford, Amy Heath, Monique van Velzen, Jules A. A. C. Heuberger, Marieke Niesters, Erik Olofsen, Celine M. Laffont, Albert Dahan, Geert Jan Groeneveld

Experimental determination of *Escherichia coli* biomass composition for constraint-based metabolic modeling

Vetle Simensen, Christian Schulz, Emil Karlsen, Signe Bråtelund, Idun Burgos, Lilja Brekke Thorfinnsdottir, Laura García-Calvo, Per Bruheim, Eivind Almaas

Cholangiocarcinoma protective factors in Greater Mekong Subregion: Critical issues for joint planning to sustainably solve regional public health problems

Nopparat Songserm, Somkiattiyos Woradet, Waratip Kankarn, Kanjanar Pintakham, Phouthong Vanhnivongkham, Nguyen Thi To Uyen, Nguyen Cong Cuu, Le Ngoc Cua, Banchob Sripa, Akhtar Ali

Comparative effectiveness of adjunct non-pharmacological interventions on maternal and neonatal outcomes in gestational diabetes mellitus patients: A systematic review and network meta-

analysis protocol of randomized controlled trials

Sumanta Saha

Correction: Maternal exposure to sulfonamides and adverse pregnancy outcomes: A systematic review and meta-analysis

Peixuan Li, Xiaoyun Qin, Fangbiao Tao, Kun Huang

Correction: Characterization of *Brassica rapa* metallothionein and phytochelatin synthase genes potentially involved in heavy metal detoxification

Jiayou Liu, Jie Zhang, Sun Ha Kim, Hyun-Sook Lee, Enrico Martinoia, Won-Yong Song

Correction: Dry eye, its clinical subtypes and associated factors in healthy pregnancy: A cross-sectional study

Kofi Asiedu, Samuel Kyei, Madison Adanusa, Richard Kobina Dadzie Ephraim, Stephen Animful, Stephen Karim Ali-Baya, Belinda Akorsah, Mabel Antwiwaa Sekyere

Dietary rescue of adult behavioral deficits in the *Fmr1* knockout mouse

Suzanne O. Nolan, Samantha L. Hodges, Matthew S. Binder, Gregory D. Smith, James T. Okoh, Taylor S. Jefferson, Brianna Escobar, Joaquin N. Lugo

Transcription factor specificity limits the number of DNA-binding motifs

Ariel A. Aptekmann, Denys Bulavka, Alejandro D. Nadra, Ignacio E. Sánchez

Identification of pharmacogenetic variants from large scale next generation sequencing data in the Saudi population

Ewa Goljan, Mohammed Abouelhoda, Mohamed M. ElKalioby, Amjad Jabaan, Nada Alghithi, Brian F. Meyer, Dorota Monies

Impact of the COVID-19 pandemic on student' sleep patterns, sexual activity, screen use, and food intake: A global survey

Passent Ellakany, Roberto Ariel Abeldaño Zuñiga, Maha El Tantawi, Brandon Brown, Nourhan M. Aly, Oliver Ezechi, Benjamin Uzochukwu, Giuliana Florencia Abeldaño, Eshrat Ara, Martin Amogre Ayanore, Balgis Gaffar, Nuraldeen Maher Al-Khanati, Anthonia Omotola Ishabiyi, Mohammed Jafer, Abeedha Tu-Allah Khan, Zumama Khalid, Folake Barakat Lawal, Joanne Lusher, Ntombifuthi P. Nzimande, Bamidele Emmanuel Osamika, Mir Faeq Ali Quadri, Mark Roque, Anas Shamala, Ala'a B. Al-Tammemi, Muhammad Abrar Yousaf, Jorma I. Virtanen, Annie Lu Nguyen, Morenike Oluwatoyin Folayan

Deep learning via LSTM models for COVID-19 infection forecasting in India

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An integrated model to study varietal diversity in traditional agroecosystems

Vitor Hirata Sanches, Cristina Adams, Fernando Fagundes Ferreira

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Kateřina Bucsuházy, Robert Zůvala, Veronika Valentová, Jiří Ambros

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Hanno Andreas Ohmann, Niclas Kuper, Jan Wacker

Understanding contributors to racial and ethnic inequities in COVID-19 incidence and mortality rates

Karen E. Joynt Maddox, Mat Reidhead, Joshua Grotzinger, Timothy McBride, Aaloke Mody, Elna Nagasako, Will Ross, Joseph T. Steensma, Abigail R. Barker

N-Acetylcysteine as a novel rapidly acting anti-suicidal agent: A pilot naturalistic study in the emergency setting

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The methylome in females with adolescent Conduct Disorder: Neural pathomechanisms and environmental risk factors

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Conspiracy endorsement and its associations with personality functioning, anxiety, loneliness, and sociodemographic characteristics during the COVID-19 pandemic in a representative sample of the German population

Nora Hettich, Manfred E. Beutel, Mareike Ernst, Clara Schliessler, Hanna Kampling, Johannes Kruse, Elmar Braehler

Prevalence and associated risk factors for tuberculosis among people living with HIV in Nepal

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Intra-cardiac transfer of fatty acids from capillary to cardiomyocyte

Ger J. van der Vusse, Theo Arts, James B. Bassingthwaite, Robert S. Reneman

Few SARS-CoV-2 infections detected in Newfoundland and Labrador in the absence of Public Health Laboratory-based confirmation

Danielle P. Ings, Keeley M. Hatfield, Kathleen E. Fifield, Debbie O. A. Harnum, Kayla A. Holder, Rodney S. Russell, Michael D. Grant

Population wide testing pooling strategy for SARS-CoV-2 detection using saliva

Eduardo Esteves, Ana Karina Mendes, Marlene Barros, Cátia Figueiredo, Joana Andrade, Joana Capelo, António Novais, Carla Rebelo, Rita Soares, Ana Nunes, André Ferreira, Joana Lemos, Ana Sofia Duarte, Raquel M. Silva, Liliana Inácio Bernardino, Maria José Correia, Ana Cristina Esteves, Nuno Rosa

Modelling the contribution of iodised salt in industrially processed foods to iodine intake in Macedonia

Neda Milevska-Kostova, Borislav Karanfilski, Jacky Knowles, Karen Codling, John H. Lazarus

Racialized economic segregation and health outcomes: A systematic review of studies that use the Index of Concentration at the Extremes for race, income, and their interaction

Anders Larrabee Sonderlund, Mia Charifson, Antoinette Schoenthaler, Traci Carson, Natasha J. Williams

Self-reported symptoms as predictors of SARS-CoV-2 infection in the general population living in the Amsterdam region, the Netherlands

Jizzo R. Bosdriesz, Feiko Ritsema, Tjalling Leenstra, Mariska W. F. Petrignani, Sylvia M. Bruisten, Liza Coyer, Anja J. M. Schreijer, Yvonne T. H. P. van Duijnhoven, Maarten F. Schim van der Loeff, Amy A. Matser

A randomized controlled trial on the effects of blue-blocking glasses compared to partial blue-blockers on sleep outcomes in the third trimester of pregnancy

Randi Liset, Janne Grønli, Roger E. Henriksen, Tone E. G. Henriksen, Roy M. Nilsen, Ståle Pallesen

Seroprevalence of SARS-CoV-2 antibodies and knowledge, attitude and practice toward COVID-19 in the Republic of Srpska-Bosnia & Herzegovina: A population-based study

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Understanding the role of village fund and administrative capacity in stunting reduction: Empirical evidence from Indonesia

Jul Indra, Khoirunurrofik Khoirunurrofik

Comprehensive profiling of bioactive compounds in germinated black soybeans via UHPLC-ESI-QTOF-MS/MS and their anti-Alzheimer's activity

Umair Shabbir, Akanksha Tyagi, Hun Ju Ham, Deog-Hwan Oh

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Carriage of antibiotic resistant bacteria in endangered and declining Australian pinniped pups

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María del Pilar Angarita-Díaz, Lilia Bernal-Cepeda, Leidy Bastidas-Legarda, Diana Forero-Escobar, Angélica Ricaurte-Avendaño, Julián Mora-Reina, Martha Vergara-Mercado, Alejandra Herrera-Herrera, Martha Rodríguez-Paz, Sandra Cáceres-Matta, Natalia Fortich-Mesa, Emilia María Ochoa-Acosta

Metformin exposure, maternal PCOS status and fetal venous liver circulation: A randomized, placebo-controlled study

Sindre Grindheim, Cathrine Ebbing, Henriette Odland Karlsen, Svein Magne Skulstad, Francisco Gómez Real, Marianne Lønnebotn, Tone Løvvik, Eszter

Assessing women's preferences towards tests that may reveal uncertain results from prenatal genomic testing: Development of attributes for a discrete choice experiment, using a mixed-methods design

Jennifer Hammond, Jasmijn E. Klapwijk, Sam Riedijk, Stina Lou, Kelly E. Ormond, Ida Vogel, Lisa Hui, Emma-Jane Sziepe, James Buchanan, Charlotta Ingvoldstad-Malmgren, Maria Johansson Soller, Eleanor Harding, Melissa Hill, Celine Lewis

Community monitoring of coliform pollution in Lake Tanganyika

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Logistic modeling to predict the minimum inhibitory concentration (MIC) of olive leaf extract (OLE) against *Listeria monocytogenes*

Renjie Du, Yuejun Qu, Min Zhao, Yanhong Liu, Phoebe X. Qi, Xingbin Sun

Identifying cow – level factors and farm characteristics associated with locomotion scores in dairy cows using cumulative link mixed models

Andreas W. Oehm, Roswitha Merle, Annegret Tautenhahn, K. Charlotte Jensen, Kerstin-Elisabeth Mueller, Melanie Feist, Yury Zablotzki

Diabetic retinopathy among type 2 diabetes mellitus patients in Sabah primary health clinics—*Addressing the underlying factors*

Nurul Athirah Naserrudin, Mohammad Saffree Jeffree, Nirmal Kaur, Syed Sharizman Syed Abdul Rahim, Mohd Yusof Ibrahim

Validation of a deep learning-based image analysis system to diagnose subclinical endometritis in dairy cows

Hafez Sadeghi, Hannah-Sophie Braun, Berner Panti, Geert Opsomer, Osvaldo Bogado Pascottini

The SH2 domain and kinase activity of JAK2 target JAK2 to centrosome and regulate cell growth and centrosome amplification

Aashirwad Shahi, Jacob Kahle, Chandler Hopkins, Maria Diakonova

Determining the factors of m-wallets adoption. A twofold SEM-ANN approach

Factors associated with treatment outcome of MDR/RR-TB patients treated with shorter injectable based regimen in West Java Indonesia

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Ronald Ssenyonga, Nelson K. Sewankambo, Solomon Kevin Mugagga, Esther Nakyejwe, Faith Chesire, Michael Mugisha, Allen Nsangi, Daniel Semakula, Matt Oxman, Laetitia Nyirazinyoye, Simon Lewin, Margaret Kaseje, Andrew D. Oxman, Sarah Rosenbaum

Detection of SARS-CoV-2 infection prevalence in 860 cancer patients with a combined screening procedure including triage, molecular nasopharyngeal swabs and rapid serological test. A report from the first epidemic wave

Anna Candoni, Giuseppe Petruzzellis, Alessandra Sperotto, Victoria Andreotti, Marco Giavarra, Carla Corvaja, Alessandro Minisini, Chiara Comuzzi, Carlo Tascini, Renato Fanin, Gianpiero Fasola

Early discontinuation of adjuvant chemotherapy in patients with early-stage pancreatic cancer correlates with inferior survival: A multicenter population-based cohort study

Javeria Muhammadzai, Kamal Haider, Michael Moser, Haji Chalchal, John Shaw, Donald Gardiner, Dorie-Anna Dueck, Osama Ahmed, Bryan Brunet, Mussawar Iqbal, Yigang Luo, Gavin Beck, Adnan Zaidi, Shahid Ahmed

Nest architecture and colony composition in two

populations of *Ectatomma ruidum* sp. 2 (*E. ruidum* species complex) in southwestern Colombia

Carlos Santamaría, Inge Armbrrecht, Jean-Paul Lachaud

Road-based line distance surveys overestimate densities of olive baboons

Christian Kiffner, Filipa M. D. Paciência, Grace Henrich, Rehema Kaitila, Idrissa S. Chuma, Pay Mbaryo, Sascha Knauf, John Kioko, Dietmar Zinner

Gut microbiota and butyrate contribute to nonalcoholic fatty liver disease in premenopause due to estrogen deficiency

Limin Liu, Qingsong Fu, Tiantian Li, Kai Shao, Xing Zhu, Yingzi Cong, Xiaoyun Zhao

An exploratory survey on community pharmacists' service provision for pregnant and lactating women in Sharjah, United Arab Emirates

Zahraa Abdullatif Akkad, Muaed Alomar, Subish Palaian

Undocumented: An examination of legal identity and education provision for children in Malaysia

Tharani Loganathan, Zhie X. Chan, Fikri Hassan, Zhen Ling Ong, Hazreen Abdul Majid

A gene expression biomarker for predictive toxicology to identify chemical modulators of NF- κ B

Katharine L. Korunes, Jie Liu, Ruili Huang, Menghang Xia, Keith A. Houck, J. Christopher Corton

Feasibility of EBUS-TBNA for histopathological and molecular diagnostics of NSCLC—A retrospective single-center experience

Marija Karadzovska-Kotevska, Hans Brunnström, Jaroslaw Kosieradzki, Lars Ek, Christel Estberg, Johan Staaf, Stefan Barath, Maria Planck

Robust and generalizable embryo selection based on artificial intelligence and time-lapse image sequences

Jørgen Berntsen, Jens Rimestad, Jacob Theilgaard Lassen, Dang Tran, Mikkel Fly Kragh

Computational prediction of intracellular targets of wild-type or mutant vesicular stomatitis matrix protein

Matthew C. Morris, Thomas M. Russell, Cole A. Lyman, Wesley K. Wong, Gordon Broderick, Maureen C. Ferran

Translating mentoring interventions research into practice: Evaluation of an evidence-based workshop for research mentors on developing trainees' scientific communication skills

Erin K. Dahlstrom, Christine Bell, Shine Chang, Hwa Young Lee, Cheryl B. Anderson, Annie Pham, Christine Maidl Pribbenow, Carrie A. Cameron

A low-cost, long-term underwater camera trap network coupled with deep residual learning image analysis

Stephanie M. Bilodeau, Austin W. H. Schwartz, Binfeng Xu, V. Paúl Pauca, Miles R. Silman

Oral nimodipine treatment has no effect on amyloid pathology or neuritic dystrophy in the 5XFAD mouse model of amyloidosis

Katherine R. Sadleir, Jelena Popovic, Ammaarah Khatri, Robert Vassar

Hierarchical development of dominance through the winner-loser effect and socio-spatial structure

Erik van Haeringen, Charlotte Hemelrijk

Social dynamics of core members in mixed-species bird flocks change across a gradient of foraging habitat quality

Katherine E. (Gentry) Richardson, Daniel P. Roche, Stephen G. Mugal, Nolan D. Lancaster, Kathryn E. Sieving, Todd M. Freeberg, Jeffrey R. Lucas

Less intensive antileukemic therapies (monotherapy and/or combination) for older adults with acute myeloid leukemia who are not candidates for intensive antileukemic therapy: A systematic review and meta-analysis

Luis Enrique Colunga-Lozano, Fernando Kenji Nampo, Arnav Agarwal, Pinkal Desai, Mark Litzow, Mikkael A. Sekeres, Gordon H. Guyatt, Romina Brignardello-Petersen

Azithromycin consumption during the COVID-19 pandemic in Croatia, 2020

Nikolina Bogdanić, Loris Močibob, Toni Vidović, Ana Soldo, Josip Begovać

The impact of COVID-19 on the dental hygienists: A cross-sectional study in the Lombardy first-wave outbreak

Elena M. Varoni, Lucrezia Cinquanta, Marta Rigoni, Giulia Di Valentin, Giovanni Lodi, Paola Muti, Andrea Sardella, Antonio Carrassi

Emergency department visits due to hand trauma and subsequent emergency hand surgery in three Finnish hospitals during the first and second waves of COVID-19 pandemic

Ilari Kuitunen, Jarkko Jokihaara, Ville Ponkilainen, Aleksi Reito, Juha Paloneva, Ville M. Mattila, Antti P. Launonen

User characteristics and service satisfaction of car sharing systems: Evidence from Hangzhou, China

Mengwei Chen, Yilin Sun, E. Owen D. Waygood, Jincheng Yu, Kai Zhu

Dynamic oxygenator blood volume during prolonged extracorporeal life support

Rik H. J. Hendrix, Eva R. Kurniawati, Sanne F. C. Schins, Jos G. Maessen, Patrick W. Weerwind

Preoperative nutritional evaluation of prostate cancer patients undergoing laparoscopic radical prostatectomy

Wang Shu, Wu Tao, Hu Chunyan, Fan Jie, Liu Yuan, Xu Yan, Zhang Huan, Xie Liang

Incidence of non-Hodgkin's lymphoma among adults in Sardinia, Italy

Giorgio Broccia, Jonathan Carter, Cansu Ozsin-Ozler, Federico Meloni, Sara De Matteis, Pierluigi Cocco

A socio-ecological examination of the primary school playground: Primary school pupil and staff perceived barriers and facilitators to a physically active playground during break and lunch-times

Michael Graham, Kevin Dixon, Liane B. Azevedo, Matthew D. Wright, Alison Innerd

Covid-19 and excess mortality in medicare beneficiaries

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Impact of Education 4.0 among engineering students for learning English language

V. Srivani, A. Hariharasudan, Nishad Nawaz, Sabina Ratajczak

Spatial approach for diagnosis of yield-limiting nutrients in smallholder agroecosystem landscape using population-based farm survey data

Stephen M. Ichami, George N. Karuku, Andrew M. Sila, Fredrick O. Ayuke, Keith D. Shepherd

mRNA Covid-19 vaccines in pregnancy: A systematic review

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Visual aids in ambulatory clinical practice: Experiences, perceptions and needs of patients and healthcare professionals

Catherine Hafner, Julie Schneider, Mélinée Schindler, Olivia Brillard

Predictors of lower limb fractures in general Japanese: NIPPON DATA90

Yoshino Saito, Katsuyuki Miura, Hisatomi Arima, Takehito Hayakawa, Naoyuki Takashima, Yoshikuni Kita, Nagako Okuda, Akira Fujiyoshi, Toshiyuki Iwahori, Naoko Miyagawa, Keiko Kondo, Sayuki Torii, Aya Kadota, Takayoshi Ohkubo, Akira Okayama, Tomonori Okamura, Hirotsugu Ueshima, for the NIPPON DATA90 Research Group

Iranian nursing students experiences regarding the status of e-learning during COVID-19 pandemic

Naiire Salmani, Imane Bagheri, Atena Dadgari

Biolayer interferometry for DNA-protein interactions

John K. Barrows, Michael W. Van Dyke

RAVAL trial: Protocol of an international, multi-centered, blinded, randomized controlled trial comparing robotic-assisted versus video-assisted lobectomy for early-stage lung cancer

Yogita S. Patel, Waël C. Hanna, Christine Fahim, Yaron Shargall, Thomas K. Waddell, Kazuhiro Yasufuku, Tiago N. Machuca, Mauricio Pipkin, Jean-Marc Baste, Feng Xie, Andrea Shiwcharan, Gary Foster, Lehana Thabane

Randomized controlled trial to test the efficacy of a brief, communication-based, substance use preventive intervention for parents of adolescents: Protocol for the SUPPER Project (Substance Use Prevention Promoted by Eating family meals Regularly)

Margie R. Skeer, Rachael A. Sabelli, Katherine M. Rancaño, Michelle Lee-Bravatti, Emma C. Ryan, Misha Eliasziw, Anthony Spirito

Correction: Influence of the shared epitope on the elicitation of experimental autoimmune arthritis biomarkers

Anastasios Karydis, Indra Sandal, Jiwen Luo, Amanda Prislovsky, Amanda Gamboa, Edward F. Rosloniec, David D. Brand

Transient dynamics of infection transmission in a simulated intensive care unit

Katelin C. Jackson, Christopher T. Short, Kellan R. Toman, Matthew S. Mietchen, Eric Lofgren, for the CDC MInD-Healthcare Program

Green returns to education: Does education affect pro-environmental attitudes and behaviors in China?

Qi Wang, Geng Niu, Xu Gan, Qiaoling Cai

More journal articles and fewer books: Publication practices in the social sciences in the 2010's

William E. Savage, Anthony J. Olejniczak

A systematic review on risk factors for khat chewing among adolescents in the African continent and Arabian Peninsula

Osman Abubakar Fiidow, Halimatus Sakdiah Minhat, Nor Afiah Mohd Zulkefli, Norliza Ahmad

Absence of association between host genetic mutations in the ORAI1 gene and COVID-19 fatality

Heba Shawer, Chew W. Cheng, Marc A. Bailey

Seasonal changes in the expression of insulin-like androgenic hormone (IAG) in the androgenic gland of the Jonah crab, *Cancer borealis*

Amanda Lawrence, Shadaesha Green, Tao Wang, Tsvetan Bachvaroff, J. Sook Chung

The Gyaros island marine reserve: A biodiversity hotspot in the eastern Mediterranean Sea

Dimitrios Damalas, Caterina Stamouli, Nikolaos Fotiadis, Maria Kikeri, Vasiliki Kousteni, Danai Mantopoulou-Palouka

The role of the common agricultural policy in contributing to jobs and growth in EU's rural areas

and the impact of employment on shaping rural development: Evidence from the Baltic States

Tomasz Grodzicki, Mateusz Jankiewicz

Combination of Xpert[®] MTB/RIF and Determine[™] TB-LAM Ag improves the diagnosis of extrapulmonary tuberculosis at Jimma University Medical Center, Oromia, Ethiopia

Asnake Simieneh, Mulualem Tadesse, Wakjira Kebede, Mulatu Gashaw, Gemed Abebe

Effect of collagen casing on the quality characteristics of fermented sausage

Xinlei Yan, Le Yang, Yanni Zhang, Wenying Han, Yan Duan

Organizational practices promoting employees' pro-environmental behaviors in a Visegrad Group country: How much does company ownership matter?

Katarzyna Piwowar-Sulej, Izabela Kołodziej

Cases of acute coronary syndrome and presumed cardiac death prior to arrival at an urban tertiary care hospital in Pakistan during the COVID-19 pandemic

Sana Sheikh, Wil Van Cleve, Vinod Kumar, Ghazal Peerwani, Saba Aijaz, Asad Pathan

Predictors of mortality among hospitalized COVID-19 patients and risk score formulation for prioritizing tertiary care—An experience from South India

Narendran Gopalan, Sumathi Senthil, Narmadha Lakshmi Prabakar, Thirumaran Senguttuvan, Adhin Bhaskar, Muthukumaran Jagannathan, Ravi Sivaraman, Jayalakshmi Ramasamy, Ponnuraja Chinnaiyan, Vijayalakshmi Arumugam, Banumathy Getrude, Gautham Sakthivel, Vignes Anand Srinivasalu, Dhanalakshmi Rajendran, Arunjith Nadukkandiyil, Vaishnavi Ravi, Sadiqa Nasreen Hifzour Rahamane, Nirmal Athur Paramasivam, Tamizhselvan Manoharan, Maheshwari Theyagarajan, Vineet Kumar Chadha, Mohan Natrajan, Baskaran Dhanaraj, Manoj Vasant Murhekar, Shanthi Malar Ramalingam, Padmapriyadarsini Chandrasekaran

Pre-training Model Based on Parallel Cross-Modality Fusion Layer

Xuwei Li, Dezhi Han, Chin-Chen Chang

Pretravel plans and discrepant trip experiences among travelers attending a tertiary care centre family travel medicine clinic

Jacqueline K. Wong, Nancy Nashid, Lisa G. Pell, Ray E. Lam, Debra M. Louch, Michelle E. Science, Shaun K. Morris

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Jelena Ilic-Zivojinovic, Igor Krdzic, Ana Jovanovic, Danka Vukasinovic, Branislav Ilic, Aleksandar Gavrilovic, Ivan Soldatovic

The effectiveness of scoring balloon angioplasty in the treatment of chronic thromboembolic pulmonary hypertension

Masao Takigami, Hideo Tsubata, Naohiko Nakanishi, Yuki Matsubara, Noriyuki Wakana, Kenji Yanishi, Kan Zen, Takeshi Nakamura, Satoaki Matoba

Clinical practice guidelines and consensus statements for antenatal oral healthcare: An assessment of their methodological quality and content of recommendations

Annika Wilson, Ha Hoang, Heather Bridgman, Leonard Crocombe, Silvana Bettiol

Integrating quantitative and qualitative approaches to assess wintertime illness-related absenteeism and its direct and indirect costs among the private sector in Ulaanbaatar

Mandukhai Ganbat, Nasantogtokh Erdenebileg, Chuluunbileg Batbold, Saruultuya Nergui, Ron Anderson, Clarence Wigfall, Narantsetseg Amarsanaa, Alex Heikens, Moiltmaa Sarantuya, David Warburton

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Helen Cleak, Sonya R. Osborne, Julian W. M. de Looze

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Daniel Schindel, Lena Mandl, Ralph Schilling, Andreas Meisel, Liane Schenk

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Marion Ripoche, Catherine Bouchard, Alejandra Irace-Cima, Patrick Leighton, Karine Thivierge

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Sabin Aslam, Sultan Habibullah Khan, Aftab Ahmad, Sriema Lalani Walawage, Abhaya M. Dandekar

Using a theory-informed approach to explore patient and staff perspectives on factors that influence clinical trial recruitment for patients with cirrhosis and small oesophageal varices

Clair Le Boutillier, Claire Snowden, Vishal Patel, Mark McPhail, Christopher Ward, Ben Carter, Ruhama Uddin, Ane Zamalloa, Vanessa Lawrence

Carbapenem-resistant *Enterobacteriaceae* in sink drains of 40 healthcare facilities in Sindh, Pakistan: A cross-sectional study

Paschal A. Apanga, Jamil Ahmed, Windy Tanner, Katherine Starcevich, James A. VanDerslice, Ubed Rehman, Najeebullah Channa, Scott Benson, Joshua V. Garn

Reduced blood pressure in sickle cell disease is associated with decreased angiotensin converting enzyme (ACE) activity and is not modulated by ACE inhibition

Pamela L. Brito, Alisson F. dos Santos, Hanan Chweih, Maria E. Favero, Erica M. F. Gotardo, Juliete A. F. Silva, Flavia C. Leonardo, Carla F. Franco-Penteado, Mariana G. de Oliveira, Wilson A. Ferreira Jr., Bruna C. Zaidan, Athanase Billis, Giorgio Baldanzi, Denise A. Mashima, Edson Antunes, Sara T. Olalla Saad, Fernando F. Costa, Nicola Conran

A novel bat pollination system involving obligate flower corolla removal has implications for global *Dillenia* conservation

Sophie Petit, Annette T. Scanlon, Alivereti Naikatini, Tara Pukala, Russell Schumann

3D engineered human gingiva fabricated with electrospun collagen scaffolds provides a platform for *in vitro* analysis of gingival seal to abutment materials

Wichurat Sakulpapong, Isabelle A. Clairmonte, Britani N. Blackstone, Binnaz Leblebicioglu, Heather M. Powell

Hidden fraction of Polish population immune to

SARS-CoV-2 in May 2021

Wiktoria Budziar, Katarzyna Gembara, Marek Harhala, Aleksander Szymczak, Natalia Jędruchiewicz, Krzysztof Baniecki, Aleksandra Pikies, Artur Nahorecki, Agnieszka Hoffmann, Amelia Kardaś, Alina Szewczyk-Dąbrowska, Tomasz Klimek, Zuzanna Kaźmierczak, Wojciech Witkiewicz, Kamil Barczyk, Krystyna Dąbrowska

Humidified and standard oxygen therapy in acute severe asthma in children (HUMOX): A pilot randomised controlled trial

Paul S. McNamara, Dannii Clayton, Caroline Burchett, Vanessa Compton, Matthew Peak, Janet Clark, Ashley P. Jones

Bullying victimization among internationally adopted adolescents: Psychosocial adjustment and moderating factors

Laura Ferrari, Simona Caravita, Sonia Ranieri, Elena Canzi, Rosa Rosnati

Systematic review and meta-analysis of myopia prevalence in African school children

Godwin Ovenseri-Ogbomo, Uchechukwu L. Osuagwu, Bernadine N. Ekpenyong, Kingsley Agho, Edgar Ekure, Antor O. Ndep, Stephen Ocansey, Khathutshelo Percy Mashige, Kovin Shunmugan Naidoo, Kelechi C. Ogbuehi

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Emmanuel R. Blankson, Patricia Nakie Tetteh, Prince Oppong, Francis Gbogbo

Inequalities in the progress of multiple chronic conditions: A systematic review of longitudinal studies

Rolla Mira, Tim Newton, Wael Sabbah

Cost-effectiveness of the TherMax blood warmer during continuous renal replacement therapy

Michael J. Blackowicz, Max Bell, Jorge Echeverri, Kai Harenski, Marcus E. Broman

Tolerability of nintedanib in the elderly with idiopathic pulmonary fibrosis: A single-center retrospective study

Masamichi Komatsu, Hiroshi Yamamoto, Takashi Ichiyama, Satoshi Kawakami, Takeshi Uehara, Yumi Yoshikawa, Yoshiaki Kitaguchi, Atsuhito Ushiki, Masanori Yasuo, Masayuki Hanaoka

Nano-insecticides against the black cutworm *Agrotis*

***ipsilon* (Lepidoptera: Noctuidae): Toxicity, development, enzyme activity, and DNA mutagenicity**

Mona Awad, El-Desoky S. Ibrahim, Engy I. Osman, Wael H. Elmenofy, Abdel Wahab M. Mahmoud, Mohamed A. M. Atia, Moataz A. M. Moustafa

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) are more prominent in retinal artery occlusion (RAO) compared to retinal vein occlusion (RVO)

Guanghao Qin, Fang He, Hongda Zhang, Emmanuel Eric Pazo, Guangzheng Dai, Qingchi Yao, Wei He, Ling Xu, Tiezhu Lin

Food habits and associated risk factors of depressed patients with cardiovascular disease

Hind E. Aljuhani, Ghedeir M. Alshammari, Ahmad N. AlHadi, Kholoud B. Alabdulkarem, Omar Sulaiman M. Albader, Mirza B. Baig, Mohammed Abdo Yahya

A scoping review of interventions to improve strength training participation

Jasmin K. Ma, Jennifer Leese, Stephanie Therrien, Alison M. Hoens, Karen Tsui, Linda C. Li

Magnetic resonance angiography derived predictors of progressive dilatation and surgery of the aortic root in Marfan syndrome

Julius Matthias Weinrich, Alexander Lenz, Gerhard Schön, Cyrus Behzadi, Isabel Molwitz, Frank Oliver Henes, Bjoern Philip Schoennagel, Gerhard Adam, Yskert von Kodolitsch, Peter Bannas

Help seeking behavior by women experiencing intimate partner violence in india: A machine learning approach to identifying risk factors

Nabamallika Dehingia, Arnab K. Dey, Lotus McDougal, Julian McAuley, Abhishek Singh, Anita Raj

Prevalence of stunting and its associated factors among children 6–59 months of age in pastoralist community, Northeast Ethiopia: A community-based cross-sectional study

Mulugeta Gebreayohanes, Awrajaw Dessie

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Joaquin Gabaldon, Ding Zhang, Lisa Lauderdale, Lance Miller, Matthew Johnson-Roberson, Kira Barton, K. Alex Shorter

Market impact shapes competitive advantage of investment strategies in financial markets

Wen-Juan Xu, Li-Xin Zhong

Impact of face masks and sunglasses on emotion recognition in South Koreans

Garam Kim, So Hyun Seong, Seok-Sung Hong, Eunsoo Choi

How do multi-morbidity and polypharmacy affect general practice attendance and referral rates? A retrospective analysis of consultations

Andrew O'Regan, Jane O'Doherty, Ray O'Connor, Walter Cullen, Vikram Niranjana, Liam Glynn, Ailish Hannigan

Antimicrobial stewardship: Attitudes and practices of healthcare providers in selected health facilities in Uganda

Isaac Magulu Kimbowa, Jaran Eriksen, Mary Nakafeero, Celestino Obua, Cecilia Stålsby Lundborg, Joan Kalyango, Moses Ocan

The rates and measurement of adherence to acamprosate in randomised controlled clinical trials: A systematic review

Kim Donoghue, Laura Hermann, Eileen Brobbin, Colin Drummond

Analysis of breast cancer survival in a northeastern Brazilian state based on prognostic factors: A retrospective cohort study

Adriane Dórea Marques, Alex Rodrigues Moura, Evânia Curvelo Hora, Érika de Abreu Costa Brito, Leonardo Souto Oliveira, Ionara Rodrigues Feitosa, Flavia Fernandes Freitas, Marcela Sampaio Lima, Íkaro Daniel de Carvalho Barreto, Marcell Oliveira Santos, Angela Maria da Silva, Carlos Anselmo Lima

Mineral biofortification of vegetables through soil-applied poultry mortality compost

Muhammad Umair Mubarak, Aysha Kiran, Ahmad Naeem Shahzad, Muhammad Farooq Qayyum, Muhammad Ishfaq, Khalid Mahmood, Abdul Wakeel

Sex- and age- dependent effect of pre-gestational chronic stress and mirtazapine treatment on neurobehavioral development of Wistar rat offspring

Mireia Viñas-Noguera, Kristína Csatlósová, Eva Šimončíková, Ezster Bögi, Eduard Ujházy, Michal Dubovický, Kristína Belovičová

The spike-and-slab elastic net as a classification tool

in Alzheimer's disease

Justin M. Leach, Lloyd J. Edwards, Rajesh Kana, Kristina Visscher, Nengjun Yi, Inmaculada Aban, for the Alzheimer's Disease Neuroimaging Initiative

“It must start with me, so it started with me”: A qualitative study of Project YES! youth peer mentor implementing experiences supporting adolescents and young adults living with HIV in Ndola, Zambia

Virginia M. Burke, Christiana Frimpong, Sam Miti, Jonathan K. Mwansa, Elizabeth A. Abrams, Katherine G. Merrill, Julie A. Denison

The role of hydraulic and geomorphic complexity in predicting invasive carp spawning potential: St. Croix River, Minnesota and Wisconsin, United States

Alan Kasprak, P. Ryan Jackson, Evan M. Lindroth, J. William Lund, Jeffrey R. Ziegeweid

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Melissa K. Peckins, Heidi B. Westerman, S. Alexandra Burt, Laura Murray, Martha Alves, Alison L. Miller, Ashley N. Gearhardt, Kelly L. Klump, Julie C. Lumeng, Luke W. Hyde

Perspectives on preparing for long-acting injectable treatment for HIV among consumer, clinical and nonclinical stakeholders: A qualitative study exploring the anticipated challenges and opportunities for implementation in Los Angeles County

Oluwadamilola Jolayemi, Laura M. Bogart, Erik D. Storholm, David Goodman-Meza, Elena Rosenberg-Carlson, Rebecca Cohen, Uyen Kao, Steve Shoptaw, Raphael J. Landovitz

Prevalence of biofilms in *Candida* spp. bloodstream infections: A meta-analysis

María Belén Atiencia-Carrera, Fausto Sebastián Cabezas-Mera, Eduardo Tejera, António Machado

Prognostic value of cardiac magnetic resonance in patients with aortic stenosis: A systematic review and meta-analysis

Chuan Zhang, Jie Liu, Shu Qin

Spatial variations in the biochemical potential of okra

[*Abelmoschus esculentus* L. (Moench)] leaf and fruit under field conditions

Samreen Sarwar, Nudrat Aisha Akram, Muhammad Hamzah Saleem, Sadia Zafar, Suliman Mohammed Alghanem, Muyassar H. Abualreesh, Aishah Alatawi, Shafaqat Ali

***Burkholderia pseudomallei* pathogenesis in human skin fibroblasts: A Bsa type III secretion system is involved in the invasion, multinucleated giant cell formation, and cellular damage**

Anek Kaewpan, Taksaon Duangurai, Amporn Rungruengkitkun, Watcharamat Muangkaew, Tapanee Kanjanapruthipong, Niramol Jitprasutwit, Sumate Ampawong, Passanesh Sukphopetch, Narisara Chantratita, Pornpan Pumirat

Costs, benefits, and cost-benefit of Collaborative Assessment and Management of Suicidality versus enhanced treatment as usual

Phoebe K. McCutchan, Brian T. Yates, David A. Jobes, Amanda H. Kerbrat, Katherine Anne Comtois

Linguistic metaconcepts can improve grammatical understanding in L1 education evidence from a Dutch quasi-experimental study

Jimmy van Rijt, Debra Myhill, Sven De Maeyer, Peter-Arno Coppen

Risk of HIV viral rebound in HIV infected patients on direct acting antivirals (DAAs) treatment for HCV

Giulia Morsica, Laura Galli, Emanuela Messina, Antonella Castagna, Sabrina Bagaglio, Stefania Salpietro, Della Torre Liviana, Caterina Uberti-Foppa, Hamid Hasson

Lateral access mechanism of LPA receptor probed by molecular dynamics simulation

Rieko Suenaga, Mizuki Takemoto, Asuka Inoue, Ryuichiro Ishitani, Osamu Nureki

Empirical estimation of marine phytoplankton assemblages in coastal and offshore areas using an *in situ* multi-wavelength excitation fluorometer

Taketoshi Kodama, Yukiko Taniuchi, Hiromi Kasai, Tamaha Yamaguchi, Misato Nakae, Yutaka Okumura

Inter- and intradialytic fluid volume changes and vascular stiffness parameters in patients on hemodialysis

Aya Lafta, Judy Ukrainetz, Sara Davison, Stephanie Thompson, Aminu Bello, Branko Braam

Development of an efficient antimicrobial susceptibility testing method with species identification by Nanopore sequencing of 16S rRNA amplicons

Yuto Kawai, Naoya Ozawa, Takako Fukuda, Noriyuki Suzuki, Kazuki Mikata

The development and pilot testing of a behavioral activation-based treatment for depressed mood and multiple health behavior change in patients with recent acute coronary syndrome

Emily C. Gathright, Katherine Diaz Vickery, Woubeshet Ayenew, Matthew C. Whited, Melissa Adkins-Hempel, Michelle Chrastek, Jill K. Carter, Rochelle K. Rosen, Wen-Chih Wu, Andrew M. Busch

Effects of a group-based weight management programme on anxiety and depression: A randomised controlled trial (RCT)

Laura Heath, Susan Jebb, Richard Stevens, Graham Wheeler, Amy Ahern, Emma Boyland, Jason Halford, Paul Aveyard

Preparedness of tertiary care hospitals to implement the national TB infection prevention and control guidelines in Bangladesh: A qualitative exploration

Md. Saiful Islam, Sayeeda Tarannum, Sayera Banu, Kamal Ibne Amin Chowdhury, Arifa Nazneen, Abrar Ahmad Chughtai, Holly Seale

Physical exercise is associated with a reduction in plasma levels of fractalkine, TGF- β 1, eotaxin-1 and IL-6 in younger adults with mobility disability

Parvin Kumar, Miranda Stiernborg, Anna Fogdell-Hahn, Kristoffer Månsson, Tomas Furmark, Daniel Berglind, Philippe A. Melas, Yvonne Forsell, Catharina Lavebratt

Use of hospital care services by chronic patients according to their characteristics and risk levels by adjusted morbidity groups

Jaime Barrio Cortes, María Martínez Cuevas, Almudena Castaño Reguillo, Mariana Bandeira de Oliveira, Miguel Martínez Martín, Carmen Suárez Fernández

Psychosis risk among pregnant women in Ghana

Samuel Adjorlolo, Gwendolyn Mensah, Caroline Dinam Badzi

The impact of interactive advertising on consumer engagement, recall, and understanding: A scoping

systematic review for informing regulatory science

Kristen Giombi, Catherine Viator, Juliana Hoover, Janice Tzeng, Helen W. Sullivan, Amie C. O'Donoghue, Brian G. Southwell, Leila C. Kahwati

ABO blood type and clinical characteristics of patients with ulcerative colitis: A hospital-based study in central Taiwan

Hsiang-Chun Lai, Jen-Wei Chou, Yi-Hua Wu, Po-Ju Huang, Ken-Sheng Cheng, Tsung-Wei Chen

Adapting to change: How has COVID-19 affected people's work and personal goals?

Laura M. Vowels, Rachel R. R. Francois-Walcott, Katherine B. Cernelley, Emily L. Checksfield

Essential medicines and technology for hypertension in primary healthcare facilities in Ebonyi State, Nigeria

Azuka Stephen Adeke, Chukwuma David Umeokonkwo, Muhammad Shakir Balogun, Augustine Nonso Odili

Predictive value of tumor mutational burden for immunotherapy in non-small cell lung cancer: A systematic review and meta-analysis

Guangxian Meng, Xiaowei Liu, Tian Ma, Desheng Lv, Ge Sun

Daily feeding rhythm linked to microbiome composition in two zooplankton species

Alaina Pfenning-Butterworth, Reilly O. Cooper, Clayton E. Cressler

Controlling an effector with eye movements: The effect of entangled sensory and motor responsibilities

John R. Schultz, Andrew B. Slifkin, Eric M. Scheerer

Unpredictability of the “when” influences prediction error processing of the “what” and “where”

Vera Tsogli, Sebastian Jentschke, Stefan Koelsch

Longitudinal increase in albumin–bilirubin score is associated with non-malignancy-related mortality and quality of life in patients with liver cirrhosis

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***In vivo* interferon-gamma induced changes in gene expression dramatically alter neutrophil phenotype**

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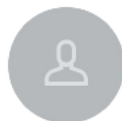
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From: Hoau-yan Wang
Sent time: 02/10/2022 10:47:02 AM
To: Steven Nicoll
Cc: Harry Acosta
Subject: renew animal protocol #1076
Attachments: protocol ^N1076 AD renew 2-10-2022.docx

Dear Dr. Nicoll and Mr. Acosta,

I hope this email find you well. I am sending this renewal of #1076 animal protocol in an effort to apply for a no-cost-extension of a R21 grant with Dr. Christine Li as PI and myself as co-PI. Under the design of the grant, Dr. Li will first assess selected genes in *c. elegans* before my lab start to assess these parameters in mouse brains. Unfortunately, the pandemics disrupted our plan and Dr. Li was unable to complete her experimental objectives. This leads to my lab to idle without using any mice under the approved protocol #1076 (2/10/2020). While we made our progress on establishing experimental procedures using frozen brains from the wild-type mice we collected in our earlier study, we are planning to move to mouse study during the coming year.

I will be grateful for your approval of the third year under the protocol #1076 so that we can send the approval letter to NIA to complete the no-cost-extension application in an effort to fulfill our planned experiments under the grant. If possible, can you please expedite this approval.

Thank you very much.

Best regards,

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.
Medical professor
CUNY SOM

The City College of NY
Institutional Animal Care & Use Committee

Instruction for submission of a RENEWAL (year two or year three) PROTOCOL

Instructions:

1. A separate form is required for each species.
2. The protocol submission form must be typed *within* the body of the form.
3. Typed name and signatures of the PI is required for every protocol to be reviewed.
4. Submit the signed original to Mr. Harry Acosta. Marshak Vivarium
5. If this research is part of a proposal for funding, submit the relevant grant proposal document with the hard copy of this protocol.
6. Email the protocol to: iacuc@ccny.cuny.edu

Notes:

1. The signed original must be received before the IACUC will review the protocol.
2. Most items are self-explanatory.
3. **Projects are approved for three years, with an annual continuing review required.**
Without the annual review, the project is terminated.
4. Justify the number of animals needed for the forthcoming year. The total number of animals have been approved for the project.
5. All animals shall be ordered by the Animal Care Facility not by the investigator.
6. All changes to the approved protocol must be discussed with the IACUC or attending Veterinarian prior to implementation. Significant changes require an amendment. Even minor changes require approval.
7. Each person with significant animal contact must have Health Clearance.

Use **Shade** or **Bold** to indicate changes in text of resubmitted materials.

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Call 650-8515 or fax 650-7545 if you need assistance

Preferred anesthesia, analgesia, and euthanasia in commonly used laboratory animal species

Small Animals

Mice	General Anesthetics	Inhalants – Isoflurane in bell jar (use hood) for short procedures (bleeding etc.) Isoflurane 1.5 – 2.5% to maintain surgical anesthetic Injectables: -Pentobarbital 40-60 mg/kg IP - Ketamine 1 mL of 100 mg/mL + xylazine 0.5 mL of 20 mg/mL + saline 8.5 mL: administer 0.1 mL/30 gm body weight IP Dose Ketamine 100 mg/kg + xylazine 10 mg/kg - Avertin (tribromoethanol) 250 mg/kg IP (0.2 ml/10 g, 1.2% sol) must be stored away from light to avoid decomposition
	Analgesics	Buprenorphine 0.1 – 0.5 mg/kg SQ, IP every 6-8 hours
	Sedation	70% CO ₂ / 30% O ₂ to effect Ketamine 44 mg/kg + acetylpromazine 0.75 mg/kg IP
	Euthanasia	100% CO ₂ to effect. <i>Note: neonates are resistant to CO₂ and require longer exposure. The chamber cannot be pre-charged prior to animal placement.</i>
Rats	General Anesthetics	Inhalants – Isoflurane in bell jar (use hood) for short procedures (bleeding etc.) Isoflurane 1.5 – 2.5% to maintain surgical anesthetic Injectables: - Pentobarbital 40-60 mg/kg IP - Ketamine 50 – 70 mg/kg with xylazine 5-7 mg/kg IP
	Analgesics	Buprenorphine 0.05 mg/kg SQ for every 8-12 hours
	Sedation	70% CO ₂ / 30% O ₂ to effect
	Euthanasia	100% CO ₂ to effect, Pentobarbital 100 mg/kg IP or IV
Rabbits	General Anesthetics	Inhalants: - Isoflurane 1.5 – 2.5% to maintain surgical anesthetic Injectables - Ketamine 35 mg/kg with xylazine 5 mg/kg IM. Incremental doses of 1/3 of the original ketamine-xylazine dose may be used to prolong anesthesia.
	Analgesics	Buprenorphine 0.03 – 0.05 mg/kg SQ every 6-12 hours
	Sedation	Ketamine and acepromazine mixed 1:1 v/v. Give 0.1 mL/kg IV Acepromazine 0.25 mg/kg IM.
	Euthanasia	Pentobarbital 100 mg/kg IV
Guinea Pigs	General Anesthetics	Inhalants: Isoflurane/ O ₂ via masks 1.5 – 2.5% to maintain surgical anesthetic Injectables Ketamine 40 – 100 mg/kg with xylazine 4 – 13 mg/kg IM Pentobarbital 15 – 40 mg/kg IP
	Analgesics	Buprenorphine 0.2 – 0.8 mg/kg SQ, IM every 6-12 hours
	Sedation	70% CO ₂ / 30% O ₂ to effect Diazepam or midazolam 1 – 5 mg/kg IM, IP Telazol 10 – 80 mg/kg IM, IP
	Euthanasia	100% CO ₂ to effect, Pentobarbital 100 mg/kg IV

PAIN OR DISTRESS CLASSIFICATION

Classification:

	B		C		D		E
--	----------	--	----------	--	----------	--	----------

Classification B: Animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery, but not yet used for such purposes.

Examples:

- Breeding colonies of animal species that are held in legal sized caging and handled in accordance with the Guide and other applicable regulations. Breeding colony includes parents and offspring.
- Newly acquired animals that are held in proper caging and handled in accordance with applicable regulations.
- Animals held under proper captive conditions or wild animals that are being observed.

Classification C: Animals upon which teaching, research, experiments, or tests will be conducted involving no pain, distress, or use of pain-relieving drugs.

Examples:

- Procedures performed correctly by trained personnel such as the administration of electrolytes/fluids, administration of oral medication, blood collection from a common peripheral vein per standard veterinary practice or catheterization of same, standard radiography, parenteral injections of non-irritating substances. (Injections, blood sampling, tube feeding, behavioral studies w/o restraint, blood pressure measurement, anesthesia without recovery for immediate organ removal, and/or minor surgical procedures under local anesthesia e.g. biopsies, catheterization.
- Euthanasia performed in accordance with the recommendations of the 2000 AVMA Panel on Euthanasia, utilizing procedures that produce rapid unconsciousness and subsequent humane death.

Classification D: Animals upon which experiments, teaching, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs will be used.

Examples:

- Major or multiple surgery conducted under anesthesia or prolonged non-survival surgical
- Administration of drugs, chemicals, toxins, or organisms that would be expected to produce pain or distress but which will be alleviated by analgesics. (Freund's adjuvant for immunization, ascites production, tumor production, etc.)
- Prolonged periods of physical restraint, induction of behavioral stress, induction of aggressive behavior producing self-mutilation, alteration of perceptual or motor functioning, application of noxious stimuli from which escape is impossible.
- Blood collection by more invasive routes such as intracardiac or periorbital collection under anesthesia.
- Minor surgical procedures conducted by trained personnel in accordance with standard veterinary practice such as biopsies, gonadectomy, exposure of blood vessels, chronic catheter implantation and laparoscopy performed under anesthesia.

Classification E: Animals upon which experiments, teaching, research, surgery, or tests will be conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs will adversely affect the procedures, results, or interpretation of the research, teaching, experiments, surgery, or tests.

Examples:

- Procedures producing pain or distress unrelieved by analgesics such as toxicity studies, microbial virulence testing, radiation sickness, and research on stress, shock, or pain. (Burn or severe trauma infliction on anesthetized animals with subsequent recovery, inducing psychotic-like behavior such as inescapable or terminal stress, use of muscle relaxants, paralytic for surgical restraint w/o anesthesia).
- Surgical and post surgical sequelae from invasion of body cavities, orthopedic procedures, dentistry or other hard or soft tissue damage that produces unrelieved pain or distress.
- Negative conditioning via electric shocks that would cause pain in humans.

Use a Separate Form for Each Species

This form must be typed and filled in completely to be reviewed

Call 650-8515 or fax 650-7545 for assistance

FOR IACUC USE ONLY

Annual Renewal ☐ 1st renewal ☐ 2nd renewal
 Protocol Number
 Review Date
 Approval Date

The City College of NY
 Institutional Animal Care & Use Committee

IACUC RENEWAL PROTOCOL FORM

FOR THE USE OF LIVE VERTEBRATES FOR RESEARCH OR
 TEACHING

ANNUAL RENEWAL OF PROTOCOL NO.: 1076 ☒ First ☐ Second

Section A – Investigator and Animal Use Information

Principal Investigator: Hou-Yan Wang E-mail Address: hywang@med.cuny.edu	Department: Molecular, Cellular and Biomedical Sciences	Mailing Address: CDI-3370 85 St. Nicholas Terrace Phone: 212-650-8813 [Office] 212-650-6682 [Lab]	Category for Pain and Distress: (required) <input type="checkbox"/> B <input checked="" type="checkbox"/> C <input type="checkbox"/> D <input type="checkbox"/> E
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Are you applying for, or receiving funds for the proposed experiments from external or
 Yes ☒ No ☐

If yes, identify the funding agency (ies) by name and I.D.# below (e.g., NHLBI,
 HL12345):

Agencies and numbers: NIA, Alzheimer Foundation, Pain Therapeutics Inc, Servier If relevant, your NIH assignment number must be provided. NIA 1R21AG065890-01		
Project Title: Translational Approaches to Understanding the Function of Human APP		
Species common name: Mice	Number of approved animals for the project: 420	Number of animals used to date: 0 Number of animals to be used for the upcoming year: 140


Investigator Assurance:

I will follow the ILAR Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act Regulations administered by the United States Department of Agriculture. I understand that these laws and regulations are applicable to all biomedical research projects using animals that are funded through and administered by City College. **As required by the Animal Welfare Act regulations, I hereby assure the IACUC that this experiment does not unnecessarily duplicate previous experiments. Furthermore,**

I will obtain the approval of the IACUC for any significant changes in the experiment before they are implemented.

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I accept responsibility for the scientific conduct of the project.

I also certify that the experiments described in this protocol faithfully reflect the work proposed in the sponsored project(s) identified on page one of this application. **("Per" signatures not acceptable)**

Signature: Principal Investigator: _____  _____ Date 2/10/2022

Typed faculty rank and/or title of PI: **Medical Professor** Date **2/10/2022**

This is an animal renewal for the above cited PROTOCOL, assigned IACUC number 1076

1. How many animals were used on this protocol in the preceding year? 0
2. Justify the need for the number of animals requested for the forthcoming year. (e.g. number of animals per group), and how you arrived at this number, i.e., power analysis, or the like.

The number of mice used in this project takes into account the following parameters to be assayed: biochemical study, immunohistochemical analysis and electrophysiological assessment after rTMS. Group differences on each of these experiments will be tested with significance level of 0.05 or better. Variation in each of those experiments is about 10-15%. A power of 80% is set for those parameters. A two-way ANOVA followed by Newman-Keuls for multiple comparisons and two-tailed Student's t test will be used in analysis of the data. Based on power calculation, a reliable and meaningful statistical evaluation can be obtained when minimal of 8 animals per group are used. To increase the statistical power, we intend to use 10 animals for each experiment (5 males, 5 females). Each brain tissues obtained will be used in many experimental conditions if size of the tissue is not a limiting factor. This design will increase statistical power and reduce the number of mice that are required to test a given experimental question.

Distribution of animals for the study

- (1) **To examine the effects of knocking down APP gene levels on insulin receptor signaling in diverse brain areas.**

	<u>E129 Wild-type</u>	
	Male	Female
3-month-old	5	5
7-month-old	5	5

(2) To examine the effects of knocking down APP gene levels on $\alpha 7$ nicotinic receptor signaling in diverse brain areas.

	<u>E129 Wild-type</u>		<u>AD transgenic</u>	
	Male	Female	Male	Female
3-month-old	5	5	5	5
7-month-old	5	5	5	5

(3) To probe synaptic and dendritic changes following APP gene knockdown.

	<u>E129 Wild-type</u>		<u>AD transgenic</u>	
	Male	Female	Male	Female
3-month-old	5	5	5	5
7-month-old	5	5	5	5

(4) To assess the function of APP interactors following APP gene knockdown.

	<u>E129 Wild-type</u>		<u>AD transgenic</u>	
	Male	Female	Male	Female
3-month-old	5	5	5	5
7-month-old	5	5	5	5

Total: 140

3. Describe in non-technical terms what was learned (PROGRESS REPORT)

Due to the pandemics, the experiments planned by Dr. Christine Li to support NIA 1R21AG065890-01 was not completed. Since our animal study depends on the results from Dr. Li's experiments on c. elegans, under the protocol #1076, we have not used any mice to obtain necessary data to support the grant.

In preparation of the mouse experiments, we used diverse brain areas from frozen brain tissues from our earlier study wild-type mice were used to decipher changes in signaling pathways associated with $\alpha 7$ nicotinic and insulin receptors in response to direct brain injection of β -amyloid peptides ($A\beta$) such as $A\beta_{42}$ the best known causal factors of Alzheimer's disease (AD). Our data show that (1) $A\beta$ peptides activates specific $\alpha 7$ nicotinic receptor but blocks insulin receptor associated signaling pathways, and (2)

heightened A β induced α 7 nicotinic receptor-dependent signaling lead to abnormalities in cell structural networks and eventual breakdown of neuronal connections, and (3) A β induced inhibition of insulin receptor signaling may contribute to insulin resistance observed in Alzheimer's disease brains. Since A β is one of the most prominent causative factors for AD, the data derived thus far enable us to fully appreciate the pathway through which A β may induce cognitive and memory impairment, either independently or in combination with other pathogenic factors such as antibodies that attack specific brain targets, in Alzheimer's disease patients.

Manuscript published

1. Wang HY, Stucky A, Liu J, Shen C, Trocme-Thibierge C, Morain P (2009) Dissociating β -amyloid from α 7 nicotinic acetylcholine receptor by a novel therapeutic agent, S 24795 normalizes α 7 nicotinic acetylcholine and NMDA receptor function in Alzheimer's disease brain. J Neurosci 29: 10961-10973.
2. Wang HY, Bakshi K, Frankfurt M, Stucky A, Goberdhan M, Shah SM, Burns LH (2012) Reducing Amyloid-related Alzheimer's disease pathogenesis by a small molecule targeting filamin A. J Neurosci 32(29): 9773-9784.
3. Wang HY, Lee K-C, Pei Z, Khan A, Bakshi K, Burns LH (2017) PTI-125 binds and reverses an altered conformation filamin A to reduce Alzheimer's disease pathogenesis. Neurobiol Aging 55: 99-114.
4. Describe how the animals reacted to the procedures, were there any adverse events that affected animal use, welfare, morbidity or mortality.
Not observed
5. Discuss any changes to the planned use of animals and/or objective.
 - a. ☒ No Changes
 - b. ☐ Changes

Discuss changes here:
6. Since the last IACUC approval, have alternatives to the use of animals become available that could be substituted to achieve your specific project aims?
No ☒ Yes ☐
7. Were Radiation Safety or Research Laboratory Biosafety Committee approval needed previously?
No ☒ Yes ☐ *If Yes – Include current approval with this application.*

8. New Literature search is **only** required for all category E protocols, and protocols involving covered species (e.g; guinea pigs, rabbits, ferrets, cats). Purpose bred mice and rats are not covered species so no new literature search is necessary for them.

Are these alternatives to animals? Yes ☐ No ☒

If the procedures cause pain or distress (e.g., category D or E experiments), Federal regulations require that you provide a written narrative of the methods used to determine whether or not alternatives exist to procedures, which may cause pain or distress.

The narrative should include:

- **Two** databases or other sources that must be consulted [such as, Biological Abstracts, Index Medicus, Agricola, PubMed, Current Research Information Service (CRIS) and Animal Welfare Information Center (AWIC)];
- Date of the search: e.g. 01/29/2020
- Years covered by the search: e.g. 1964 – 2020
- Key words and/or search strategy: e.g. identify painful procedure such as: ascites, blood draw in rabbits, etc.
- Other methods used to determine whether there are no alternatives.

Enter description of the literature search here:

A search for alternatives to painful procedures was performed on January 29th, 2022 using AGRICOLA (1970-2021) that searches alternative methods to study brain tissue response to autoantibodies and/or β -amyloid. This search yields no alternative methods for the current procedure used in this proposed study. In addition, no paper describes alternatives to painful procedures when LPS and distress were used as the key words. In addition, the above mentioned databases were consulted to identify painful procedure using intraventricular injection, pain, infection as key words. There were no indication of pain or infection were indicated using this procedure.

PubMed was used to search for research redundancy in β -amyloid associated pathologies and brain autoantibodies from 1970 to 2021. Key words used were β -amyloid, Alzheimer's disease, brain injection, cognitive impairment and brain. There are 102 articles have investigated the effect of β -amyloid and autoantibodies induced pathologies (6 from my laboratory). However, other than publications from my laboratories none of these investigations have studied the parameters this planned study intend to achieve, especially evaluation of novel Alzheimer's disease therapeutic agents. In this regard, the proposed study is novel.

8. Does this protocol involve survival surgery?

No ☒ Skip to 9 (below).

Yes ☐ **Complete the following:**

Location of Surgical Site

Date of IACUC inspection and approval

All changes from the last approval must be discussed with the Attending Veterinarian (Dr. Popilskis):

Have there been any changes in the protocol since the last approval?

No ☐ Skip to 9 (below).

Yes ☐ **Complete the following:**

Discuss changes and provide addendum describing any changes from the last submission:

9. Signature: _____

PROTOCOL NUMBER to be renewed: 1076



PI Signature:

Date: 2/10/2022

10. Persons to be contacted in case of emergency.

Name: Hoau-Yan Wang
Title: Ph.D.
Position: Medical Professor

Telephone number: 212-650-8813, 212-650-6682
Cell phone number: 215-917-7765

11. Provide the following information for ALL RESEARCH PERSONNEL involved in animal contact:

<p>Name: Hoau-Yan Wang, Ph.D.</p>	<p>Indicate the person's <u>role on the project</u>? Describe the qualifications and experience with the <u>procedures</u> and the <u>species</u> used in the experiments:</p> <p>He has 25+ years of experience in behavioral monitoring, tissue extraction, injection and euthanization of the rats. CITI IACUC completion report 713185</p>	<p>Clearances: Policy: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Health Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Facility Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Wet Lab Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> CITI Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>
<p>Name: Kuo-Chieh Lee, MS</p>	<p>Indicate the person's <u>role on the project</u>? Describe the qualifications and experience with the <u>procedures</u> and the <u>species</u> used in the experiments:</p> <p>Has performed injections and euthanization and tissue extraction on rats for 20 years. CITI IACUC completion report 5314494</p>	<p>Clearances: Policy: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Health Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Facility Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Wet Lab Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> CITI Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>

Name:	Indicate the person's <u>role on the project</u> ? Describe the qualifications and experience with the <u>procedures</u> and the <u>species</u> used in the experiments:	Clearances: Policy: Yes <input type="checkbox"/> No <input type="checkbox"/> Health Yes <input type="checkbox"/> No <input type="checkbox"/> Facility Yes <input type="checkbox"/> No <input type="checkbox"/> Wet Lab Yes <input type="checkbox"/> No <input type="checkbox"/> CITI Yes <input type="checkbox"/> No <input type="checkbox"/>
Name:	Indicate the person's <u>role on the project</u> ? Describe the qualifications and experience with the <u>procedures</u> and the <u>species</u> used in the experiments:	Clearances: Policy: Yes <input type="checkbox"/> No <input type="checkbox"/> Health Yes <input type="checkbox"/> No <input type="checkbox"/> Facility Yes <input type="checkbox"/> No <input type="checkbox"/> Wet Lab Yes <input type="checkbox"/> No <input type="checkbox"/> CITI Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>

Each person with significant animal contact must have Health clearance.

IACUC USE BELOW THIS LINE

IACUC AUTHORIZATION

APPROVAL: Signature: _____
--

From: Oluebubechukwu C Ezeh
Sent time: 02/14/2022 11:00:49 AM
To: Hoau-yan Wang
Cc: Awards
Subject: Re: Hahn S36601 R01MH116463 sub amendment
Attachments: FCOI_72762-0003 (TJU) Wang_2.9.22.pdf

Good evening Prof. Wang,

Please see the updated forms attached- I combined them into a single pdf, along with your response.

Regards,
Ebube Ezeh
Grants Assistant – Post Award
Pronouns - She/Her

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue, Shepard Hall - Suite 16
New York, NY 10031
Phone: 212-650-7000
GSP - <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Hoau-yan Wang
Sent: Wednesday, February 9, 2022 5:33 PM
To: Oluebubechukwu C Ezeh
Subject: Re: Hahn S36601 R01MH116463 sub amendment

Ebube,

Please kindly send a copy of the form1 and 2 for my record after you change the date.

Thank you.

Best,

Hoau-Yan Wang

From: Oluebubechukwu C Ezeh
Sent: Wednesday, February 9, 2022 4:39 PM
To: Hoau-yan Wang
Cc: Holli-Anne S Tai; Awards
Subject: Fw: Hahn S36601 R01MH116463 sub amendment

Dear Prof. Wang,

We received the attached amendment for PRSY# 72762-0003. Also attached is the last valid FCOI documentation that we have on file for this project. Before we submit the CIF to Legal, kindly review and let us know whether there have been any changes since last year.

Thank you,
Ebube Ezeh
Grants Assistant – Post Award
Pronouns - She/Her

Grants and Sponsored Programs
The City College of New York
160 Convent Avenue, Shepard Hall - Suite 16
New York, NY 10031
Phone: 212-650-7000
GSP - <https://www.ccny.cuny.edu/research/gsp>
PARS - <https://www.ccny.cuny.edu/research/pars>

From: Sawyer, Jay <Jay_Sawyer@rfcunyc.org>
Sent: Monday, February 7, 2022 9:32 AM

To: Legal Affairs; Awards
Cc: Li, Yan; Brigid Czyszczonec
Subject: [EXTERNAL] FW: Hahn S36601 R01MH116463 sub amendment

Good morning, Legal Affairs and CCNY Awards-

Please log in the attached Amendment No. 2 to RF Contract Log No. 23129 for review and processing.

Thank you,

Jay Sawyer
Paralegal Associate
Office of Legal Affairs
212-417-8366
Jay_Sawyer@rfcuny.org
<http://www.rfcuny.org>

PLEASE NOTE OUR OFFICE IS CURRENTLY TELEWORKING DUE TO THE HEALTH CRISIS, SO EMAIL IS THE MOST RELIABLE MEANS OF COMMUNICATION. THANK YOU FOR YOUR PATIENCE AND UNDERSTANDING.

From: Brigid Czyszczonec <Brigid.Czyszczonec@jefferson.edu>
Sent: Monday, February 7, 2022 9:08 AM
To: Sawyer, Jay <Jay_Sawyer@rfcuny.org>; Li, Yan <Yan_Bing_Li@rfcuny.org>; Awards <awards@ccny.cuny.edu>
Cc: Feratovic, Harijana <Harijana_Feratovic@rfcuny.org>; Hoau-yan Wang <hwang@ccny.cuny.edu>
Subject: Hahn S36601 R01MH116463 sub amendment

Hello. Attached find the draft sub agreement for the project referenced above. Please review, sign and return to me. Let me know if you have questions or concerns. Thanks.

Brigid Czyszczonec
Subawards Manager
Jefferson – Center City Campus
833 Chestnut Street, Suite 900
Philadelphia, PA 19107
Phone: 215.503.2056
Brigid.Czyszczonec@Jefferson.edu
Website: <http://www.Jefferson.edu>

[Please provide feedback on ORA here](#)



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CUNY Significant Financial Interest Disclosure (SFI) Form for PHS Funded Research

* to be completed by each investigator on the project

Name of Investigator: Hoau-Yan Wang

Phone: 212-650-8813

Email: hywang@med.cuny.edu

CUNY College/Site of Research: CUNY School of Medicine/CDI-3211

Title of Research Project: mGluR5 hypoactivity is integral to glutamatergic dysregulation in schizophrenia

Funding Agency: NIMH/Thomas Jefferson University

Disclosure submission for:

- ☒ New funding proposal or application
☐ Annual progress report
☐ Material change in a previously disclosed SFI
☐ Discovery or acquisition of a new SFI
☐ New investigator joining an ongoing research project at CUNY

Please indicate whether **you, your spouse or your dependent children** have any of the following financial interests that may reasonably be related to your institutional responsibilities¹:

Please note that this form must be completed by all individuals responsible for the design, conduct, or reporting of research.

EXCLUSIONS: This does NOT apply to any salary, royalties, or other remuneration paid by CUNY if you are currently employed or otherwise appointed by CUNY; income from seminars, lectures, or teaching engagements sponsored by a **United States** federal, state, or local government agency, an institution of higher education², an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education; or income from service on advisory committees or review panels for such agencies or other entities.

1. With respect to any publicly traded entity , a total of (a) salary and any payment for services not otherwise identified as a salary (for example, consulting fees, honoraria, paid authorship) received from the entity in the past 12 months <u>AND</u> (b) the value of any equity interest in the entity (including any stock, stock option, or other ownership interest), as determined through reference to public prices or other reasonable measures of fair market value as of the date of this disclosure, in excess of \$5,000.	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
2. With respect to any non-publicly traded entity , a total of salary and any payment for services not otherwise identified as a salary (for example, consulting fees, honoraria, paid authorship) received from the entity in the past 12 months in excess of \$5,000.	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

¹ Professional responsibilities on behalf of CUNY, performed in the course of and within the scope of your appointment or employment by CUNY, which may include activities such as research, research consultation, teaching, professional practice, institutional committee memberships, and service on panels such as Institutional Review Boards.

² As defined at 20USC1001(a)

3. With respect to any non-publicly traded entity , any equity interest in the entity (including any stock, stock option, or other ownership interest), regardless of value.	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
4. Intellectual property rights and interests (for example, patents and copyrights).	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

For **yourself** ONLY:

5. If you are responsible for developing, discovering, or creating CUNY-owned intellectual property, are you aware of the acquisition or intention to acquire ownership of, or a license to, that intellectual property by any corporation, partnership, or other legal entity (excluding entities controlled by the U.S. government, the State or City of New York, or CUNY) in or from which you have a financial interest described in any of Items 1, 2, or 3 above? NOTE: If you answered "Yes" to this question you must also complete the CUNY Acquisition of or License to CUNY Intellectual Property (CALCIP) form and submit it to your College Conflicts Officer and the Director of the CUNY Technology Commercialization Office (TCO).	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A <input type="checkbox"/>
6. Do you teach, supervise, or otherwise have control over any student or postdoctoral associate at CUNY who might be involved in work for any corporation, partnership, or other legal entity (excluding entities controlled by the U.S. government, the State or City of New York, or CUNY) in or from which you have a financial interest described in any of Items 1, 2, or 3 above?	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
7. Any reimbursed or sponsored travel (<i>i.e.</i> , travel paid on your behalf and not reimbursed to you so that the exact monetary value may not be readily available), related to your institutional responsibilities. EXCLUSIONS: This does NOT apply to travel reimbursed or sponsored by a United States federal, state or local government agency, an institution of higher education ³ , an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education.	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

If you responded "yes" to any of the questions above, you must also complete a CUNY Significant Financial Interest Supplement Form. This Form and the Supplement Form, if required, should be submitted to your College Conflicts Officer, with a copy to your Grants Officer.

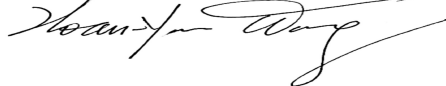
If you have any questions about this Form or the information it seeks, please refer to the research conflict of interest web site at <http://www.cuny.edu/research/compliance/conflictinterestpolicy.html>.

Agreement & Signature:

By signing this form, I certify the following:

- The above statements are complete, true and accurate.
- I will submit an updated Form annually, prior to submission of annual progress reports; and also within 30 days of any material change to the above-disclosed Significant Financial Interest(s) or discovering or acquiring a new Significant Financial Interest.
- I will comply with all applicable regulations, CUNY policies, sponsor requirements and any conflict of interest management and oversight plans issued by CUNY.

³ As defined at 20USC1001(a)



2/9/2022

Signature

Date

Name of Investigator: Hoau-Yan Wang

Nature of Employment/Affiliation with CUNY (e.g. Full-time Faculty, Adjunct Faculty, Independent Contractor, Full-time Staff, Post Doc, Student, etc.): Medical Professor

CUNY College/Site of Research: CUNY School of Medicine/CDI-3211

Title of Research Project: mGluR5 hypoactivity is integral to glutamatergic dysfunction in schizophrenia

Funding Source: NIMH/ Thomas Jefferson University

Does this project involve human subjects research? Yes ☐ No ☒

Please provide requested details regarding your positive responses made on the CUNY Significant Financial Interest Disclosure Form and, if necessary, use additional Supplement Forms:

1. Salary and any payment for other services (for example, consulting fees, honoraria, paid authorship) received from a **publicly traded entity** in the past 12 months:

Name of person or persons (and relationship to self) to whom the salary or payment was made:

Hoau-Yan Wang

Name of **publicly traded entity**:

CASSAVA Sciences

Nature of salary, payment for other services, or royalties (description of work performed for remuneration):

Consultancy

Amount of salary or payment received:

\$24,000

Relationship to your institutional responsibilities:

None

2. Equity interest (including any stock, stock option, or other ownership interest) in a **publicly traded entity**:

Name of person or persons (and relationship to self) who hold(s) the equity interest:

Hoau-Yan Wang

Name of **publicly traded entity**:

CASSAVA Sciences

Type of equity interest:

stock, stock option

Current value of equity interest:

\$125,000

Relationship to your institutional responsibilities:

None

3. Salary and any payment for other services (for example, consulting fees, honoraria, paid authorship) received from a **non-publicly traded entity** in the past 12 months:

Name of person or persons (and relationship to self) to whom the salary or payment was made:

N/A

Name of **non-publicly traded entity**:

Nature of salary, payment for other services, or royalties (description of work performed for remuneration):

Amount of salary or payment received:

Relationship to your institutional responsibilities:

4. Equity interest (including any stock, stock option, or other ownership interest) in a **non-publicly traded entity**:

Name of person or persons (and relationship to self) who hold(s) the equity interest:

N/A

Name of **non-publicly traded entity**:

Type of equity interest:

Relationship to your institutional responsibilities:

5. Intellectual property rights and interests (for example, patents and copyrights):

Owner(s) of the intellectual property:

Hoau-Yan Wang, Lindsay H. Burns

Description of the intellectual property:

compounds for Alzheimer's disease treatment

Description of any royalties or income you currently receive or may receive in the future:

None

Relationship to your institutional responsibilities:

None

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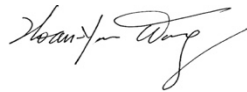
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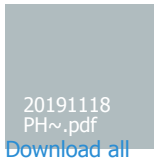
Hoau-yan Wang

Wed 2/9/2022 5:29 PM

To: Oluebubechukwu C Ezech;

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Ebube,

I have edited the form 2 (attached). However, I was unable to change the date on both form 1 and 2. Can you please kindly change the date to 2/09/2022. Otherwise, the budget is fine.

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Best,

Hoau-Yan Wang

From: Oluebubechukwu C Ezech

Sent: Wednesday, February 9, 2022 4:39 PM

To: Hoau-yan Wang

Cc: Holli-Anne S Tai; Awards

Subject: Fw: Hahn S36601 R01MH116463 sub amendment

Dear Prof. Wang,

We received the attached amendment for PRSY# 72762-0003. Also attached is the last valid FCOI documentation that we have on file for this project. Before we submit the CIF to Legal, kindly review and let us know whether there have been any changes since last year.

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From: Khosrow Kashfi <drkho@verizon.net>
Sent time: 02/20/2022 08:03:15 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Fwd: Book chapter revision required
Attachments: PastedGraphic-1.tiff ATT00001.htm Chapter 11-FF 197-215.docx ATT00002.htm Chapter 11 Comments.docx ATT00003.htm

Dear Hoau-Yan

Hope all is well. Please see below.

Thanks

Kho

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Editor: International Journal of Molecular Sciences
Associate Medical Professor
Department of Molecular, Cellular & Biomedical Sciences
City University of New York School of Medicine
160 Convent Avenue, New York, NY 10031
Tel: (212) 650-6641
Fax: (212) 650-7692
[Email: kashfi@med.cuny.edu](mailto:kashfi@med.cuny.edu)
Website: www.avicennatherapeutics.com

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CHAPTER 11

Brain Insulin Resistance, Nitric Oxide and Alzheimer's Disease Pathology

Zhe Pei¹, Kuo-Chieh Lee¹, Amber Khan^{1,2}, Hoau-Yan Wang^{1,2*}

¹Department of Molecular, Cellular and Biomedical Sciences, City University of New York School of Medicine, 160 Convent Avenue, New York, New York 10031, USA.

²Department of Biology, Neuroscience Program, Graduate School of The City University of New York, 365 Fifth Avenue, New York, New York 10061, U.S.A.

Abstract: Alzheimer's disease (AD) is a devastating age-related neurodegenerative disease characterized by progressive pathological changes and functional and cognitive impairments. Among several pathological mechanisms, brain insulin resistance appears to contribute significantly to the pathology and cognitive deficits. Brain insulin resistance has been demonstrated in animal models of AD and postmortem human brain tissue from patients with AD dementia. Studies conducted in AD models and in humans suggest that attenuating brain insulin resistance by agents such as glucagon-like peptide1 (GLP-1) analogs and small molecule drug candidate PTI-125 also reduces many AD pathologic features and symptoms. Insulin affects NO levels by activating endothelial and neuronal nitric oxide synthase (eNOS, nNOS), and systemic insulin resistance has been linked to reduced nitric oxide (NO) bioavailability. Increasing NO availability reduces systemic insulin resistance, and the insulin signaling pathway is associated with activation of eNOS, implying a causal relationship. This chapter explores this relationship and the role of impaired NO availability in brain insulin resistance in AD dementia.

Keywords: CaMKII (calcium-calmodulin-dependent kinase II), gamma-Aminobutyric acid (GABA) receptor, glutamate, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, insulin resistance, NADPH oxidase 2 (Nox2), NADPH oxidase subunit NOX2, NG-monomethyl-L-arginine (L-NMMA), nitric oxide synthase (NOS), N-methyl-D-aspartate (NMDA) receptor, reactive oxygen species (ROS), type-2 diabetes (T2D)

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that includes many underlying pathophysiological changes that gradually lead to dementia [1-4]. The lack of effective treatments for AD dementia and the enormous socioeconomic

***Corresponding author Hoau-Yan Wang:** Department of Molecular, Cellular and Biomedical Sciences, City University of New York School of Medicine, 160 Convent Avenue, New York, NY 10031, USA. Email: hywang@med.cuny.edu

impact to society underscores the urgent need to develop effective treatments for this devastating disease [5, 6]. Many promising therapeutic agents in development for AD aim to reduce brain insulin resistance, a common early pathological feature of AD dementia with or without diabetes [7-10]. The pathological factors that contribute to brain insulin resistance are not fully understood. Nitric oxide (NO) is one of several biological molecules that interact with the insulin signaling pathway bi-directionally. In this chapter, we discuss the role of the NO system in the development of brain insulin resistance and explore the possibility that manipulating NO might be therapeutic for AD dementia.

INSULIN RECEPTOR SIGNALING AND ITS INTERACTION WITH NO SYSTEM

Insulin, a peptide secreted by the beta (β) cells in pancreas, crosses the blood-brain barrier in a regulated and saturable manner to enter the central nervous system (CNS). Although de novo synthesis of insulin in the brain is still debated, support for local brain insulin synthesis includes the detection of C-peptide and insulin mRNA in various brain regions in humans with the mRNA levels were especially high in hippocampus, striatum, and thalamus [11-15]. Insulin expression is decreased in AD compared to normal controls [14].

Insulin produces its cellular actions by binding its cognate insulin receptors (IRs) present on all cells including neurons and glia in brain regions such as olfactory bulb, cerebral cortex, hippocampus, hypothalamus and amygdala [8, 16, 17]. IRs are more concentrated in neurons relative to glial cells and are particularly highly expressed in post-synaptic densities [8, 16-18]. Upon insulin binding to the extracellular α -subunit domains of IRs, the intracellular IR β -subunit domains dimerize, leading to activation of their intrinsic tyrosine kinase to cause autophosphorylation. Insulin-like growth factor-1 (IGF-1) also binds and activates IRs, although with lower affinity, leading to the same trophic and metabolic actions as insulin, including neuronal plasticity [19, 20].

In addition to regulation of glucose utilization and homeostasis, insulin activates PI3K-Akt (Phosphoinositide 3-kinase - Protein kinase B/Akt) and mTOR (Mechanistic target of rapamycin) signaling via recruitment of insulin receptor substrate family (IRS) proteins such as IRS-1 and IRS-2. This insulin-stimulated PI3K/Akt/mTOR pathway has many other functions in cells throughout the body including the neuronal and vascular systems. Insulin activates Akt via IRS1-PI3K to directly phosphorylate serine1177 residues and activate vascular endothelial NO synthase (eNOS), leading to NO production and consequent vasodilation and

increased capillary blood flow [21, 22]. Insulin signaling promoting NO-mediated vasodilation in the brain is supported by increased blood flow in the insular cortex following intranasal insulin in men, independent of cortisol manipulation [23]. Expression of eNOS has been shown not only in endothelium of the cerebrovasculature, but more importantly, in dendritic spines [24]. Innate eNOS activity confers protection against secondary neuronal injury; thus, impaired eNOS due to insufficient insulin signaling in the brain can conceivably contribute to pathologies in AD leading to cognitive impairments [25].

Insulin has been shown to modulate a wide range of neuronal function. Insulin regulates 1) trafficking of ligand-gated ion channels, 2) expression and localization of GABA (γ -Aminobutyric acid), NMDA (N-Methyl-D-aspartic acid or N-Methyl-D-aspartate), and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, 3) catecholamine release and uptake, and 4) synaptic plasticity shown by long-term potentiation (LTP) and depression (LTD) in a NMDA receptor and PI3K dependent manner [26-29]. Insulin also promotes dendritic spine formation and excitatory synaptic development, and insulin regulates the development and health of excitatory synapses by activating PI3K/Akt/mTOR and Rac1/Cdc42 signaling [30].

Activation of the NMDA receptor recruits and activates neuronal NO synthase (nNOS) via Akt- and CaMKII (Ca^{2+} /calmodulin-dependent protein kinase II) - mediated phosphorylation of nNOS to promote production of NO in the postsynaptic field [31, 32]. The activation of nNOS was also found to elevate AMPA receptor levels [32]. Thus, insulin can increase NO production in postsynaptic neurons by stimulating nNOS via activation of NMDA receptors. Increased NO promotes NADPH oxidase 2 (NOX2)-dependent ROS production postsynaptically, which may damage the dendritic field. Dendritic field destruction is one of the pathological changes in AD [33].

Reciprocally, NO can influence insulin signaling. This reciprocal influence is supported by insulin resistance in muscle following either genetically eliminating eNOS or blocking insulin signaling by knockout of IRS2 in the endothelium [34, 35]. Selective knockout of the endothelial IRS2 blocks insulin-evoked microvascular recruitment and reduces insulin delivery to muscle interstitium [35]. The reduced insulin availability to the peripheral tissues is therefore related to the impaired vasodilation resulting from reduced insulin-mediated NO production [36, 37]. In addition to insulin-mediated vasodilation, NO can promote trans-endothelial

insulin transport directly by enhancing protein S-nitrosylation in the endothelial cells [38].

The importance of NO in modulating insulin receptor activity has also been illustrated by blockade of the phosphatases SHP-1 (Src homology region 2 domain-containing phosphatase-1), SHP-2 (SH2 domain-containing protein tyrosine phosphatase-2), and PTP1B (Protein Tyrosine Phosphatase 1B) by S-nitrosylation of the cysteine residue at the enzyme's active sites concomitantly with a burst of NO production in response to insulin [38, 39]. Inhibition of the PTP1B, SHP-1, SHP-2 by S-nitrosylation release inhibition of tyrosine phosphatases on insulin signaling. Hence, increased NO levels can promote NO-dependent tyrosine-phosphorylated insulin receptor and its downstream effectors IRS-1, thereby facilitating insulin signaling [39, 40]. Such potentiation of the insulin signaling could offset insulin resistance and related pathologies in AD.

In contrast to the positive action of NO on insulin signaling in the endothelial cells, intracerebroventricular infusion of the NO donor S-nitrosoglutathione (GSNO) impairs insulin signaling and induces inducible NO synthase (iNOS) expression in the hypothalamus. This impaired insulin signaling and induction of iNOS recapitulates the food consumption pattern of obese individuals [41]. This NO-mediated suppression of insulin signaling was linked to S-nitrosylation of IR and its downstream signaling molecule, Akt in the hypothalamus [41].

In accord, inhibition of iNOS or blocking S-nitrosylation of insulin signaling pathway reduces hypothalamic insulin resistance and normalizes energy homeostasis. However, the effects of intraventricular infusion of GSNO on levels of insulin signaling in other brain regions, especially the cognition-relevant hippocampus and cortex remain unclear. Moreover, although these studies highlight the reciprocal interactions between the NO system and the insulin signaling pathways that are important for maintaining functionality of a cell or of the much more complex brain, especially in the presence of diseases such as Alzheimer's disease (Figure 1), these studies also indicate that NO's influence on insulin signaling is cell-type-dependent, such that the functional output of diverse organs and brain regions are differentially affected.

THE INTER-RELATIONSHIP BETWEEN BRAIN INSULIN SIGNALING AND MEMORY/COGNITIVE PERFORMANCE

Brain insulin signaling is an important regulator of food intake, body weight, reproduction, and learning and memory [10, 42]. Among the many physiological

activities regulated by brain insulin signaling, memory is the most relevant to AD pathogenesis. Several lines of evidence support the notion that brain insulin signaling plays a critical role in modulating cognitive function. Intranasal insulin administration improves cognition, including short- and long-term objective memory and working memory in both animals and humans [42-47].

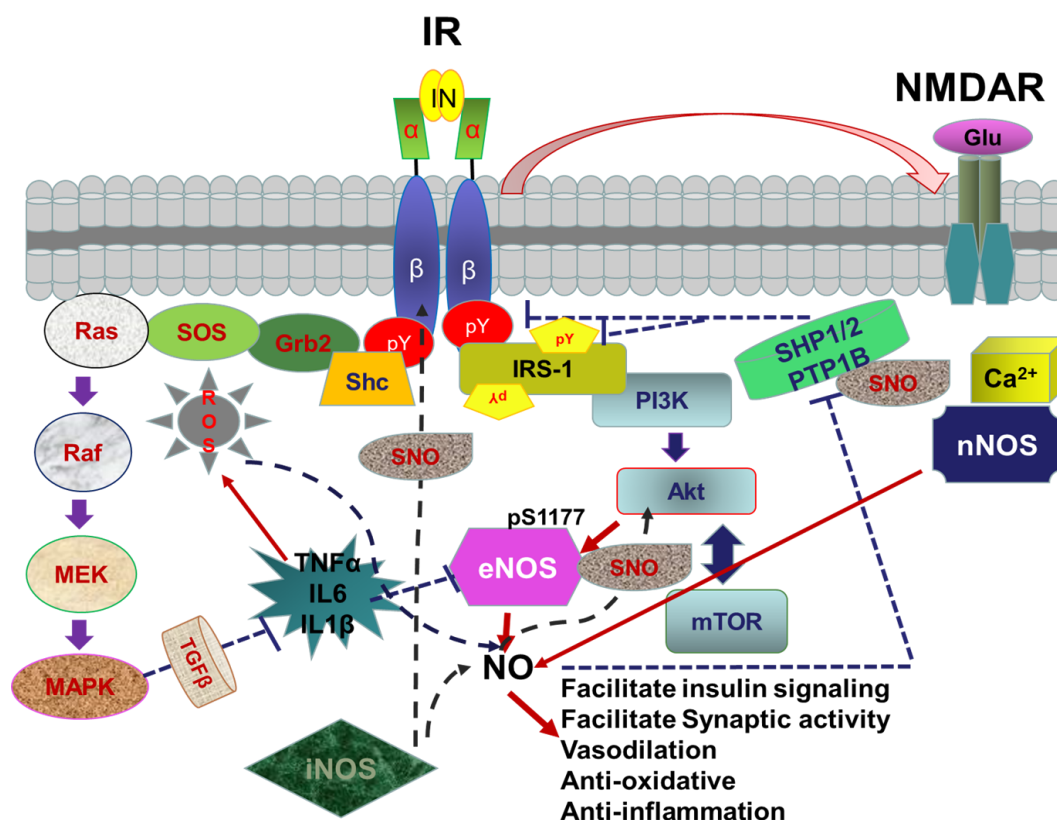


Figure 1: Reciprocal interactions between insulin signaling cascades and nitric oxide (NO) system in the brain. Insulin signaling is initiated by the binding of insulin (IN) to its cognate receptor, insulin receptors (IRs). This leads to autophosphorylation on tyrosine residues (pY) and activation of the IRs. The activation of IRs recruits (and tyrosine-phosphorylated) IRS-1 and the adaptor, Shc leading to the activation of two parallel downstream PI3K/Akt/mTOR and Ras/Raf/MEK/MAPK pathways, respectively. Activation of PI3K/Akt/mTOR pathway can activate eNOS expressed in endothelium of the cerebrovasculature and dendritic field by triggering phosphorylation on serine¹¹⁷⁷ residue of endothelial NO synthase (eNOS) thereby increase NO production. IR activation can also potentiate NMDA receptors (NMDARs) activities to increase intracellular Ca^{2+} as well as recruitment and activation of the neuronal NO synthase (nNOS) resulting in increased NO production. The increase in NO production facilitates insulin-induced IR signaling and synaptic activation by inhibiting phosphatases including PTP1B, SHP1 and SHP2 by promoting S-nitrosylation of these molecules, cause direct vasodilation and promote anti-oxidative and -inflammatory activities under physiological conditions. Insulin signaling through activation of the Ras/Raf/MEK/MAPK cascade can suppress production of

proinflammatory cytokines such as tumor necrotic factor α (TNF α) via activation of transforming growth factor β (TGF β) thereby reduces ROS production. Conversely, the aberrantly elevated proinflammatory cytokines in the brain of neurodegenerative diseases such as Alzheimer's disease can disrupt the redox balance and increase reactive oxygen species (ROS) leading to brain insulin resistance, NMDAR impairments and endothelial dysfunction by reducing eNOS expression, thereby reduces NO availability. In contrast to the positive effects of NO on insulin signaling, inducible NO synthase (iNOS), a mediator of inflammation, plays an important role in stress-induced insulin resistance probably by promoting S-nitrosylation of the IR and its downstream signaling molecule, Akt. Lastly, the heightened inflammatory processes in neurodegeneration can increase NO levels and the potential for brain insulin resistance, thereby accelerate pathology and cognitive impairment in Alzheimer's disease. IRS-1: insulin receptor substrate-1; PI3 kinase: phosphatidylinositol 3 kinase; NMDAR: N-methyl-D-aspartate receptors; MAPK: mitogen-activated protein kinase; PTP1B: protein tyrosine phosphatase 1B; SHIP1: SH-2 containing inositol 5' polyphosphatase 1; SHIP2: SH-2 containing inositol 5' polyphosphatase 2; IL-6: Interleukin 6; IL-1 β : Interleukin 1 β .

Intraventricular insulin administration improves memory and reduces chronic neuroinflammation in young but not old rats [48]. Intracerebroventricular administration of insulin improves passive avoidance task performance [49].

Similarly, direct intra-hippocampal administration enhances spatial learning and memory [50-52]. In addition, increased IR mRNA and protein levels in the hippocampal CA1 region after a spatial memory task correlates with short-term memory formation [53]. The critical role of brain insulin signaling in modulating cognition is also supported by genetic modulation of the insulin signaling cascade. Selective disruption of insulin signaling by antisense knockdown of the IR gene in hippocampi of rats impairs synaptic plasticity and spatial learning [54].

After learning-induced long-term memory consolidation, gene expression of IR in the hippocampal CA1 and CA3 regions was increased and decreased, respectively, together with reduction in IR protein levels [55]. Learning experience and long-term memory formation also results in specific increases in levels of downstream molecules such as IRS-1 and Akt, together with decreases in Akt activation (phosphorylation), recruitment of adaptor Shc and activation of ERK1/2 (Extracellular signal - regulated protein kinase1/2) [55]. These studies imply that activation of the brain insulin signaling facilitates cognitive function and that learning and memory formation reciprocally promotes neuronal insulin signaling. The notion that brain insulin signaling is critical to cognition was however not supported by a report showing that mice that had lost 95% of IRs and downstream signaling due to neuron-specific insulin receptor knockout (NIRKO) show unimpaired learning and memory or behavior in various cognitive tests [56].

Accumulating evidence also supports the notion that insulin positively influences neuronal activities in brain and cognition in humans. Activation of brain insulin signaling by acute intranasal insulin administration promotes various

neuroelectrophysiological activities such as event-related and transcortical direct current shift [57, 58]. Similarly, intranasal insulin application also positively influences neuroimaging measurements [59, 60]. Acute and chronic intranasal administration of insulin improve memory and cognitive performance in healthy young adults, obese or type-2 diabetic older subjects and even memory-impaired subjects ([42, 43, 61-67]. In contrast, no cognitive or functional benefits were observed with 12-month intranasal insulin administration to mild cognitive impairment and AD dementia patients in a randomized (1:1) double-blind clinical trial [68].

In contrast to the positive role of brain insulin signaling on cognitive performance, disruption of insulin signaling makes neurons more vulnerable to metabolic stress and accelerates neuronal dysfunction, leading to cognitive decline and dementia, including AD [8, 69-73]. Severity-correlated reduction in cognitive performance in type-2 diabetes (T2D) and AD are associated with a decrease in brain IR expression and the phosphorylation of the insulin signaling molecules with lower CSF (Cerebrospinal fluid) insulin levels in both AD and T2D patient brains [74].

Decreased insulin signaling, including altered IR kinase activity and IRS expression, and increased basal (non-stimulated) activation (indicated by IRS-1 phosphorylation) become more prominent as AD progresses [8, 75-77]. Although IR protein levels were comparable in AD and control brains, the IR was distributed throughout the cell soma and dendrites of neurons in controls but was predominantly intracellular in AD neurons [8, 9, 76, 78]. Consistent with reduced insulin signaling in AD brain, the decreases in IRS-1 and IRS-2 levels and elevated phosphorylated S312- and S616- IRS-1 were strongly co-localized with neurofibrillary tangles [76].

Impaired brain insulin signaling indicated by an increased basal AKT phosphorylation, is associated with AD neuropathology and lower cognitive function [79]. Resonating with the concept that decreased brain insulin signaling is a key pathogenic event in AD, the brain areas with the highest IR levels such as the hippocampus and temporal lobe have the greatest neuronal vulnerability and neurodegenerative pathology in AD [80, 81]. Together, the data reviewed here suggest that impaired insulin signaling is a key contributor to cognitive decline and the neuropathology of AD.

THE ROLE OF NO IN BRAIN INSULIN RESISTANCE AND COGNITIVE PERFORMANCE

Brain insulin resistance refers to a reduced or failed response to insulin of brain cells. It may be caused by reduced IR protein levels, reduced binding affinity, or inability to recruit adaptor proteins and activate downstream signaling cascades such as PI3K-Akt. Reduced insulin responsiveness contributes to impaired neuroplasticity, neurotransmission with aberrant receptor regulation and/or neurotransmitter release, glucose uptake into GLUT4 (Glucose transporter type 4)-expressing neurons, and altered insulin-elicited homeostatic or inflammatory responses in glial cells. Ultimately, brain insulin resistance can disturb systemic metabolism, impair cognition and cause psychiatric problems. Brain insulin resistance in AD can occur without apparent systemic insulin resistance or metabolic syndromes such as T2D [8, 9, 78]. Although the causal factors of brain insulin resistance are clearly diverse and not yet fully elucidated, studies on systemic insulin resistance suggest that changes in the NO system interacting with IR signaling may contribute. Table 1 summarizes the reports regarding cause-effect relationship between NOS changes and insulin resistance and/or cognitive performance.

Table 1: Studies examine the cause-and-effect relationship between altered NO availability and insulin receptor signaling, cognition and/or Alzheimer's disease pathology.

NOS	Species/manipulation	NO Level	IR	Cognitive Effects/AD Pathology	Ref.
nNOS	Hu. None	↑	-	None	[82]
nNOS	APP23 mice	↑	-	associate astrocytic APP	[83]
nNOS eNOS	NOS-KO Mice ICV L-NMMA	↓	+	None	[84]
nNOS	Rat ICV L-NMMA	↓	+	None	[85]
nNOS	Rat/Rabbit L-NMMA	↓	-	Impaired learning	[86]
nNOS	Rat L-NMMA	↓	-	NO contributes spatial memory	[87]
nNOS	Hu. None	↑	-	AD Dementia Rate 0-3	[88]
nNOS	Mice NOS-KO 7-NI	↓	-	Increase reactive oxygen species and NMDAR activation in brain	[33]
nNOS	Rat TRIM/7-NI	↓	-	Impaired learning and memory	[89]
nNOS	Mice 7-NI	↓	-	nNOS/eNOS both affect memory	[90]

nNOS	Rat 7-NI	↓	-	Impaired learning and memory formation	[91]
nNOS	Rat L-arginine/ 7-NI	↓	-	NO positively affects working memory	[92]
iNOS	Hu. None	↑	-	iNOS and eNOS were highly expressed in astrocytes in AD	[82]
iNOS	Hu. None	↑	-	iNOS expression increases in temporal cortical neurons and astrocytes	[88]
iNOS	Mice Tg2576 APP	↑	-	Calcium-dependent NOS enzymatic activity decreases; iNOS increases (neuron, microglia) in AD model	[93]
iNOS	Rat 1400W/PGE2/Aminoguanidine	↑	-	iNOS inhibition changes retinal glial activation	[94]
iNOS	Mice/Rat iNOS KO ICV GSNO	↑	+	Not determined	[41]
iNOS	Mice iNOS shRNA ICV L-NIL /L-NAME	↓	+	Not determined	[95]

Table 1: cont.

eNOS	Mice eNOS+/-	↓	+	Early cerebral infarctions at 3-6 months, amyloid angiopathy and cognitive impairment	[96]
eNOS	Mice SweArc tg AD mice	↓	-	AD model	[97]
eNOS	Mice eNOS+/-	↓	-	Increased cerebrovascular beta amyloid	[98]
eNOS	Mice eNOS KO	↓	-	Increased APP, BACE1, amyloid beta in brains	[99]
eNOS	Mice eNOS KO; APP/PS1/eNOS KO	↓	-	Increased tau phosphorylation, p25/p35 ratio, CDK5 activity	[100]
eNOS	Cell line/Mice eNOS KO L-NAME	↓	-	Increased APP, amyloid beta and BACE1 levels	[101]
eNOS	Hu. eNOS T-786C	↓	-	metabolic syndrome is associated with worse cognition only in the presence of the eNOS-786C allele	[102]
eNOS	Rat shRNA	↑	-	eNOS affects neuronal survival and functional	[24]

1400W, N-[[3-(aminomethyl)phenyl]methyl]-ethanimidamide, dihydrochloride; 7-NI, 7-Nitroindazole; AD, Alzheimer's disease; APP23 mouse, an Alzheimer mouse model with an overexpression of mutant human APP/Amyloid Beta Precursor Protein (Swedish mutation); BACE1, Beta-secretase 1/beta-site APP cleaving enzyme 1; CDK5, Cyclin-dependent kinase 5; eNOS, Endothelial Nitric Oxide Synthase; GSNO, S-Nitrosoglutathione; Hu., Human; ICV,

Intracerebroventricular injection; iNOS, Inducible nitric oxide synthase; IR, Insulin resistance; IHC, Immunohistochemistry; KO, knock-out; L-NAME, N(ω)-nitro-L-arginine methyl ester; L-NIL, L-N6-(1-iminoethyl)-lysine; L-NMMA, L-NG-monomethyl Arginine acetate; NMDAR, N-methyl-D-aspartate receptor; nNOS, Neuronal nitric oxide synthase; PGE₂, 9-oxo-11 α ,15S-dihydroxy-prosta-5Z,13E-dien-1-oic acid; TRIM, 1-(α,α,α -trifluoro-o-tolyl)-Imidazole.

The availability of NO is regulated by enzymatic activity and levels of NOS isoforms as well as by levels of reactive species such as superoxide that can quench and reduce NO. NO is generated by three NOS isoforms that are expressed in tissue-specific expression patterns [103-105]. While nNOS (NOS1) is predominantly found in neuronal tissue, NOS2 or inducible NOS (iNOS) is upregulated in activated macrophages, and NOS3 (eNOS) is abundantly expressed in endothelium and also found in dendritic spines [24, 105]. eNOS and nNOS, which catalyze the Ca²⁺-dependent constitutive NO production, occur predominantly in blood vessels and neural tissues, respectively. NO is also rapidly elevated during inflammation and may be a primary mediator of the inflammatory injury that occurs in neurodegenerative disorders such as AD [105, 106]. Thus, elevated NO levels, directly resulting from inflammatory processes in neurodegeneration, likely increase potential for insulin resistance, and accelerate pathology and cognitive impairment in AD. Manipulation of the NO system can affect insulin resistance: intravenous administration of a competitive NOS inhibitor, NG-monomethyl-L-arginine (L-NMMA) to rats induced systemic insulin resistance and hypertension [36].

Interestingly, systemic and presumably brain insulin resistance together with insulin secretory defects are observed when NOS activity in the brain is inhibited by intracerebroventricular (ICV) injection of L-NMMA in free-moving rats [85]. In contrast, ICV infusion of S-nitrosoglutathione (GSNO), a NO donor in mice impaired insulin signaling in hypothalamus and replicated the food intake pattern of obese individuals by causing nitrosation of IR and its downstream Akt [41]. Further, S-nitrosation of the IR, IRS-1, and Akt (protein kinase B) can lead to insulin resistance [107, 108]. Genetically eliminating iNOS (iNOS null) or inhibiting iNOS using iNOS targeting antisense oligonucleotides both reduce hypothalamic insulin resistance and normalize energy homeostasis [41]. Targeted disruption of iNOS also protects against obesity-linked insulin resistance in muscle, suggesting that increased iNOS is tied to impaired insulin signaling in muscles of obese individuals [109].

Modulation of NOS can also affect cognitive performance. Systemic administration of the NO synthase inhibitor nitro-L-arginine methyl ester (L-NAME) in rats

and rabbits impairs maze (spatial) learning in rats [86, 110] as well as the conditioned eye-blink response in rabbits [86]. Inhibition of NOS by 7-nitroindazole, L-NAME or N-MMA, impairs passive-avoidance and elevated pulse-maze memory performance [111], T-maze [112] and memory of shock avoidance [113]. Conversely, administration of the NO precursor L-arginine or NO donors such as sodium nitroprusside, S-nitroso-N-acetylpenicillamine (SNAP), and molsidomine improves learning and memory including avoidance memory, maze performance and objective recognition [113-116] and prevents age-related memory deficits [113].

While these data collectively suggest that chemical manipulation of the NO system can lead to systemic and brain region-specific insulin resistance as well as changes in cognitive performance, whether brain insulin resistance is induced by perturbing brain NOS was not explicitly demonstrated in the cognitive tests. Furthermore, effects on cognitive performance were not assessed together with insulin signaling changes. Thus, the contribution to altered cognition and dementia by altered NO availability caused by insulin signaling changes is still unclear.

To further elucidate the inter-relationship between brain insulin signaling and cognitive performance, genetic manipulations of the NO system have been employed and polymorphisms of the NOS have been examined. Emerging data from animal models and humans indicates that polymorphisms in the eNOS gene influence susceptibility to insulin resistance and metabolic disturbances leading to T2D [117-120].

The increased risk of insulin resistance by reduced eNOS levels and NO production is demonstrated in genetically manipulated mice. Mice that are eNOS null show insulin resistance and metabolic disturbances [121], and partial knockdowns (eNOS+/-) are insulin resistant and hypertensive only when fed a high-fat diet [122]. Similarly, nNOS and eNOS knockout mice show insulin resistance in a tissue-dependent manner. The nNOS KO mice are insulin resistant only in the peripheral tissues, whereas the eNOS null mice are insulin resistant at the level of the liver and peripheral tissues [34]. Genetic polymorphism of eNOS gene (G894T) increases susceptibility of the south Indian but not Pakistani population to insulin resistance in type 2 diabetes patients [123, 124]. In addition, eNOS gene (T786C) mutation decreases insulin sensitivity and thus promotes insulin resistance in patients with coronary artery disease [125]. However, eNOS T786C and E298D mutations do not increase the risk of sporadic AD [126, 127]. Similarly, NOS gene polymorphisms do not alter disease risk in the majority of late-onset AD and Lewy body dementia cases [128].

Further analysis of the E298 allele reveals its association with higher risk of AD in the MIRAGE African American but not Caucasian population [129]. Additionally, iNOS activity is considerably higher in the hippocampus of AD patients compared to controls [130]. Although these studies suggest a causative role of reduced eNOS levels and sensitivity in the development of systemic insulin resistance, metabolic disturbance and blood vessel resistance in animal models and in eNOS polymorphisms in humans do not appear to affect brain insulin signaling and play a minor role in the AD progression. While these data indicate that genetic or polymorphism-induced changes in the NOS system and in NO availability influence systemic insulin resistance liability, such changes have little impact on brain insulin signaling and cognition. Decreased NO availability leads to many features of the diabetic state and may be an important molecular mechanism underlying the development of insulin resistance in the peripheral tissues [131]. Hence, the modulation of NO availability appears to influence insulin signaling in peripheral tissues rather than in brain.

Moreover, the impact on cognitive performance of altered NO availability resulting from compromised brain insulin signaling remains unclear. NO has long been regarded as a part of neurotoxic insult derived from neuroinflammation driven in part by elevation of pro-inflammatory cytokines including TNF α , IL-6 and IL-1 β in the AD brain. Proinflammatory cytokines such as TNF α disrupt gene expression to reduce eNOS protein levels in endothelium and probably in dendritic spines by decreasing eNOS mRNA stability [132-135]. Through activating the TNF receptor 1, TNF α also reduces eNOS expression in cultured white and brown adipocytes and in muscle satellite cells of obese mice [136]. Genetic deletion of the eNOS in animals exhibits many features of systemic insulin resistance and hypertension even in the absence of obesity [34, 121, 122, 137]. Hence, by reducing eNOS levels, proinflammatory cytokines such as TNF α can interfere with insulin signaling to evoke tissue-specific insulin resistance.

Once insulin resistance is established, oxidative stress in β -cells of pancreatic islets and peripheral tissues further reduces insulin secretion in pancreatic β -cells and insulin affinity to IR in the peripheral tissues [138]. Hence, chronic inflammation can lead to localized insulin resistance via auto/paracrine proinflammatory cytokine signaling; whereas, systemic insulin resistance via endocrine proinflammatory cytokine signaling leads to metabolic disturbance. AD is associated with sustained neuroinflammation with elevated proinflammatory cytokines in the brain, especially in areas important for cognition such as hippocampus and cortical regions [8, 9, 78]. Hence, the insulin resistance induced by proinflammatory cytokines may be intertwined with neurodegeneration and dementia.

Conversely, stimulation of insulin signaling via PI3K-Akt can activate eNOS by phosphorylating the enzyme on the serine1177 residue. Insulin signaling can also potentiate adiponectin signaling to activate AMP kinase that in turn activates eNOS through phosphorylation of S1177 to promote glucose uptake in GluT4 expression neurons [105, 139] .

Activation of eNOS also requires its localization in the caveolae and linkage with heat shock protein 90 (HSP90). Obesity-associated insulin resistance can decrease eNOS activity by reducing caveolin-1 in caveolae and disrupting eNOS interaction with HSP90 and insulin signaling cascade [140, 141]. Hence, elevated proinflammatory cytokines and reactive oxygen species (ROS) in AD brain can lead to reduced eNOS phosphorylation and activation, resulting in decreased NO availability and insulin resistance in endothelium as well as impaired vasodilation [142, 143]. Finally, superoxide rapidly reacts with NO to produce the more potent oxidant peroxynitrite, leading to endothelial dysfunction, reduced NO availability, exacerbating brain insulin resistance and promoting AD pathogenesis.

CONCLUDING REMARKS

In conclusion, ample of evidence from animal models and humans illustrates that impairments in the NO system contribute to the development of insulin resistance and associated metabolic disturbance in peripheral tissues. However, the direct contribution of reduced NO availability to brain insulin resistance is much less clear. Insulin is a critical regulator of multiple brain functions, including synaptic plasticity, learning and memory. Importantly, impaired insulin signaling (insulin resistance) in AD brain can occur without apparent systemic insulin signaling defects. Thus, clarifying the causal relationship of changes in the NO system to insulin signaling perturbations might increase our understanding of AD pathogenic mechanisms and identify new therapeutic approaches such as modulating NO availability to slow progression of the disease. Since NO levels are influenced by diet and physical activity, it is possible that simple life style changes may help reduce brain insulin resistance and associated brain function impairments in AD patients.

CONFLICT OF INTEREST

None Declare

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CONSENT OF PUBLICATION

None

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Chapter 11:

1. The section on interactions of insulin and NO in the brain is unclear. There appear to be areas where insulin action in the CNS is detrimental as might be the effect of NO (from iNOS). There is discussion of eNOS in muscle and other tissues which perhaps confuses the issue. Perhaps this section could be more clear.
2. Fig 1: please identify the significance of the different types of arrows, in the legend.
3. There is much evidence cited for the influence of insulin on cognitive brain function and its impairment when insulin is dysfunctional. However, also cited, is evidence that increasing the availability of insulin, or eliminating its signaling does not alter cognitive function or improve AD. These are very interesting observations. In a review, it would be of even more interest to attempt some reconciliation of these experimental results.
4. The conclusion concerning insulin resistance and AD appears to be that it is marginally involved. Alternately brain and systemic insulin resistance are not the same. The role of NO in any brain insulin resistance appears even less clear. Since there is a lot of interest in this potential aspect of AD, this chapter is important and needs to be carefully written. One aspect which may help, is to decrease or eliminate discussion of systemic or peripheral insulin resistance. It is dealt with elsewhere in the book and tends to obscure the discussion of this chapter which is on the brain and AD. There is even more discordant evidence for the role of NO in brain IR and AD as the authors point out. Again the discussion should focus on the brain. Positive results in the periphery, discussed at length, serve rather to confuse the discussion. There is some evidence that brain IR and NO interactions may be of significance in the brain and in AD etiology. From what one can glean from the chapter, it is quite controversial and unresolved. It appears however that the authors want to emphasize the possibility of the roles of IR and NO in AD. They do this by interjecting descriptions of the peripheral processes. This makes the discussion difficult to follow. This persists right up to the concluding remarks where interventions in diet and physical activity are suggested for help in preventing AD. So there seems to be a need to focus and to marshal arguments that support the conclusion, whatever it may be. Uncertainty, is a completely valid conclusion.

Begin forwarded message:

From: Asghar Ghasemi <[REDACTED]@gmail.com>
Subject: Book chapter revision required
Date: February 20, 2022 at 12:00:34 AM EST
To: Khosrow Kashfi <drkho@verizon.net>

Dear Prof. Kashfi

Salaam

Hope you are doing well. Attached please find chapter 11 of our book and comments raised by reviewers. I would be grateful if you ask the authors to provide the requested changes and also respond to reviewers on the attached files.

Best wishes

Asghar

[Asghar Ghasemi , Ph.D.,](#)

[Professor of Physiology,](#)

[Academic Faculty Member,](#)

[Director of Endocrine Physiology Research Center](#)

[Research Institute for Endocrine Sciences,](#)

[Shahid Beheshti University of Medical Sciences](#)

[Email: Ghasemi@endocrine.ac.ir](mailto:Ghasemi@endocrine.ac.ir)

[Tel: +9821-22432500](tel:+9821-22432500)

[Fax: +9821-22416264](tel:+9821-22416264)

[Work address: No. 24, Parvaneh Street, Yaman Street, Velenjak, Tehran, I.R. Iran. P.O. Box: 19395-4763](#)

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To: Khosrow Kashfi <drkho@verizon.net>
Cc: [REDACTED]@hotmail.com
Subject: Re: [EXTERNAL] Fwd: Book chapter revision required
Attachments: Chapter 11-FF 197-215-HYW_edited20220228.docx

Dear Kho,

Enclosed is the finalized book chapter that had been edited according to the comments you sent. As suggested, I eliminated most systemic insulin resistance (and associated references) so that the book chapter is more focused on brain insulin resistance. Please note, this book chapter is one page less than the original. (197-214)

Please lead us know if you have any questions.

Thanks.

Best,

Hoau

From: Khosrow Kashfi <drkho@verizon.net>
Sent: Sunday, February 20, 2022 8:03 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Fwd: Book chapter revision required

Dear Hoau-Yan

Hope all is well. Please see below.

Thanks
Kho

Khosrow Kashfi, PhD, FRSC, FRSB
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Associate Medical Professor
Department of Molecular, Cellular & Biomedical Sciences
City University of New York School of Medicine
160 Convent Avenue, New York, NY 10031
Tel: (212) 650-6641
Fax: (212) 650-7692
[Email: kashfi@med.cuny.edu](mailto:kashfi@med.cuny.edu)
Website: www.avicennatherapeutics.com

CHAPTER 11

Brain Insulin Resistance, Nitric Oxide and Alzheimer's Disease Pathology

Zhe Pei¹, Kuo-Chieh Lee¹, Amber Khan^{1,2}, Hoau-Yan Wang^{1,2*}

¹*Department of Molecular, Cellular and Biomedical Sciences, City University of New York School of Medicine, 160 Convent Avenue, New York, New York 10031, USA.*

²*Department of Biology, Neuroscience Program, Graduate School of The City University of New York, 365 Fifth Avenue, New York, New York 10061, U.S.A.*

Abstract: Alzheimer's disease (AD) is a devastating age-related neurodegenerative disease characterized by progressive pathological changes and functional and cognitive impairments. Among several pathological mechanisms, brain insulin resistance appears to contribute significantly to the pathology and cognitive deficits. Brain insulin resistance has been demonstrated in animal models of AD and postmortem human brain tissue from patients with AD dementia. Studies conducted in AD models and in humans suggest that attenuating brain insulin resistance by agents such as glucagon-like peptide1 (GLP-1) analogs and small molecule drug candidate PTI-125 also reduces many AD pathologic features and symptoms. Insulin affects NO levels by activating endothelial and neuronal nitric oxide synthase (eNOS, nNOS), and systemic insulin resistance has been linked to reduced nitric oxide (NO) bioavailability. Increasing NO availability reduces systemic insulin resistance, and the insulin signaling pathway is associated with activation of eNOS, implying a causal relationship. This chapter explores this relationship and the role of impaired NO availability in brain insulin resistance in AD dementia.

Keywords: CaMKII (calcium-calmodulin-dependent kinase II), gamma-Aminobutyric acid (GABA) receptor, glutamate, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, insulin resistance, NADPH oxidase 2 (Nox2), NADPH oxidase subunit NOX2, NG-monomethyl-L-arginine (L-NMMA), nitric oxide synthase (NOS), N-methyl-D-aspartate (NMDA) receptor, reactive oxygen species (ROS), type-2 diabetes (T2D)

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that includes many underlying pathophysiological changes that gradually lead to dementia [1-4].

***Corresponding author Hoau-Yan Wang:** Department of Molecular, Cellular and Biomedical Sciences, City University of New York School of Medicine, 160 Convent Avenue, New York, NY 10031, USA. Email: hywang@med.cuny.edu

The lack of effective treatments for AD dementia and the enormous socioeconomic impact to society underscores the urgent need to develop effective treatments for this devastating disease [5, 6]. Many promising therapeutic agents in development for AD aim to reduce brain insulin resistance, a common early pathological feature of AD dementia with or without diabetes [7-10]. The pathological factors that contribute to brain insulin resistance are not fully understood. Nitric oxide (NO) is one of several biological molecules that interact with the insulin signaling pathway bi-directionally. In this chapter, we discuss the role of the NO system in the development of brain insulin resistance and explore the possibility that manipulating NO might be therapeutic for AD dementia.

INSULIN RECEPTOR SIGNALING AND ITS INTERACTION WITH NO SYSTEM

Insulin, a peptide secreted by the beta (β) cells in pancreas, crosses the blood-brain barrier in a regulated and saturable manner to enter the central nervous system (CNS). Although de novo synthesis of insulin in the brain is still debated, support for local brain insulin synthesis includes the detection of C-peptide and insulin mRNA in various brain regions in humans with the mRNA levels were especially high in hippocampus, striatum, and thalamus [11-15]. Insulin expression is decreased in AD compared to normal controls [14].

Insulin produces its cellular actions by binding its cognate insulin receptors (IRs) present on all cells including neurons and glia in brain regions such as olfactory bulb, cerebral cortex, hippocampus, hypothalamus and amygdala [8, 16, 17]. IRs are more concentrated in neurons relative to glial cells and are particularly highly expressed in post-synaptic densities [8, 16-18]. Upon insulin binding to the extracellular α -subunit domains of IRs, the intracellular IR β -subunit domains dimerize, leading to activation of their intrinsic tyrosine kinase to cause autophosphorylation. Insulin-like growth factor-1 (IGF-1) also binds and activates IRs, although with lower affinity, leading to the same trophic and metabolic actions as insulin, including neuronal plasticity [19, 20].

In addition to regulation of glucose utilization and homeostasis, insulin activates PI3K-Akt (Phosphoinositide 3-kinase - Protein kinase B/Akt) and mTOR (Mechanistic target of rapamycin) signaling via recruitment of insulin receptor substrate family (IRS) proteins such as IRS-1 and IRS-2. This insulin-stimulated PI3K/Akt/mTOR pathway has many other functions in cells throughout the body including the neuronal and vascular systems. Insulin activates Akt via IRS1-PI3K to directly phosphorylate serine1177 residues and activate vascular endothelial NO

synthase (eNOS), leading to NO production and consequent vasodilation and increased capillary blood flow [21, 22]. Insulin signaling promoting NO-mediated vasodilation in the brain is supported by increased blood flow in the insular cortex following intranasal insulin in men, independent of cortisol manipulation [23]. Expression of eNOS has been shown not only in endothelium of the cerebrovasculature, but more importantly, in dendritic spines [24]. Innate eNOS activity confers protection against secondary neuronal injury; thus, impaired eNOS due to insufficient insulin signaling in the brain can conceivably contribute to pathologies in AD leading to cognitive impairments [25].

Insulin has been shown to modulate a wide range of neuronal function. Insulin regulates 1) trafficking of ligand-gated ion channels, 2) expression and localization of GABA (γ -Aminobutyric acid), NMDA (N-Methyl-D-aspartic acid or N-Methyl-D-aspartate), and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, 3) catecholamine release and uptake, and 4) synaptic plasticity shown by long-term potentiation (LTP) and depression (LTD) in a NMDA receptor and PI3K dependent manner [26-29]. Insulin also promotes dendritic spine formation and excitatory synaptic development, and insulin regulates the development and health of excitatory synapses by activating PI3K/Akt/mTOR and Rac1/Cdc42 signaling [30].

Activation of the NMDA receptor recruits and activates neuronal NO synthase (nNOS) via Akt- and CaMKII (Ca^{2+} /calmodulin-dependent protein kinase II) - mediated phosphorylation of nNOS to promote production of NO in the postsynaptic field [31, 32]. The activation of nNOS was also found to elevate AMPA receptor levels [32]. Thus, insulin can increase NO production in postsynaptic neurons by stimulating nNOS via activation of NMDA receptors. Increased NO promotes NADPH oxidase 2 (NOX2)-dependent ROS production postsynaptically, which may damage the dendritic field. Dendritic field destruction is one of the pathological changes in AD [33].

The importance of NO in modulating insulin receptor activity has also been illustrated by blockade of the phosphatases SHP-1 (Src homology region 2 domain-containing phosphatase-1), SHP-2 (SH2 domain-containing protein tyrosine phosphatase-2), and PTP1B (Protein Tyrosine Phosphatase 1B) by S-nitrosylation of the cysteine residue at the enzyme's active sites concomitantly with a burst of NO production in response to insulin [34, 35]. Inhibition of the PTP1B, SHP-1, SHP-2 by S-nitrosylation release inhibition of tyrosine phosphatases on insulin signaling. Hence, increased NO levels can promote NO-dependent tyrosine-

phosphorylated insulin receptor and its downstream effectors IRS-1, thereby facilitating insulin signaling [35, 36]. Such potentiation of the insulin signaling could offset insulin resistance and related pathologies in AD.

In contrast to the positive action of NO on insulin signaling in the endothelial cells, intracerebroventricular infusion of the NO donor S-nitrosoglutathione (GSNO) impairs insulin signaling and induces inducible NO synthase (iNOS) expression in the hypothalamus. This impaired insulin signaling (insulin resistance) and induction of iNOS recapitulates the food consumption pattern of obese individuals [37]. This NO-mediated suppression of insulin signaling was linked to S-nitrosylation of IR and its downstream signaling molecule, Akt in the hypothalamus [37].

In accord, inhibition of iNOS or blocking S-nitrosylation of insulin signaling pathway reduces hypothalamic insulin resistance and normalizes energy homeostasis. However, the effects of intraventricular infusion of GSNO on levels of insulin signaling in other brain regions, especially the cognition-relevant hippocampus and cortex remain unclear. Moreover, although these studies highlight the reciprocal interactions between the NO system and the insulin signaling pathways that are important for maintaining functionality of a cell or of the much more complex brain, especially in the presence of diseases such as Alzheimer's disease (Figure 1), these studies also indicate that NO's influence on insulin signaling is cell-type-dependent, such that the functional output of diverse organs and brain regions are differentially affected.

THE INTER-RELATIONSHIP BETWEEN BRAIN INSULIN SIGNALING AND MEMORY/COGNITIVE PERFORMANCE

Brain insulin signaling is an important regulator of food intake, body weight, reproduction, and learning and memory [10, 38]. Among the many physiological activities regulated by brain insulin signaling, memory is the most relevant to AD pathogenesis. Several lines of evidence support the notion that brain insulin signaling plays a critical role in modulating cognitive function. Intranasal insulin administration improves cognition, including short- and long-term objective memory and working memory in both animals and humans [38-43].

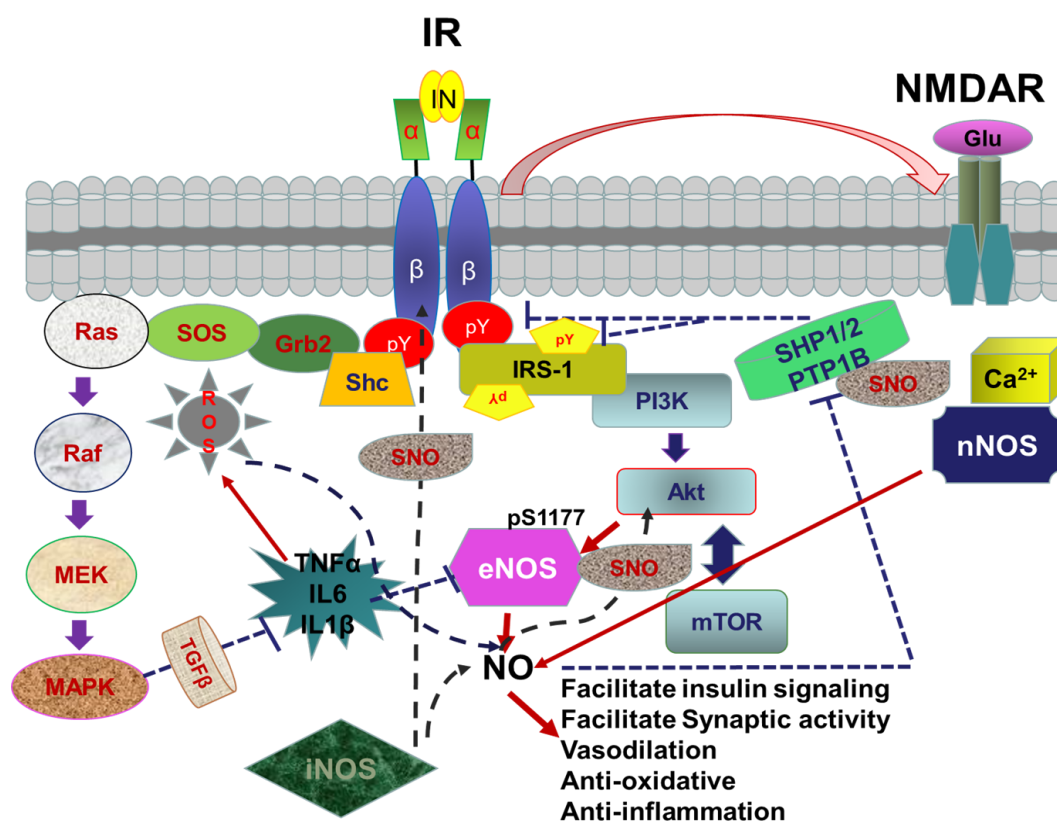


Figure 1: Reciprocal interactions between insulin signaling cascades and nitric oxide (NO) system in the brain. Insulin signaling is initiated by the binding of insulin (IN) to its cognate receptor, insulin receptors (IRs). This leads to autophosphorylation on tyrosine residues (pY) and activation of the IRs. The activation of IRs recruits (and tyrosine-phosphorylated) IRS-1 and the adaptor, Shc leading to the activation of two parallel downstream PI3K/Akt/mTOR and Ras/Raf/MEK/MAPK pathways, respectively. Activation of PI3K/Akt/mTOR pathway can activate eNOS expressed in endothelium of the cerebrovasculature and dendritic field by triggering phosphorylation on serine¹¹⁷⁷ residue of endothelial NO synthase (eNOS) thereby increase NO production. IR activation can also potentiate NMDA receptors (NMDARs) activities to increase intracellular Ca²⁺ as well as recruitment and activation of the neuronal NO synthase (nNOS) resulting in increased NO production. The increase in NO production facilitates insulin-induced IR signaling and synaptic activation by inhibiting phosphatases including PTP1B, SHIP1 and SHIP2 by promoting S-nitrosylation of these molecules, cause direct vasodilation and promote anti-oxidative and -inflammatory activities under physiological conditions. Insulin signaling through activation of the Ras/Raf/MEK/MAPK cascade can suppress production of proinflammatory cytokines such as tumor necrotic factor α (TNF α) via activation of transforming growth factor β (TGF β) thereby reduces ROS production. Conversely, the aberrantly elevated proinflammatory cytokines in the brain of neurodegenerative diseases such as Alzheimer's disease can disrupt the redox balance and increase reactive oxygen species (ROS) leading to brain insulin resistance, NMDAR impairments and endothelial dysfunction by reducing eNOS expression, thereby reduces NO availability. In contrast to the positive effects of NO on insulin signaling, inducible NO synthase (iNOS), a mediator of inflammation, plays an important role in stress-induced insulin resistance probably by promoting S-nitrosylation of the IR and its downstream signaling molecule, Akt. Lastly, the heightened inflammatory processes in neurodegeneration can

increase NO levels and the potential for brain insulin resistance, thereby ~~accelerate~~ pathology and cognitive impairment in Alzheimer's disease. IRS-1: insulin receptor substrate-1; PI3 kinase-~~phosphatidylinositol~~ 3 kinase; NMDAR: N-methyl-D-aspartate receptors; MAPK: mitogen-activated protein kinase; PTP1B: protein tyrosine phosphatase 1B; SHIP1: SH-2 containing inositol 5' polyphosphatase 1; SHIP2: SH-2 containing inositol 5' polyphosphatase 2; IL-6: Interleukin 6; IL-1 β : Interleukin 1 β . positive contributor, indicates a minor or potential positive contributor, indicates a prominent positive contributor, indicates a negative contributor.

Intraventricular insulin administration improves memory and reduces chronic neuroinflammation in young but not old rats [44]. Intracerebroventricular administration of insulin improves passive avoidance task performance [45].

Similarly, direct intra-hippocampal administration enhances spatial learning and memory [46-48]. In addition, increased IR mRNA and protein levels in the hippocampal CA1 region after a spatial memory task correlates with short-term memory formation [49]. The critical role of brain insulin signaling in facilitating cognition is also supported by genetic modulation of the insulin signaling cascade. Selective disruption of insulin signaling by antisense knockdown of the IR gene in hippocampi of rats impairs synaptic plasticity and spatial learning [50].

After learning-induced long-term memory consolidation, gene expression of IR in the hippocampal CA1 and CA3 regions was increased and decreased, respectively, together with reduction in IR protein levels [51]. Learning experience and long-term memory formation also results in specific increases in levels of downstream molecules such as IRS-1 and Akt, together with decreases in Akt activation (phosphorylation), recruitment of adaptor Shc and activation of ERK1/2(Extracellular signal - regulated protein kinase1/2) [51]. These studies imply that activation of the brain insulin signaling facilitates cognitive function and that learning and memory formation reciprocally promotes neuronal insulin signaling. The notion that brain insulin signaling is critical to cognition was however not supported by a report showing that mice that had lost 95% of IRs and downstream signaling due to neuron-specific insulin receptor knockout (NIRKO) show unimpaired learning and memory or behavior in various cognitive tests [52].

Accumulating evidence also supports the notion that insulin positively influences neuronal activities in brain and cognition in humans. Activation of brain insulin signaling by acute intranasal insulin administration promotes various neuroelectrophysiological activities such as event-related and transcortical direct current shift [53, 54]. Similarly, intranasal insulin application also positively influences neuroimaging measurements [55, 56]. Acute and chronic intranasal administration of insulin improve memory and cognitive performance in healthy young adults, obese or type-2 diabetic older subjects and even memory-impaired

subjects ([38, 39, 57-63]. In contrast, no cognitive or functional benefits were observed with 12-month intranasal insulin administration to mild cognitive impairment and AD dementia patients in a randomized (1:1) double-blind clinical trial [64].

In contrast to the positive role of brain insulin signaling on cognitive performance, disruption of insulin signaling makes neurons more vulnerable to metabolic stress and accelerates neuronal dysfunction, leading to cognitive decline and dementia, including AD [8, 65-69]. Severity-correlated reduction in cognitive performance in type-2 diabetes (T2D) and AD are associated with a decrease in brain IR expression and the phosphorylation of the insulin signaling molecules with lower CSF (Cerebrospinal fluid) insulin levels in both AD and T2D patient brains [70].

Decreased insulin signaling, including altered IR kinase activity and IRS expression, and increased basal (non-stimulated) activation (indicated by IRS-1 phosphorylation) become more prominent as AD progresses [8, 71-73]. Although IR protein levels were comparable in AD and control brains, the IR was distributed throughout the cell soma and dendrites of neurons in controls but was predominantly intracellular in AD neurons [8, 9, 72, 74]. The reduced insulin signaling in AD brain was correlated with decreased IRS-1 and IRS-2 levels as well as the robust co-localization of the elevated phosphorylated S312- and S616- IRS-1 with neurofibrillary tangles [72].

Impaired brain insulin signaling indicated by an increased basal AKT phosphorylation and implied compromised insulin-driven AKT activation, is associated with AD neuropathology and lower cognitive function [75]. Resonating with the concept that decreased brain insulin signaling is a key pathogenic event in AD, the brain areas with the highest IR levels such as the hippocampus and temporal lobe have the greatest neuronal vulnerability and neurodegenerative pathology in AD [76, 77]. Together, the data reviewed here suggest that impaired insulin signaling is a key contributor to cognitive decline and the neuropathology of AD. Hence, failure to improve cognition by the 12-month intranasal insulin administration to mild cognitive impairment and AD dementia patients may be due to the insulin resistance is too severe in these trial subjects [64].

THE ROLE OF NO IN BRAIN INSULIN RESISTANCE AND COGNITIVE PERFORMANCE

Brain insulin resistance refers to a reduced or failed response to insulin of brain cells. It may be caused by reduced IR protein levels, reduced binding affinity, or

inability to recruit adaptor proteins and activate downstream signaling cascades such as PI3K-Akt. Reduced insulin responsiveness contributes to impaired neuroplasticity, neurotransmission with aberrant receptor regulation and/or neurotransmitter release, glucose uptake into GLUT4 (Glucose transporter type 4)-expressing neurons and altered insulin-elicited homeostatic or inflammatory responses in glial cells. Ultimately, brain insulin resistance can disturb systemic metabolism, impair cognition, and cause psychiatric problems. Brain insulin resistance in AD can occur without apparent systemic insulin resistance or metabolic syndromes such as T2D [8, 9, 74]. Although the causal factors of brain insulin resistance are clearly diverse and not yet fully elucidated, studies on systemic insulin resistance suggest that changes in the NO system interacting with IR signaling may contribute. Table 1 summarizes the reports regarding cause-effect relationship between NOS changes and insulin resistance and/or cognitive performance.

Table 1: Studies examine the cause-and-effect relationship between altered NO availability and insulin receptor signaling, cognition and/or Alzheimer's disease pathology.

NOS	Species/manipulation	NO Level	IR	Cognitive Effects/AD Pathology	Ref.
nNOS	Hu. None	↑	-	None	[78]
nNOS	APP23 mice	↑	-	associate astrocytic APP	[79]
nNOS eNOS	NOS-KO Mice ICV L-NMMA	↓	+	None	[80]
nNOS	Rat ICV L-NMMA	↓	+	None	[81]
nNOS	Rat/Rabbit L-NMMA	↓	-	Impaired learning	[82]
nNOS	Rat L-NMMA	↓	-	NO contributes spatial memory	[83]
nNOS	Hu. None	↑	-	AD Dementia Rate 0-3	[84]
nNOS	Mice NOS-KO 7-NI	↓	-	Increase reactive oxygen species and NMDAR activation in brain	[33]
nNOS	Rat TRIM/7-NI	↓	-	Impaired learning and memory	[85]
nNOS	Mice 7-NI	↓	-	nNOS/eNOS both affect memory	[86]
nNOS	Rat 7-NI	↓	-	Impaired learning and memory formation	[87]

nNOS	Rat L-arginine/ 7-NI	↓	-	NO positively affects working memory	[88]
iNOS	Hu. None	↑	-	iNOS and eNOS were highly expressed in astrocytes in AD	[78]
iNOS	Hu. None	↑	-	iNOS expression increases in temporal cortical neurons and astrocytes	[84]
iNOS	Mice Tg2576 APP	↑	-	Calcium-dependent NOS enzymatic activity decreases; iNOS increases (neuron, microglia) in AD model	[89]
iNOS	Rat 1400W/PGE2/Aminoguanidine	↑	-	iNOS inhibition changes retinal glial activation	[90]
iNOS	Mice/Rat iNOS KO ICV GSNO	↑	+	Not determined	[37]
iNOS	Mice iNOS shRNA ICV L-NIL /L-NAME	↓	+	Not determined	[91]

Table 1: cont.

eNOS	Mice eNOS+/-	↓	+	Early cerebral infarctions at 3-6 months, amyloid angiopathy and cognitive impairment	[92]
eNOS	Mice SweArc tg AD mice	↓	-	AD model	[93]
eNOS	Mice eNOS+/-	↓	-	Increased cerebrovascular beta amyloid	[94]
eNOS	Mice eNOS KO	↓	-	Increased APP, BACE1, amyloid beta in brains	[95]
eNOS	Mice eNOS KO; APP/PS1/eNOS KO	↓	-	Increased tau phosphorylation, p25/p35 ratio, CDK5 activity	[96]
eNOS	Cell line/Mice eNOS KO L-NAME	↓	-	Increased APP, amyloid beta and BACE1 levels	[97]
eNOS	Hu. eNOS T-786C	↓	-	metabolic syndrome is associated with worse cognition only in the presence of the eNOS-786C allele	[98]
eNOS	Rat shRNA	↑	-	eNOS affects neuronal survival and functional	[24]

1400W, N-[[3-(aminomethyl)phenyl]methyl]-ethanimidamide, dihydrochloride; 7-NI, 7-Nitroindazole; AD, Alzheimer's disease; APP23 mouse, an Alzheimer mouse model with an overexpression of mutant human APP/Amyloid Beta Precursor Protein (Swedish mutation); BACE1, Beta-secretase 1/beta-site APP cleaving enzyme 1; CDK5, Cyclin-dependent kinase 5; eNOS, Endothelial Nitric Oxide Synthase; GSNO, S-Nitrosoglutathione; Hu., Human; ICV, Intracerebroventricular injection; iNOS, Inducible nitric oxide synthase; IR, Insulin resistance; IHC, Immunohistochemistry; KO, knock-out; L-NAME, N(ω)-nitro-L-arginine methyl ester; L-

NIL, L-N6-(1-iminoethyl)-lysine; L-NMMA, L-NG-monomethyl Arginine acetate; NMDAR, N-methyl-D-aspartate receptor; nNOS, Neuronal nitric oxide synthase; PGE₂, 9-oxo-11 α ,15S-dihydroxy-prosta-5Z,13E-dien-1-oic acid; TRIM, 1-(α,α,α -trifluoro-o-tolyl)-Imidazole.

The availability of NO is regulated by enzymatic activity and levels of NOS isoforms as well as by levels of reactive species such as superoxide that can quench and reduce NO. NO is generated by three NOS isoforms that are expressed in tissue-specific expression patterns [99-101]. While nNOS (NOS1) is predominantly found in neuronal tissue, NOS2 or inducible NOS (iNOS) is upregulated in activated macrophages, and NOS3 (eNOS) is abundantly expressed in endothelium and also found in dendritic spines [24, 101]. eNOS and nNOS, which catalyze the Ca²⁺-dependent constitutive NO production, occur predominantly in blood vessels and neural tissues, respectively. NO is also rapidly elevated during inflammation and may be a primary mediator of the inflammatory injury that occurs in neurodegenerative disorders such as AD [101, 102]. Thus, elevated NO levels, directly resulting from inflammatory processes in neurodegeneration, likely increase potential for insulin resistance, and accelerate pathology and cognitive impairment in AD.

Interestingly, systemic and presumably brain insulin resistance together with insulin secretory defects are observed when NOS activity in the brain is inhibited by intracerebroventricular (ICV) injection of L-NMMA in free-moving rats [81]. In contrast, ICV infusion of S-nitrosoglutathione (GSNO), a NO donor in mice impaired insulin signaling in hypothalamus and replicated the food intake pattern of obese individuals by causing nitrosation of IR and its downstream Akt [37]. Further, S-nitrosation of the IR, IRS-1, and Akt (protein kinase B) can lead to insulin resistance [103, 104]. Genetically eliminating iNOS (iNOS null) or inhibiting iNOS using iNOS targeting antisense oligonucleotides both reduce hypothalamic insulin resistance and normalize energy homeostasis [37]. Thus, selective manipulation of brain NO system can lead to systemic and brain insulin signaling defects but the role of NO in brain insulin resistance remains controversial.

Modulation of NOS can also affect cognitive performance. Systemic administration of the NO synthase inhibitor nitro-L-arginine methyl ester (L-NAME) in rats and rabbits impairs maze (spatial) learning in rats [82, 105] as well as the conditioned eye-blink response in rabbits [82]. Inhibition of NOS by 7-nitroindazole, L-NAME or N-MMA, impairs passive-avoidance and elevated pulse-maze memory performance [106], T-maze [107] and memory of shock

avoidance [108]. Conversely, administration of the NO precursor L-arginine or NO donors such as sodium nitroprusside, S-nitroso-N-acetylpenicillamine (SNAP), and molsidomine improves learning and memory including avoidance memory, maze performance and objective recognition [108-111] and prevents age-related memory deficits [108].

While these data collectively suggest that chemical manipulation of the NO system can lead to systemic and brain region-specific insulin resistance as well as changes in cognitive performance, whether brain insulin resistance is induced by perturbing brain NOS was not explicitly demonstrated in the cognitive tests. Furthermore, effects on cognitive performance were not assessed together with insulin signaling changes. Thus, the contribution to altered cognition and dementia by altered NO availability caused by insulin signaling changes is still unclear.

To further elucidate the inter-relationship between brain insulin signaling and cognitive performance, genetic manipulations of the NO system have been employed and polymorphisms of the NOS have been examined. Emerging data from animal models and humans indicates that polymorphisms in the eNOS gene influence susceptibility to systemic insulin resistance and metabolic disturbances leading to T2D [112-115]. In contrast, eNOS T786C and E298D mutations do not increase the risk of sporadic AD [116, 117]. Similarly, NOS gene polymorphisms do not alter disease risk in the majority of late-onset AD and Lewy body dementia cases [118]. Further analysis of the E298 allele reveals its association with higher risk of AD in the MIRAGE African American but not Caucasian population [119]. Although these studies suggest a causative role of reduced eNOS levels and sensitivity in the development of systemic insulin resistance, metabolic disturbance, and blood vessel resistance in animal models, eNOS polymorphisms in humans do not appear to affect brain insulin signaling and play a minor role in the AD progression. In addition to eNOS, iNOS activity is considerably higher in the hippocampus of AD patients compared to controls [120]. Together with the demonstration that decreased NO availability leads to many features of the diabetic state [121], the modulation of NO availability including genetic or polymorphism-induced changes in the NOS system appears to influence insulin signaling in peripheral tissues and may be an important molecular mechanism underlying the development of insulin resistance in the peripheral tissues. However, such changes in NO availability have little impact on brain insulin signaling and cognition.

Moreover, the impact on cognitive performance of altered NO availability resulting from compromised brain insulin signaling remains unclear. NO has long been regarded as a part of neurotoxic insult derived from neuroinflammation driven in part by elevation of pro-inflammatory cytokines including TNF α , IL-6 and IL-1 β

in the AD brain. Proinflammatory cytokines such as TNF α disrupt gene expression to reduce eNOS protein levels in endothelium and probably in dendritic spines by decreasing eNOS mRNA stability [122-125]. Thus, by reducing eNOS levels, proinflammatory cytokines such as TNF α can interfere with insulin signaling to evoke tissue-specific insulin resistance. Since AD is associated with sustained neuroinflammation with elevated proinflammatory cytokines in the brain, especially in areas important for cognition such as hippocampus and cortical regions [8, 9, 74], the insulin resistance induced by proinflammatory cytokines may be intertwined with neurodegeneration and dementia.

Conversely, stimulation of insulin signaling via PI3K-Akt can activate eNOS by phosphorylating the enzyme on the serine1177 residue. Insulin signaling can also potentiate adiponectin signaling to activate AMP kinase that in turn activates eNOS through phosphorylation of S1177 to promote glucose uptake in GluT4 expression neurons [101, 126]. Activation of eNOS also requires its localization in the caveolae and linkage with heat shock protein 90 (HSP90). Obesity-associated insulin resistance can decrease eNOS activity by reducing caveolin-1 in caveolae and disrupting eNOS interaction with HSP90 and insulin signaling cascade [127, 128]. Hence, elevated proinflammatory cytokines and reactive oxygen species (ROS) in AD brain can lead to reduced eNOS phosphorylation and activation, resulting in decreased NO availability and insulin resistance in endothelium as well as impaired vasodilation [129, 130]. Finally, superoxide rapidly reacts with NO to produce the more potent oxidant peroxynitrite, leading to endothelial dysfunction, reduced NO availability, exacerbating brain insulin resistance and promoting AD pathogenesis. Although these data point to the possible contribution of reduced NO by the elevated proinflammatory cytokines to insulin resistance in AD brain, the inter-relationships among proinflammatory cytokines, NO system and insulin resistance needs to be more clearly defined.

CONCLUDING REMARKS

In conclusion, ample of evidence from animal models and humans illustrates that impairments in the NO system contribute to the development of insulin resistance and associated metabolic disturbance in peripheral tissues. However, the direct contribution of reduced NO availability to brain insulin resistance is much less clear. Insulin is a critical regulator of multiple brain functions, including synaptic plasticity, learning and memory. Importantly, impaired insulin signaling (insulin resistance) in AD brain can occur without apparent systemic insulin signaling defects. Thus, clarifying the causal relationship of changes in the NO system to insulin signaling perturbations might increase our understanding of AD pathogenic

mechanisms and identify new therapeutic approaches such as modulating NO availability in brain to slow progression of the disease.

CONFLICT OF INTEREST

None Declare

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From: Aleksandar Mihajloski <mihajloski@mplaw.mk>
Sent time: 03/01/2022 06:23:14 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] CUNY investigation
Attachments: image002.png

Dear Mr. Wang,

Hope you are doing well.

As a long term investor in Cassava Science from 2019 year would like to inform you that the majority of my family's wealth is connected to the success of Sumiflam trails.

As you are aware Cassava shorts did huge damage to Cassava reputation as a Company spreading FUD, and the foundation of their short thesis is that you have manipulated the data and the WB.

So, I would be very happy if you can share any data regarding the CUNY investigation. I'm aware that the investigation is confidential, but this confidently is to protect your reputation during the investigation/proceedings.

If you decide to go public you can do it freely. Therefore for the sake of my family's financial security I'm begging you to share some light of this investigation.

I would be very grateful.

Thank you,

Wish you all the best to you and your family.

Aleksandar Mihajloski
Attorney at Law
Mihajloski & Popovska
Law and Patent Office
Crvena Voda 7/3
1000 Skopje
Macedonia

+38975443389
www.mplaw.mk
@alekmih
<https://mk.linkedin.com/in/aleksandarmihajloski>

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From: Simon Spichak <[REDACTED]@gmail.com>
Sent time: 03/01/2022 08:00:00 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Interview Request: Drug Discovery and Cassava Sciences

Dear Dr. Wang,

Hope this email finds you well! I'm a health and science journalist working on a story about Cassava Sciences for *Futurism*. I am interested in the controversy surrounding the allegations of fraud levelled against some of your publications. I'm wondering if you'd be interested in chatting about it or simufilem in general. Let me know if you're available to chat: calendly.com/simonspichak/30min

Cheers,

Simon Spichak (he/him)

Neuroscientist | Writer

Mobile: 647 876 7758

Website: simonspichak.com

From: Hoau-yan Wang
Sent time: 03/01/2022 10:21:11 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] Interview Request: Drug Discovery and Cassava Sciences

From: Simon Spichak <[REDACTED]@gmail.com>
Sent: Tuesday, March 1, 2022 8:00 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Interview Request: Drug Discovery and Cassava Sciences

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Cheers,

Simon Spichak (he/him)
Neuroscientist | Writer

Mobile: 647 876 7758
Website: simonspichak.com

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent time: 03/01/2022 10:21:18 AM
To: Hoau-yan Wang
Subject: [REDACTED] [EXTERNAL] Interview Request: Drug Discovery and Cassava Sciences

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To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] CUNY investigation
Attachments: image002.png

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If you decide to go public you can do it freely. Therefore for the sake of my family's financial security I'm begging you to share some light of this investigation.

I would be very grateful.

Thank you,

Wish you all the best to you and your family.

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Attorney at Law
Mihajloski & Popovska
Law and Patent Office
Crvena Voda 7/3
1000 Skopje
Macedonia

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Subject: [EXTERNAL] Congratulations Hoau-Yan, you reached a milestone

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Subject: [EXTERNAL] Lindsay Burns and others share their thoughts on LinkedIn



Hoau-Yan Wang

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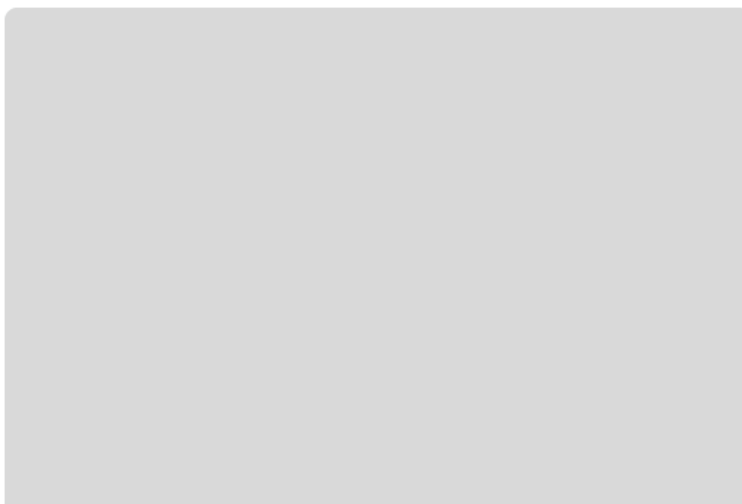
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To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau-Yan Wang,

There's a new comment on your article entitled: **PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiology of Aging**

This link will log you in so that you can respond to the comment; please do not share the link with anyone else

See comment and respond

Regards,
PubPeer

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There's a new comment on your article entitled: **PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiology of Aging**

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From: Pubpeer <alerts@pubpeer.com>
Sent time: 03/14/2022 06:51:35 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau-Yan Wang,

There's a new comment on your article entitled: **PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiology of Aging**

This link will log you in so that you can respond to the comment; please do not share the link with anyone else

See comment and respond

Regards,
PubPeer

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From: Pubpeer <alerts@pubpeer.com>
Sent time: 03/15/2022 02:16:48 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau-Yan Wang,

There's a new comment on your article entitled: **PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiology of Aging**

This link will log you in so that you can respond to the comment; please do not share the link with anyone else

See comment and respond

Regards,
PubPeer

If you're having trouble clicking the "See comment and respond" button, copy and paste the URL below into your web browser:

<https://pubpeer.com/publications/80DD10169D3C375C5828BC2711A49B/author-response/29583036?signature=0cc8fcfd3e13bc58c6dcaeadf75cd0a200b7883f7ba6b9b2ac3e403fc3df6f7>

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From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent time: 03/15/2022 04:08:56 PM
To: PLOS Pub Ethics <pub-ethics@plos.org>
Cc: lburns@cassavasciences.com; maya.frankfurt@hofstra.edu; Maya Frankfurt; Hoau-yan Wang
Subject: [EXTERNAL] Re: URGENT Please Respond - PLOS ONE: Editorial decision on the publication ethics concerns raised with your article
<https://doi.org/10.1371/journal.pone.0001554>
Attachments: 39788242-v3-Response to Retraction Dr. Zalm-REV BACK-F.pdf Spruck_letter12212021.pdf FDA and Burns letters.pdf
PLOS.2008.2009.pdf

Dear Dr. Zalm,

I (H-Y W) strongly disagree with retraction and I (H-Y W) stand by the article's findings.

2008 PLOS ONE article, "High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence" (<https://doi.org/10.1371/journal.pone.0001554>).

Please find the enclosed a Response to retraction Dr. Zalm memorandum that states clearly the reasons that the retraction is not warranted as well as a letter by an independent reviewer who indicates there is no manipulation of the data.

Thank you.

Respectfully

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

On Tue, Mar 1, 2022 at 11:30 AM PLOS Pub Ethics <pub-ethics@plos.org> wrote:

Dear Dr. Wang and colleagues,

I am writing from the PLOS Publication Ethics team in regard to your 2008 PLOS ONE article, "High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence" (<https://doi.org/10.1371/journal.pone.0001554>). Thank you for engaging with us in the discussion of concerns raised about this article.

We have now completed our editorial assessment of this case and decided to retract the above article. This decision was reached in discussion with the PLOS Publication ethics team and senior members of the journal's Editorial team. Together, we carefully considered the concerns raised, comments and data you provided, and the implications of the concerns for the reliability of results reported in the article. PLOS ONE abides by guidance of the Committee on Publication Ethics (COPE) in following up on concerns raised to the journal and addressing issues in the published literature. In this case we consider that retraction is warranted due to concerns about results presented in Figures 1 and 7, as well as concerns about the underlying data provided for this article and four other articles mentioned in the retraction notice copied below.

We plan to notify your institution of this issue and editorial decision, per the journal's standard procedure.

The specific issues that underlie this decision are explained in the retraction notice, which is included below my signature and will be posted on your article at the time of retraction. If you have any comments on the issues raised in the notice, or if you see any inaccuracies in the notice, **please reply with your comments no later than 08 March 2022.**

As discussed in COPE's Retraction Guidelines, the purpose of the public retraction notice is to correct the literature and relay the reasons for the editorial decision. Per PLOS' standards we also include standardized statements in retraction notices to indicate authors' positions with regard to the editorial decision. To inform these statements, we ask that each of you **reply individually by 08 March 2022** with your responses to both of the following questions:

1. Please add your initials next to the phrase that indicates your position with regard to the retraction decision:

- agree with retraction
- disagree with retraction

2. Add your initials next to the relevant phrase(s) if either of the following applies in your case and you would like a corresponding statement added to the public retraction notice:

- stand by the article's findings
- apologize for the issues with the published article

Please note that we will not consider requests for custom text in author position statements. We do not consider retraction notices to be an appropriate forum for discussion of items that go beyond the information readers should be provided around the circumstances and basis for the retraction. If you wish to comment publicly on information relayed in the retraction notice you may do so by posting a public Comment on the article or retraction webpage. Please note that any Comment posted on a PLOS webpage must abide by the Good Practice guidelines outlined at <https://journals.plos.org/plosone/s/comments>, and must include a Competing Interests statement which in this case should include your authorship of the retracted article.

After the specified reply deadline the notice text will be finalized and we will not consider further responses or queries regarding the retraction. If we do not receive your **reply by 08 March 2022**, or if you do not provide a reply to question 1 by this deadline, we will include a statement in the notice to indicate that you 'did not reply directly or could not be reached'.

If you have questions about this information you may reach me directly by replying to this email. Please reference Case 7282710 in any messages related to this matter.

I realize this will likely be a disappointing outcome and I am sorry I do not have more positive news to relay on this occasion.

Best regards,
Maria

Maria Zalm, Ph.D
Senior Editor Publication Ethics | she, her

PLOS | pub-ethics@plos.org
Empowering researchers to transform science
Carlyle House, Carlyle Road, Cambridge CB4 3DN | United Kingdom

California (U.S.) corporation #C2354500, based in San Francisco

Retraction: High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor-Gs Coupling Underlying Opioid Tolerance and Dependence

The PLOS ONE Editors

Following the publication of this article [1], concerns were raised regarding results presented in Figures 1 and 7. Specifically,

- There appear to be horizontal and vertical irregularities suggestive of splice lines in the following panels:
 - Between lanes between lanes 4-5 of the Figure 1A left and right FLNA panels, right MOR panel, and left and right Gα panels.
 - Between the 92.3kDa and the 50.4kDa marker of the Figure 1A left MOR panel.
 - Between lanes 2-3 of the Figure 7A Morphine + NLX + FLNA₂₅₅₀₋₂₅₆₀ panel.
 - Around multiple bands presented in the Figure 7A MOR and Gα panels
- In Figure 1C, neither the published panels nor the underlying data provided in follow-up discussions include a positive control sample. The absence of a positive control calls into question the reliability of the results presented in Figure 1C.
- The Figure 7A NLX and FLNA₂₅₅₀₋₂₅₆₀ panels appear similar.

The corresponding author noted that the Figure 7A NLX and FLNA₂₅₅₀₋₂₅₆₀ panels were inadvertently duplicated and provided a replacement panel for the FLNA₂₅₅₀₋₂₅₆₀ panel. However, the corresponding author disagreed with the Figures 1A concerns, stating that the observations are likely the result of image compression artefacts.

The corresponding author provided image data to support the contested western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS' assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. Furthermore, the supporting data files did not contain molecular weight markers or positive controls as needed to verify the reliability of the results. In response to these concerns, the corresponding author stated that the repetitive features in the background noise of the image data are likely the result of scanner artifacts and noted that the protein sizes on the blot were verified against pre-stained molecular weight markers. The explanation given for the background image similarities does not resolve the journal's concerns in light of PLOS' assessment of the data files.

The data and comments provided did not resolve the concerns about the integrity and reliability of data presented in this article. In light of these issues, the PLOS ONE Editors retract this article.

[Author initials] agreed with the retraction. [author initials] either did not respond directly or could not be reached. [author initials] did not agree with the retraction.

References

1. Wang H-Y, Frankfurt M, Burns LH (2008) High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence. PLoS ONE 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>
2. Wang H-Y, Burns LH (2009) Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor–Gs Coupling and CREB Activation of Acute Morphine. PLoS ONE 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>
3. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP. PLoS ONE 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>
4. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins. PLoS ONE 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>
5. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling. PLoS ONE 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>

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Case Number: 07282710

ref:_00DU0Ifis._5004P1dRVNC:ref_

DATE: March 14, 2022
 TO: Dr. Zalm
 Senior Editor Publication Ethics
 FROM: Dr. Hoau-Yan Wang

Re: Response to editorial notice

I write this memorandum in response to PLOS One's retraction notice regarding various articles authored or co-authored by me.¹ I respectfully but unequivocally disagree with your preliminary decision, as it is contrary to the evidence and not supported by COPE's retraction guidelines. As a result, I strongly urge you to reconsider the retraction or, alternatively, to consider a re-publication or corrigendum, for the reasons outlined below.

A. Introduction

In more than four decades as a research scientist, I have been motivated by the desire to help people and society and to pursue curiosity-driven research. My long and stable academic career includes over 120 peer reviewed publications and R&D collaborations with industry. Developing new drugs that help those suffering from debilitating illnesses, like Alzheimer's disease, is how I hope to make a difference. The importance of that work justifies working long days in my lab in New York City, a job that requires a five-hour round-trip daily commute to my home in Philadelphia. I also have a full teaching load as a Tenured Medical Professor at the CUNY School of Medicine that I must balance with my research responsibilities, as I also cherish playing a role in educating the next generation of doctors. Forty years of consistently ethical behavior have earned me a pristine reputation among colleagues, collaborators, and scientists. I value my reputation and would never do anything to jeopardize it. For instance, I run blinded studies where I do not know the treatment parameters and/or diagnoses of any samples, so that neither I nor anyone else in my lab could manipulate data for any improper end. While research scientists are fallible human beings capable of making inadvertent errors, I have always strived to honestly and ethically report methods, procedures, and data.

As you can imagine, the last few months have been absolutely devastating on a personal and

¹ The following five articles are at issue:

1. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) *Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling*. PLOS ONE 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>;
2. Wang H-Y, Frankfurt M, Burns LH (2008) *High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor-Gs Coupling Underlying Opioid Tolerance and Dependence*. PLOS ONE 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>;
3. Wang H-Y, Burns LH (2009) *Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor-Gs Coupling and CREB Activation of Acute Morphine*. PLOS ONE 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>;
4. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) *Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP*. PLOS ONE 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>; and
5. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) *Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins*. PLOS ONE 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>.

professional level. I have been repeatedly and unfairly attacked by people who, at best, do not understand the relevant scientific principles or, at worst, have an admitted financial or competing interest in undermining my research. I urge you to consider the motivations that drive the allegations. The allegations of research misconduct were prompted by a Citizen Petition filed with the FDA by a law firm with no expertise in Western blots, for the financial benefit of two individuals, David Bredt and Geoffrey Pitt. After filing the Citizen Petition, both Bredt and Pitt admitted that they hold short positions in the stock of my industry collaborator, Cassava Sciences, Inc.² A short position means that they can only profit if Cassava's stock price declines, which obviously provides an ample incentive to attack my research for Cassava.³ In December 2021, the DOJ announced "an extensive probe" into "the relationship among the hedge fund [investors] and firms that publish negative reports on certain companies, often with the aim of sending the stock lower."⁴ The short sellers certainly fall within this category that has come under DOJ scrutiny as lacking credibility and improperly motivated. What's more, the FDA has dismissed the Citizen Petition in its entirety and have declined to investigate its allegations further.⁵

In summary, I respectfully disagree with PLOS One's retraction notice for several reasons. First, contrary to COPE guidelines, PLOS One has failed to present "clear evidence" that my publications are unreliable or that any data has been falsified because there is no evidence for such allegations. In fact, none of the allegations are supported by reliable indirect evidence (e.g., a whistleblower, such as a lab technician, co-author, etc.). Second, several independent experts with specific expertise in Western blot imaging as well as editors of prestigious journals who have reviewed the matter have cleared me of wrongdoing.⁶ Third, the FDA has dismissed the Citizen Petition in its entirety, likely recognizing that the short sellers who initially raised allegations of misconduct have significant adverse financial motivations and are not credible. Fourth, PLOS One has not established "credible grounds" to discuss these issues with my employer. These four points are outlined in greater detail below.

B. PLOS ONE has failed to cite "clear evidence" of unreliability, contrary to COPE's retraction guidelines.

² Two days after the announcement of the Citizen Petition, a lawyer at the law firm representing the short sellers issued a press release admitting that his clients have taken a short position on Cassava's stock price. See <https://www.businesswire.com/news/home/20210826005765/en/Rebuttal-to-82521-Cassava-Sciences-Press-Release>.

³ According to media reports, after filing the Citizen Petition, short sellers (presumably including Bredt and Pitt) had made **\$100 million in profits** from their short positions in Cassava. See "Cassava Short Sellers Reap \$100 Million in August Stock Rout," *Bloomberg* (Aug. 31, 2021), available at: <https://www.bloomberg.com/news/articles/2021-08-31/cassava-short-sellers-reap-100-million-in-august-stock-rout>. Unlike the short sellers, I did not profit in any way from stock price changes in Cassava.

⁴ See <https://www.reuters.com/markets/europe/us-doj-launches-expansive-probe-into-short-selling-bloomberg-news-2021-12-10/>

⁵ See FDA letter dated February 10, 2022, attached hereto as Exhibit "A."

⁶ See findings by the Editor of Journal of Neuroscience, Marina Picciotto, PhD; Editor of Neuroscience, Prof. Juan Lerma, PhD; and Western blot expert, Dr. Charles Spruck.

PLOS One has failed to present “clear evidence” that my publications are unreliable or that I falsified data. COPE guidelines for retraction state editors should consider retraction if:

[T]hey have **clear evidence** that the findings are unreliable, either as a result of major error (e.g., miscalculation or experimental error), or as a result of fabrication (e.g., of data) or falsification (e.g., image manipulation).

COPE Retraction Guidelines, at 2. COPE guidelines also state editors should **state the reason(s)** for retractions and mention the reasons and basis for the retraction to enable readers to understand why the article is unreliable. *Id.* at 4.

Here, PLOS One has provided the following reasons for the retraction:

The corresponding author provided image data to support the contested western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS’ assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. Furthermore, the supporting data files did not contain molecular weight markers or positive controls as needed to verify the reliability of the results. In response to these concerns, the corresponding author stated that the repetitive features in the background noise of the image data are likely the result of scanner artifacts and noted that the protein sizes on the blot were verified against pre-stained molecular weight markers. The explanation given for the background image similarities does not resolve the journal’s concerns in light of PLOS’ assessment of the data files.

This explanation simply states PLOS One has “concerns” with the published data, but it fails to cite “clear evidence” for the retraction other than a summary conclusion or to discount my explanation for the issues other than saying they “do[] not resolve the journal’s concerns.”

As an initial matter, the responses to the inquiries of the five publications were due on a very short notice, often within mere days. I have done my best to gather as many of the original blots that were in my possession as possible. But, as you know, the personnel in a lab fluctuates, with students coming and going as they pursue their degrees. Notably, the oldest of these papers, the PLOS One 2008 paper, was published 14 years ago. However, I was still able to locate most of the original files and provide them to PLOS One. If PLOS One needs additional, specific information for its analysis, I would be happy to discuss how and whether I am able to locate that information.

A major concern of PLOS One appears to be the blot strips and absence of molecular weight markers. I agree with the team at PLOS One that whole blots would be one way to reflect potential cross-reactivity of an antibody with other proteins in a sample. However, I have, as any good scientist would, conducted a control experiment to assess such cross-reactivity before making the decision to cut the blot into strips. This was not indicated in the publication and could be corrected with a republication or corrigendum. Moreover, the decision to cut blots into strips was a budgetary decision. My lab operates on a strict budget, and we simply do not have the resources to process whole blots for all experiments, which would require ordering batch after batch of antibodies. In view of the high specificity of the antibody used, we felt it was justified to cut the blot into strips before probing. This

monetary decision to cut the blots into strips certainly does not indicate “clear evidence” of concerning conduct, as required by the COPE guidelines.

With regard to the molecular weight standards, as is generally known to those in the scientific community, an antibody will not react with the proteins contained in a molecular weight marker sample. Therefore, positions of molecular weight markers in blots are often indicated by pen after protein transfer to the blot. We follow this common practice. In support of this practice, replicated below is an original exemplary blot image that I was able to locate in my files. It shows the blot strips, and the positions of the molecular weight standards indicated with a pen to the right side of the blot strips (**red arrow**). This practice may not have been indicated in the publication and could likewise be corrected with a republication or a corrigendum.

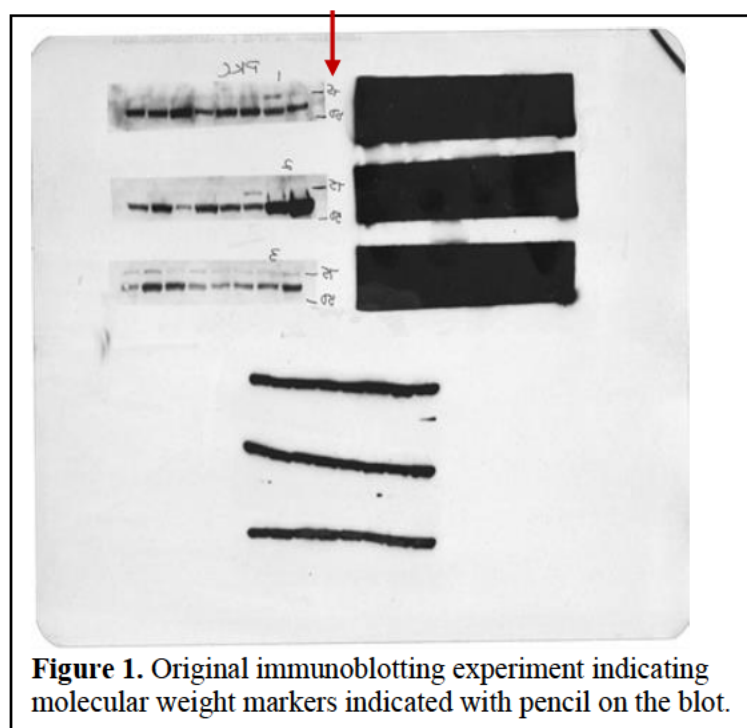


Figure 1. Original immunoblotting experiment indicating molecular weight markers indicated with pencil on the blot.

Some additional concerns relate to similarity in the appearance of bands in a blot. After 40 years of experience and with a steady hand, I am able to load samples in a way that the bands will appear similar in a gel. The original full width blots that I provided illustrate that I did not cut or paste any bands or otherwise commit scientific malpractice.

With regard to similarities in background patterns of the various blots presented, I have provided a very reasonable – and the only – explanation. Before we were able to acquire a more sophisticated scanner, all radiographic images were scanned with a simple scanner (again, due to the limited budget on which my lab operates). The inside of the lid of the scanner is a white sheet that becomes the background of any transparent image that is being scanned, like the blots. Consequently, the same background image is visible on all radiographic images scanned with that same scanner.

I realize PLOS One may have remaining concerns regarding uneven backgrounds, lines, and the like. I have given the best explanations that I have, as some of these visual appearances puzzle me as well. For those images I would urge PLOS One to consider the application of artificial intelligence

(“AI”) as it will prove I did not manipulate any blots. Other journals have applied this technology and have subsequently cleared me. The responses of those journals, and editors in charge, are summarized in section D below.

C. Numerous respected research journals and experts have cleared me of wrongdoing

Faced with similar allegations as PLOS One (presumably raised by the same short sellers), the editors of three respected research journals – Journal of Neuroscience (Marina Picciotto, PhD), Neuroscience (Prof. Juan Lerma, PhD), and Behavioral Pharmacology (Dr. VanderSchuren) – ***have cleared me of all allegations of data manipulation*** made by the short sellers. These clearances are from neutral parties who are experts in the field, all of whom agree I did not engage in data manipulation. The editors’ conclusions followed a thorough examination of raw data, and include the application of AI for Western blots analysis, in four separate papers. For all four papers, the editors-in-chief found “no evidence of data manipulation.” I hope PLOS One will at least consider these editorial decisions in view of its own, follow their lead in applying AI, and reconsider retraction.

Similarly, an independent expert on Western blots, Dr. Charles Spruck, has also examined and refuted the short seller’s allegations of manipulation of my Western blot images across many papers, as shown in the letter by Dr. Spruck attached to this letter. Dr. Spruck is a molecular biologist and researcher at Sanford Burnham, whose academic lab runs approximately 1,000 Western blots each year. After a close examination of the allegations and my data, Dr. Spruck concludes that certain “examples shown as evidence of data manipulation support the opposite.” Dr. Spruck also refutes allegations of scientific misconduct in a letter he wrote to the editors of *Journal of Prevention of Alzheimer’s Disease*:

After objectively reviewing the [Citizen Petition], I have concluded that the vast majority of concerns raised regarding the WB [Western blots] data are baseless and demonstrate a general lack of understanding of the technique and data interpretation. Evidence provided as potentially “altered” or “manipulated” data are effects we see routinely in our WB analyses.

See the letter by Dr. Spruck attached to this letter as Exhibition B. I did not know Dr. Spruck prior to the short sellers’ allegations. Instead, Dr. Spruck is acting independently to ensure that the correct conclusion is reached with respect to the sanctity of this important research. Dr. Spruck’s bio is available at the following link: <https://www.sbpdiscovery.org/our-scientists/charles-spruck-phd>.

D. The individuals who raised these allegations have significant adverse financial motivations.

As discussed above, this investigation was prompted by the reports of financially motivated short sellers of Cassava stock, including Bredt and Pitt. Further, one of the short sellers, Bredt, is first author on a newly issued patent that directly competes with Cassava. Given the short sellers’ goal of destroying the value of Cassava’s stock price, and apparently of favoring the patent Bredt holds over Cassava’s, the short sellers have launched attacks on me, and my entire academic research career based on unfounded claims of data manipulation. While I have conducted work for Cassava over the past ten years, that work has been a very small portion of my entire forty-year career as a research scientist. Moreover, all of the clinical biomarker work I conducted for Cassava was blinded as to all relevant research parameters (treatment group and/or timepoint), meaning that it would have been impossible for me to have

manipulated data in the way the short sellers suggest. In fact, even the FDA has declined to investigate the Citizen Petition, as mentioned above.

COPE retraction guidelines state “retraction notices . . . should specify who is retracting the article and possibly *how the matter came to the Journal’s attention*.” In light of these guidelines, I strongly request that the Journal disclose the identities of the individual(s) and/or entit(ies) who have raised these allegations so the public can evaluate their propriety. This biased sourcing of the report also tips the scale of how much “clear evidence” should be required to conclude that I have engaged in improper conduct: where I can provide an accurate and innocent explanation for my conduct, the financially motivated and biased views of Bredt, Pitt, and others should not be permitted to override that and certainly do not provide “clear evidence” of concerning conduct.

E. PLOS One has no basis to communicate with my employer under COPE guidelines.

PLOS One has neither indicated – let alone proven with “clear evidence” – that I committed scientific misconduct, and therefore no basis exists to contact my employer under COPE guidelines. COPE retraction guidelines state: “When editors have credible grounds to suspect misconduct, this should be brought to the attention of the authors’ institution.” *See* COPE Guidelines, at 6.

Dr. Zalm stated, “We plan to notify your institution of this issue and editorial decision, per the journal’s standard procedure,” which deviates from the COPE retraction guidelines because PLOS One *has not provided credible grounds to suspect misconduct* (as stated above). At the absolute worst, the Journal admittedly has only raised “concerns.” But as you know, scientific “concerns” and “credible grounds to suspect misconduct” are not the same thing. Absent proof of scientific misconduct, there is no basis to contact my employer under COPE guidelines.

F. Conclusion

In conclusion, over my four-decade career, I have engaged in rigorous and scientifically- sound practices of the research community. There is simply no clear evidence to support a finding of research misconduct and no reason why I would jeopardize my 40-year academic career to engage in the conduct that is alleged. Again, I urge you to consider the substantial profit motive of the individuals who initiated the underlying allegations, who are reported to have shared an outrageous \$100 million financial windfall from these allegations. Further, I would encourage you to consider that three journal editors and an independent expert on Western blots have carefully examined my Western blots in four publications and have concluded there is no evidence to support allegations of data manipulation and that the FDA has declined to further investigate the Citizen Petition.

For these reasons, I respectfully request that you *reconsider the retraction notice, or alternatively, consider republication or a corrigendum*, which would be a much more appropriate result given the issues raised. I am available to provide any additional information in person as needed.

Enclosures

Exhibit A



Jordan A. Thomas
Labaton Sucharow
140 Broadway
New York, NY 10005

February 10, 2022

Re: Docket Nos. FDA-2021-P-0930 and FDA-2021-P-0967

Dear Mr. Thomas:

This letter responds to your citizen petition received on August 23, 2021 (August Petition), with supplements dated August 30, 2021, September 9, 2021, November 17, 2021, and December 8, 2021 (Docket No. FDA-2021-P-0930) and your citizen petition received on September 1, 2021 (September Petition), with a supplement dated September 9, 2021 (Docket No. FDA-2021-P-0967) (collectively, your Petitions).

Your August Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that the Food and Drug Administration (FDA or Agency):

- halt the current clinical studies of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [investigational new drug application (IND)] for Simulifam's [sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease...
- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(August Petition at 1-2).

You further state that “[t]he ongoing clinical trials should be paused until the satisfactory completion of these investigations” (August Petition at 2).

Similarly, your September Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that FDA:

- halt the new clinical study of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT05026177), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [IND] for Simulifam's

[sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease; . . .

- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(September Petition at 1-2).

You further state that “[t]he upcoming clinical trial should be paused until the satisfactory completion of these investigations”¹ (September Petition at 2).

On November 17, 2021, you submitted a third supplement to the August Petition (the Third Supplement) stating that based on increasing evidence of purported wrongdoing, “FDA has a duty to immediately halt the simufilam (PT1-125) 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” (Third Supplement at 1).

FDA has carefully considered your Petitions and acknowledges the importance of the issues they raise. But as a threshold matter, by their own terms, your Petitions do not purport to set forth all relevant factual information. Rather, you call on FDA to initiate an investigation and fact-finding process. We are denying your Petitions to the extent that they request, through the citizen petition process, that FDA initiate an investigation. Under § 10.30 (21 CFR 10.30), citizen petitions can request that FDA issue, amend, or revoke a regulation or an order, or take or refrain from taking an administrative action,² and are to be resolved based on information in the administrative record.³ An investigation is not an administrative action, and, as your Petitions implicitly acknowledge, investigations necessarily require fact finding beyond what is presented in the current administrative record.

Moreover, issuing a response to your requests would appear to require FDA to publicly disclose information about an investigational new drug that, by law, FDA generally cannot publicly disclose. The Trade Secrets Act, 18 U.S.C. 1905, prohibits the disclosure of confidential commercial information unless doing so is authorized by law. FDA’s regulations regarding confidential commercial information provide that if the existence of an unapproved application has not previously been publicly disclosed, “no data or information in the application . . . is available for public disclosure.”⁴ In addition, FDA’s regulations provide that “the existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.”⁵ Thus, if the product sponsor has not previously

¹ In your September 9, 2021, supplements to the August Petition and the September Petition, you also “respectfully recommend rescinding the recently announced [Special Protocol Assessment] for Simufilam” (September 9, 2021, supplement at 8).

² See § 10.30(b)(3).

³ See § 10.30(j).

⁴ § 314.430(c) (21 CFR 314.430(c)).

⁵ 21 CFR 312.130(a).


made public the filing of an IND, FDA will not disclose the IND's existence. Nor will FDA disclose any information submitted as part of the IND: the application "includes all data and information submitted with or incorporated by reference in any application or abbreviated application, including investigational new drug applications."⁶ If the sponsor has already disclosed the existence of an IND for a not-yet-approved product, FDA may confirm the existence of the IND.⁷ However, FDA still will not make any "data or information contained in the application . . . available for public disclosure before the agency sends an approval letter," aside from narrow exceptions that are not relevant here.⁸ Accordingly, restrictions on disclosure of nonpublic information contained in an IND file apply both when a sponsor has already disclosed the existence of an IND, and when a sponsor has not.

With respect to your supplemental request that FDA report findings "to interested law enforcement and regulatory authorities," such a request is similarly not amenable to the citizen petition process. Decisions regarding enforcement actions are made on a case-by-case basis and are within the discretion of FDA. Requests for the Agency to initiate enforcement action and related regulatory activity are expressly excluded from the scope of FDA's citizen petition procedures.⁹

We take the issues you raise seriously. Please note that your Petitions are being denied solely on the grounds that your requests are not the appropriate subject of a citizen petition. This response does not represent a decision by the Agency to take or refrain from taking any action relating to the subject matter of your Petitions.

Sincerely,

**Patrizia A.
Cavazzoni -S**

 Digitally signed by Patrizia A.
Cavazzoni -S
Date: 2022.02.09 19:26:42 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

⁶ § 314.430(a).

⁷ § 314.430(b).

⁸ § 314.430(d)(1).

⁹ § 10.30(k).

Exhibit B

From: Lindsay Burns <lburns@cassavasciences.com>
Sent time: 03/15/2022 04:19:23 PM
To: Hoau-Yan Wang <[REDACTED]@gmail.com>; PLOS Pub Ethics <pub-ethics@plos.org>
Cc: maya.frankfurt@hofstra.edu; Hoau-yan Wang
Subject: [EXTERNAL] Re: URGENT Please Respond - PLOS ONE: Editorial decision on the publication ethics concerns raised with your article
<https://doi.org/10.1371/journal.pone.0001554>

Dear Dr. Zalm,

For the reasons outlined in Dr. Wang's letter and the letters of an independent Western blot expert reviewer, I strongly disagree with retracting this 2008 PLOS paper. We consider a retraction to be outside the scope of COPE guidelines, which require evidence of data manipulation. There is none. We request a correction to provide a corrected Figure 7A, correcting the inadvertently duplicated image.

Respectfully,
Lindsay Burns

Lindsay H. Burns, PhD

SVP, Neuroscience
Cassava Sciences, Inc.
O: 512-501-2484 C: 512-574-4238
www.cassavasciences.com



From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent: Tuesday, March 15, 2022 3:08 PM
To: PLOS Pub Ethics <pub-ethics@plos.org>
Cc: Lindsay Burns <lburns@cassavasciences.com>; mfrank@sci.ccny.cuny.edu <mfrank@sci.ccny.cuny.edu>; maya.frankfurt@hofstra.edu <maya.frankfurt@hofstra.edu>; hywang@sci.ccny.cuny.edu <hywang@sci.ccny.cuny.edu>
Subject: Re: URGENT Please Respond - PLOS ONE: Editorial decision on the publication ethics concerns raised with your article
<https://doi.org/10.1371/journal.pone.0001554>

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. Zalm,

I (H-Y W) strongly disagree with retraction and I (H-Y W) stand by the article's findings.

2008 PLOS ONE article, "High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor-Gs Coupling Underlying Opioid Tolerance and Dependence" (<https://doi.org/10.1371/journal.pone.0001554>).

Please find the enclosed a Response to retraction Dr. Zalm memorandum that states clearly the reasons that the retraction is not warranted as well as a letter by an independent reviewer who indicates there is no manipulation of the data.

Thank you.

Respectfully

Hoau-Yan Wang

Hoau-Yan Wang, Ph.D.
Medical Professor
CUNY SOM

On Tue, Mar 1, 2022 at 11:30 AM PLOS Pub Ethics <pub-ethics@plos.org> wrote:

Dear Dr. Wang and colleagues,

I am writing from the PLOS Publication Ethics team in regard to your 2008 PLOS ONE article, "High-Affinity Naloxone Binding

to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence" (<https://doi.org/10.1371/journal.pone.0001554>). Thank you for engaging with us in the discussion of concerns raised about this article.

We have now completed our editorial assessment of this case and decided to retract the above article. This decision was reached in discussion with the PLOS Publication ethics team and senior members of the journal's Editorial team. Together, we carefully considered the concerns raised, comments and data you provided, and the implications of the concerns for the reliability of results reported in the article. PLOS ONE abides by guidance of the Committee on Publication Ethics (COPE) in following up on concerns raised to the journal and addressing issues in the published literature. In this case we consider that retraction is warranted due to concerns about results presented in Figures 1 and 7, as well as concerns about the underlying data provided for this article and four other articles mentioned in the retraction notice copied below.

We plan to notify your institution of this issue and editorial decision, per the journal's standard procedure.

The specific issues that underlie this decision are explained in the retraction notice, which is included below my signature and will be posted on your article at the time of retraction. If you have any comments on the issues raised in the notice, or if you see any inaccuracies in the notice, **please reply with your comments no later than 08 March 2022**.

As discussed in COPE's Retraction Guidelines, the purpose of the public retraction notice is to correct the literature and relay the reasons for the editorial decision. Per PLOS' standards we also include standardized statements in retraction notices to indicate authors' positions with regard to the editorial decision. To inform these statements, we ask that each of you **reply individually by 08 March 2022** with your responses to both of the following questions:

1. Please add your initials next to the phrase that indicates your position with regard to the retraction decision:
 - agree with retraction
 - disagree with retraction
2. Add your initials next to the relevant phrase(s) if either of the following applies in your case and you would like a corresponding statement added to the public retraction notice:
 - stand by the article's findings
 - apologize for the issues with the published article

Please note that we will not consider requests for custom text in author position statements. We do not consider retraction notices to be an appropriate forum for discussion of items that go beyond the information readers should be provided around the circumstances and basis for the retraction. If you wish to comment publicly on information relayed in the retraction notice you may do so by posting a public Comment on the article or retraction webpage. Please note that any Comment posted on a PLOS webpage must abide by the Good Practice guidelines outlined at <https://journals.plos.org/plosone/s/comments>, and must include a Competing Interests statement which in this case should include your authorship of the retracted article.

After the specified reply deadline the notice text will be finalized and we will not consider further responses or queries regarding the retraction. If we do not receive your **reply by 08 March 2022**, or if you do not provide a reply to question 1 by this deadline, we will include a statement in the notice to indicate that you 'did not reply directly or could not be reached'.

If you have questions about this information you may reach me directly by replying to this email. Please reference Case 7282710 in any messages related to this matter.

I realize this will likely be a disappointing outcome and I am sorry I do not have more positive news to relay on this occasion.

Best regards,
Maria

Maria Zalm, Ph.D
Senior Editor Publication Ethics | she, her

PLOS | pub-ethics@plos.org
Empowering researchers to transform science
Carlyle House, Carlyle Road, Cambridge CB4 3DN | United Kingdom

California (U.S.) corporation #C2354500, based in San Francisco

Retraction: High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence

The *PLOS ONE* Editors

Following the publication of this article [1], concerns were raised regarding results presented in Figures 1 and 7. Specifically,

- There appear to be horizontal and vertical irregularities suggestive of splice lines in the following panels:
 - Between lanes between lanes 4-5 of the Figure 1A left and right FLNA panels, right MOR panel, and left and right Gα panels.
 - Between the 92.3kDa and the 50.4kDa marker of the Figure 1A left MOR panel.
 - Between lanes 2-3 of the Figure 7A Morphine + NLX + FLNA₂₅₅₀₋₂₅₆₀ panel.
 - Around multiple bands presented in the Figure 7A MOR and Gα panels
- In Figure 1C, neither the published panels nor the underlying data provided in follow-up discussions include a positive control sample. The absence of a positive control calls into question the reliability of the results presented in Figure 1C.
- The Figure 7A NLX and FLNA₂₅₅₀₋₂₅₆₀ panels appear similar.

The corresponding author noted that the Figure 7A NLX and FLNA₂₅₅₀₋₂₅₆₀ panels were inadvertently duplicated and provided a replacement panel for the FLNA₂₅₅₀₋₂₅₆₀ panel. However, the corresponding author disagreed with the Figures 1A concerns, stating that the observations are likely the result of image compression artefacts.

The corresponding author provided image data to support the contested western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS' assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. Furthermore, the supporting data files did not contain molecular weight markers or positive controls as needed to verify the reliability of the results. In response to these concerns, the corresponding author stated that the repetitive features in the background noise of the image data are likely the result of scanner artifacts and noted that the protein sizes on the blot were verified against pre-stained molecular weight markers. The explanation given for the background image similarities does not resolve the journal's concerns in light of PLOS' assessment of the data files.

The data and comments provided did not resolve the concerns about the integrity and reliability of data presented in this article. In light of these issues, the *PLOS ONE* Editors retract this article.

[Author initials] agreed with the retraction. [author initials] either did not respond directly or could not be reached. [author initials] did not agree with the retraction.

References

1. Wang H-Y, Frankfurt M, Burns LH (2008) High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence. *PLoS ONE* 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>
2. Wang H-Y, Burns LH (2009) Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor–Gs Coupling and CREB Activation of Acute Morphine. *PLoS ONE* 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>
3. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP. *PLoS ONE* 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>
4. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins. *PLoS ONE* 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>
5. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling. *PLoS ONE* 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>

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Case Number: 07282710

ref:_00DU0Ifis_5004P1dRVNC:ref

From: Hoau-Yan Wang [REDACTED]@gmail.com>
Sent time: 03/15/2022 04:26:04 PM
To: PLOS Pub Ethics <pub-ethics@plos.org>
Cc: [REDACTED]@hotmail.com; [REDACTED]@gmail.com; [REDACTED]@gmail.com; Satindra Goswami; Eitan Friedman; Hoau-yan Wang
Subject: [EXTERNAL] Re: URGENT Please Respond - PLOS ONE: Editorial decision on the publication ethics concerns raised with your article
<https://doi.org/10.1371/journal.pone.0091671>
Attachments: 39788242-v3-Response to Retraction Dr. Zalm-REV BACK-F.pdf FDA and Burns letters.pdf Spruck_letter12212021.pdf Letter 1.pdf

Dear Dr. Zalm,

I (H-Y W) strongly disagree with retraction and I (H-Y W) stand by the article's findings.

2014 PLOS ONE article, "Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins" (<https://doi.org/10.1371/journal.pone.0091671>).

Please find the enclosed a Response to retraction Dr. Zalm memorandum that states clearly the reasons that the retraction is not warranted as well as a letter by an independent reviewer who indicates there is no manipulation of the data.

Thank you.

Respectfully

Hoau-Yan Wang

*Hoau-Yan Wang, Ph.D.
Medical Professor*

On Tue, Mar 1, 2022 at 11:40 AM PLOS Pub Ethics <pub-ethics@plos.org> wrote:

Dear Dr. Wang and colleagues,

I am writing from the PLOS Publication Ethics team in regard to your 2014 PLOS ONE article, "Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins" (<https://doi.org/10.1371/journal.pone.0091671>). Thank you for engaging with us in the discussion of concerns raised about this article.

We have now completed our editorial assessment of this case and decided to retract the above article. This decision was reached in discussion with the PLOS Publication ethics team and senior members of the journal's Editorial team. Together, we carefully considered the concerns raised, comments you provided, and the implications of the concerns for the reliability of results reported in the article. PLOS ONE abides by guidance of the Committee on Publication Ethics (COPE) in following up on concerns raised to the journal and addressing issues in the published literature. In this case we consider that retraction is warranted due to concerns about results presented in Figures 2 and 5, as well as concerns about the underlying data provided for this article and four other articles mentioned in the retraction notice copied below.

We plan to notify your institution of this issue and editorial decision, per the journal's standard procedure.

The specific issues that underlie this decision are explained in the retraction notice, which is included below my signature and will be posted on your article at the time of retraction. If you have any comments on the issues raised in the notice, or if you see any inaccuracies in the notice, **please reply with your comments no later than 08 March 2022.**

As discussed in COPE's Retraction Guidelines, the purpose of the public retraction notice is to correct the literature and relay the reasons for the editorial decision. Per PLOS' standards we also include standardized statements in retraction notices to indicate authors' positions with regard to the editorial decision. To inform these statements, we ask that each of you **reply individually by 08 March 2022** with your responses to both of the following questions:

1. Please add your initials next to the phrase that indicates your position with regard to the retraction decision:
 - agree with retraction
 - disagree with retraction
2. Add your initials next to the relevant phrase(s) if either of the following applies in your case and you would like a corresponding statement added to the public retraction notice:
 - stand by the article's findings

- apologize for the issues with the published article

Please note that we will not consider requests for custom text in author position statements. We do not consider retraction notices to be an appropriate forum for discussion of items that go beyond the information readers should be provided around the circumstances and basis for the retraction. If you wish to comment publicly on information relayed in the retraction notice you may do so by posting a public Comment on the article or retraction webpage. Please note that any Comment posted on a PLOS webpage must abide by the Good Practice guidelines outlined at <https://journals.plos.org/plosone/s/comments>, and must include a Competing Interests statement which in this case should include your authorship of the retracted article.

After the specified reply deadline the notice text will be finalized and we will not consider further responses or queries regarding the retraction. If we do not receive your reply **by 08 March 2022**, or if you do not provide a reply to question 1 by this deadline, we will include a statement in the notice to indicate that you 'did not reply directly or could not be reached'.

If you have questions about this information you may reach me directly by replying to this email. Please reference Case 07282700 in any messages related to this matter.

I realize this will likely be a disappointing outcome and I am sorry I do not have more positive news to relay on this occasion.

Best regards,
Maria

Maria Zalm, Ph.D
Senior Editor Publication Ethics | she, her

PLOS | pub-ethics@plos.org
Empowering researchers to transform science
Carlyle House, Carlyle Road, Cambridge CB4 3DN | United Kingdom

California (U.S.) corporation #C2354500, based in San Francisco

Retraction: Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins

The *PLOS ONE* Editors

Following the publication of this article [1], concerns were raised regarding results presented in Figures 2 and 5. Specifically,

- In the Figure 2A Frontal cortex Homer1 panel, there appears to be a horizontal discontinuity in the background above the bands in lanes 1 and 2, as well as horizontal and vertical discontinuities around the top band in lane 4.
- The band in the fourth lane of the Figure 2A Frontal cortex mGluR1 panel appears similar to the band in the first lane of the Figure 5A Frontal cortex mGluR1 panel.
- The bands in lanes 2 and 3 of the Figure 2A Hippocampus mGluR1 panel appear similar to the bands in the Figure 5A Hippocampus mGluR1 panel.

The corresponding author disagrees with the concerns raised with Figures 2 and 5. Regarding the irregularities in the Figure 2A Homer 1 panel, the corresponding author suggests that the observed irregularities are likely the result of image artefacts or experimental artefacts such as reagent remnants or patches intrinsic to the membrane. Furthermore, the corresponding author stated that the mGluR1 panels presented in Figure 2A and Figure 5A were obtained from separate blots.

The corresponding author provided image data to support their published result in this [1] and other PLOS ONE articles [2-5]. Per PLOS' assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected from data obtained in independent experiments. The corresponding author stated that the repetitive features in the background noise of the underlying data are likely the result of scanner artefacts. The image data provided did not contain any size markers to confirm protein size. The corresponding author explained that the proteins on the blot were verified against pre-stained molecular weight markers.

The data and comments provided to PLOS did not resolve the concerns about the integrity and reliability of the reported data. In light of these issues, the *PLOS ONE* Editors retract this article.

[Author initials] agreed with the retraction. [author initials] either did not respond directly or could not be reached. [author initials] did not agree with the retraction.

References

1. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins. *PLoS ONE* 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>
2. Wang H-Y, Frankfurt M, Burns LH (2008) High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence. *PLoS ONE* 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>
3. Wang H-Y, Burns LH (2009) Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor–Gs Coupling

and CREB Activation of Acute Morphine. PLoS ONE 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>

4. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP. PLoS ONE 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>
5. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling. PLoS ONE 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>

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Case Number: 07282700

ref:_00DU0Ifis_5004P1dRVJA:ref

DATE: March 14, 2022
 TO: Dr. Zalm
 Senior Editor Publication Ethics
 FROM: Dr. Hoau-Yan Wang

Re: Response to editorial notice

I write this memorandum in response to PLOS One's retraction notice regarding various articles authored or co-authored by me.¹ I respectfully but unequivocally disagree with your preliminary decision, as it is contrary to the evidence and not supported by COPE's retraction guidelines. As a result, I strongly urge you to reconsider the retraction or, alternatively, to consider a re-publication or corrigendum, for the reasons outlined below.

A. Introduction

In more than four decades as a research scientist, I have been motivated by the desire to help people and society and to pursue curiosity-driven research. My long and stable academic career includes over 120 peer reviewed publications and R&D collaborations with industry. Developing new drugs that help those suffering from debilitating illnesses, like Alzheimer's disease, is how I hope to make a difference. The importance of that work justifies working long days in my lab in New York City, a job that requires a five-hour round-trip daily commute to my home in Philadelphia. I also have a full teaching load as a Tenured Medical Professor at the CUNY School of Medicine that I must balance with my research responsibilities, as I also cherish playing a role in educating the next generation of doctors. Forty years of consistently ethical behavior have earned me a pristine reputation among colleagues, collaborators, and scientists. I value my reputation and would never do anything to jeopardize it. For instance, I run blinded studies where I do not know the treatment parameters and/or diagnoses of any samples, so that neither I nor anyone else in my lab could manipulate data for any improper end. While research scientists are fallible human beings capable of making inadvertent errors, I have always strived to honestly and ethically report methods, procedures, and data.

As you can imagine, the last few months have been absolutely devastating on a personal and

¹ The following five articles are at issue:

1. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) *Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling*. PLOS ONE 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>;
2. Wang H-Y, Frankfurt M, Burns LH (2008) *High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor-Gs Coupling Underlying Opioid Tolerance and Dependence*. PLOS ONE 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>;
3. Wang H-Y, Burns LH (2009) *Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor-Gs Coupling and CREB Activation of Acute Morphine*. PLOS ONE 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>;
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5. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) *Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins*. PLOS ONE 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>.

professional level. I have been repeatedly and unfairly attacked by people who, at best, do not understand the relevant scientific principles or, at worst, have an admitted financial or competing interest in undermining my research. I urge you to consider the motivations that drive the allegations. The allegations of research misconduct were prompted by a Citizen Petition filed with the FDA by a law firm with no expertise in Western blots, for the financial benefit of two individuals, David Bredt and Geoffrey Pitt. After filing the Citizen Petition, both Bredt and Pitt admitted that they hold short positions in the stock of my industry collaborator, Cassava Sciences, Inc.² A short position means that they can only profit if Cassava's stock price declines, which obviously provides an ample incentive to attack my research for Cassava.³ In December 2021, the DOJ announced "an extensive probe" into "the relationship among the hedge fund [investors] and firms that publish negative reports on certain companies, often with the aim of sending the stock lower."⁴ The short sellers certainly fall within this category that has come under DOJ scrutiny as lacking credibility and improperly motivated. What's more, the FDA has dismissed the Citizen Petition in its entirety and have declined to investigate its allegations further.⁵

In summary, I respectfully disagree with PLOS One's retraction notice for several reasons. First, contrary to COPE guidelines, PLOS One has failed to present "clear evidence" that my publications are unreliable or that any data has been falsified because there is no evidence for such allegations. In fact, none of the allegations are supported by reliable indirect evidence (e.g., a whistleblower, such as a lab technician, co-author, etc.). Second, several independent experts with specific expertise in Western blot imaging as well as editors of prestigious journals who have reviewed the matter have cleared me of wrongdoing.⁶ Third, the FDA has dismissed the Citizen Petition in its entirety, likely recognizing that the short sellers who initially raised allegations of misconduct have significant adverse financial motivations and are not credible. Fourth, PLOS One has not established "credible grounds" to discuss these issues with my employer. These four points are outlined in greater detail below.

B. PLOS ONE has failed to cite "clear evidence" of unreliability, contrary to COPE's retraction guidelines.

² Two days after the announcement of the Citizen Petition, a lawyer at the law firm representing the short sellers issued a press release admitting that his clients have taken a short position on Cassava's stock price. *See* <https://www.businesswire.com/news/home/20210826005765/en/Rebuttal-to-82521-Cassava-Sciences-Press-Release>.

³ According to media reports, after filing the Citizen Petition, short sellers (presumably including Bredt and Pitt) had made **\$100 million in profits** from their short positions in Cassava. *See* "Cassava Short Sellers Reap \$100 Million in August Stock Rout," *Bloomberg* (Aug. 31, 2021), available at: <https://www.bloomberg.com/news/articles/2021-08-31/cassava-short-sellers-reap-100-million-in-august-stock-rout>. Unlike the short sellers, I did not profit in any way from stock price changes in Cassava.

⁴ *See* <https://www.reuters.com/markets/europe/us-doj-launches-expansive-probe-into-short-selling-bloomberg-news-2021-12-10/>

⁵ *See* FDA letter dated February 10, 2022, attached hereto as Exhibit "A."

⁶ *See* findings by the Editor of Journal of Neuroscience, Marina Picciotto, PhD; Editor of Neuroscience, Prof. Juan Lerma, PhD; and Western blot expert, Dr. Charles Spruck.

PLOS One has failed to present “clear evidence” that my publications are unreliable or that I falsified data. COPE guidelines for retraction state editors should consider retraction if:

[T]hey have **clear evidence** that the findings are unreliable, either as a result of major error (e.g., miscalculation or experimental error), or as a result of fabrication (e.g., of data) or falsification (e.g., image manipulation).

COPE Retraction Guidelines, at 2. COPE guidelines also state editors should **state the reason(s)** for retractions and mention the reasons and basis for the retraction to enable readers to understand why the article is unreliable. *Id.* at 4.

Here, PLOS One has provided the following reasons for the retraction:

The corresponding author provided image data to support the contested western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS’ assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. Furthermore, the supporting data files did not contain molecular weight markers or positive controls as needed to verify the reliability of the results. In response to these concerns, the corresponding author stated that the repetitive features in the background noise of the image data are likely the result of scanner artifacts and noted that the protein sizes on the blot were verified against pre-stained molecular weight markers. The explanation given for the background image similarities does not resolve the journal’s concerns in light of PLOS’ assessment of the data files.

This explanation simply states PLOS One has “concerns” with the published data, but it fails to cite “clear evidence” for the retraction other than a summary conclusion or to discount my explanation for the issues other than saying they “do[] not resolve the journal’s concerns.”

As an initial matter, the responses to the inquiries of the five publications were due on a very short notice, often within mere days. I have done my best to gather as many of the original blots that were in my possession as possible. But, as you know, the personnel in a lab fluctuates, with students coming and going as they pursue their degrees. Notably, the oldest of these papers, the PLOS One 2008 paper, was published 14 years ago. However, I was still able to locate most of the original files and provide them to PLOS One. If PLOS One needs additional, specific information for its analysis, I would be happy to discuss how and whether I am able to locate that information.

A major concern of PLOS One appears to be the blot strips and absence of molecular weight markers. I agree with the team at PLOS One that whole blots would be one way to reflect potential cross-reactivity of an antibody with other proteins in a sample. However, I have, as any good scientist would, conducted a control experiment to assess such cross-reactivity before making the decision to cut the blot into strips. This was not indicated in the publication and could be corrected with a republication or corrigendum. Moreover, the decision to cut blots into strips was a budgetary decision. My lab operates on a strict budget, and we simply do not have the resources to process whole blots for all experiments, which would require ordering batch after batch of antibodies. In view of the high specificity of the antibody used, we felt it was justified to cut the blot into strips before probing. This

monetary decision to cut the blots into strips certainly does not indicate “clear evidence” of concerning conduct, as required by the COPE guidelines.

With regard to the molecular weight standards, as is generally known to those in the scientific community, an antibody will not react with the proteins contained in a molecular weight marker sample. Therefore, positions of molecular weight markers in blots are often indicated by pen after protein transfer to the blot. We follow this common practice. In support of this practice, replicated below is an original exemplary blot image that I was able to locate in my files. It shows the blot strips, and the positions of the molecular weight standards indicated with a pen to the right side of the blot strips (**red arrow**). This practice may not have been indicated in the publication and could likewise be corrected with a republication or a corrigendum.

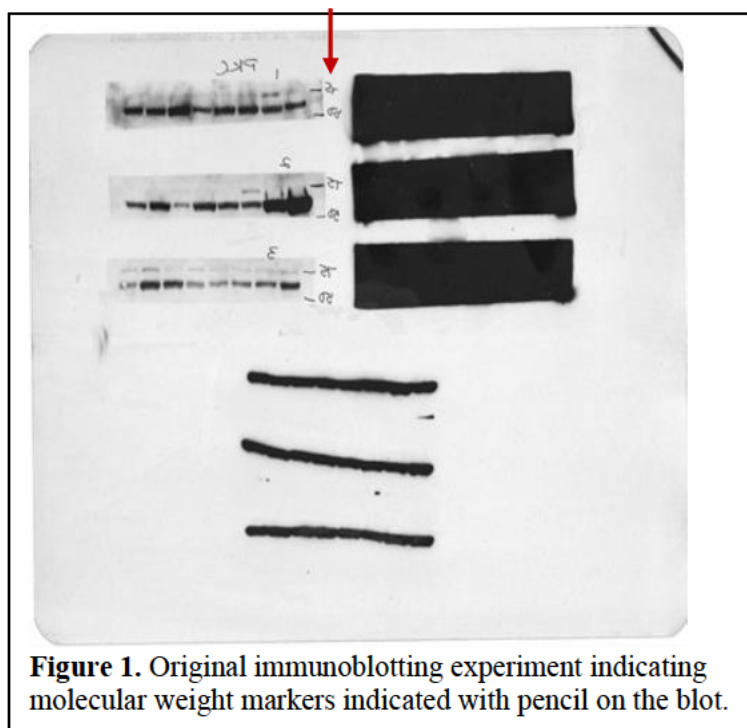


Figure 1. Original immunoblotting experiment indicating molecular weight markers indicated with pencil on the blot.

Some additional concerns relate to similarity in the appearance of bands in a blot. After 40 years of experience and with a steady hand, I am able to load samples in a way that the bands will appear similar in a gel. The original full width blots that I provided illustrate that I did not cut or paste any bands or otherwise commit scientific malpractice.

With regard to similarities in background patterns of the various blots presented, I have provided a very reasonable – and the only – explanation. Before we were able to acquire a more sophisticated scanner, all radiographic images were scanned with a simple scanner (again, due to the limited budget on which my lab operates). The inside of the lid of the scanner is a white sheet that becomes the background of any transparent image that is being scanned, like the blots. Consequently, the same background image is visible on all radiographic images scanned with that same scanner.

I realize PLOS One may have remaining concerns regarding uneven backgrounds, lines, and the like. I have given the best explanations that I have, as some of these visual appearances puzzle me as well. For those images I would urge PLOS One to consider the application of artificial intelligence

(“AI”) as it will prove I did not manipulate any blots. Other journals have applied this technology and have subsequently cleared me. The responses of those journals, and editors in charge, are summarized in section D below.

C. Numerous respected research journals and experts have cleared me of wrongdoing

Faced with similar allegations as PLOS One (presumably raised by the same short sellers), the editors of three respected research journals – Journal of Neuroscience (Marina Picciotto, PhD), Neuroscience (Prof. Juan Lerma, PhD), and Behavioral Pharmacology (Dr. VanderSchuren) – ***have cleared me of all allegations of data manipulation*** made by the short sellers. These clearances are from neutral parties who are experts in the field, all of whom agree I did not engage in data manipulation. The editors’ conclusions followed a thorough examination of raw data, and include the application of AI for Western blots analysis, in four separate papers. For all four papers, the editors-in-chief found “no evidence of data manipulation.” I hope PLOS One will at least consider these editorial decisions in view of its own, follow their lead in applying AI, and reconsider retraction.

Similarly, an independent expert on Western blots, Dr. Charles Spruck, has also examined and refuted the short seller’s allegations of manipulation of my Western blot images across many papers, as shown in the letter by Dr. Spruck attached to this letter. Dr. Spruck is a molecular biologist and researcher at Sanford Burnham, whose academic lab runs approximately 1,000 Western blots each year. After a close examination of the allegations and my data, Dr. Spruck concludes that certain “examples shown as evidence of data manipulation support the opposite.” Dr. Spruck also refutes allegations of scientific misconduct in a letter he wrote to the editors of *Journal of Prevention of Alzheimer’s Disease*:

After objectively reviewing the [Citizen Petition], I have concluded that the vast majority of concerns raised regarding the WB [Western blots] data are baseless and demonstrate a general lack of understanding of the technique and data interpretation. Evidence provided as potentially “altered” or “manipulated” data are effects we see routinely in our WB analyses.

See the letter by Dr. Spruck attached to this letter as Exhibition B. I did not know Dr. Spruck prior to the short sellers’ allegations. Instead, Dr. Spruck is acting independently to ensure that the correct conclusion is reached with respect to the sanctity of this important research. Dr. Spruck’s bio is available at the following link: <https://www.sbpdiscovery.org/our-scientists/charles-spruck-phd>.

D. The individuals who raised these allegations have significant adverse financial motivations.

As discussed above, this investigation was prompted by the reports of financially motivated short sellers of Cassava stock, including Bredt and Pitt. Further, one of the short sellers, Bredt, is first author on a newly issued patent that directly competes with Cassava. Given the short sellers’ goal of destroying the value of Cassava’s stock price, and apparently of favoring the patent Bredt holds over Cassava’s, the short sellers have launched attacks on me, and my entire academic research career based on unfounded claims of data manipulation. While I have conducted work for Cassava over the past ten years, that work has been a very small portion of my entire forty-year career as a research scientist. Moreover, all of the clinical biomarker work I conducted for Cassava was blinded as to all relevant research parameters (treatment group and/or timepoint), meaning that it would have been impossible for me to have

manipulated data in the way the short sellers suggest. In fact, even the FDA has declined to investigate the Citizen Petition, as mentioned above.

COPE retraction guidelines state “retraction notices . . . should specify who is retracting the article and possibly *how the matter came to the Journal’s attention*.” In light of these guidelines, I strongly request that the Journal disclose the identities of the individual(s) and/or entit(ies) who have raised these allegations so the public can evaluate their propriety. This biased sourcing of the report also tips the scale of how much “clear evidence” should be required to conclude that I have engaged in improper conduct: where I can provide an accurate and innocent explanation for my conduct, the financially motivated and biased views of Bredt, Pitt, and others should not be permitted to override that and certainly do not provide “clear evidence” of concerning conduct.

E. PLOS One has no basis to communicate with my employer under COPE guidelines.

PLOS One has neither indicated – let alone proven with “clear evidence” – that I committed scientific misconduct, and therefore no basis exists to contact my employer under COPE guidelines. COPE retraction guidelines state: “When editors have credible grounds to suspect misconduct, this should be brought to the attention of the authors’ institution.” *See* COPE Guidelines, at 6.

Dr. Zalm stated, “We plan to notify your institution of this issue and editorial decision, per the journal’s standard procedure,” which deviates from the COPE retraction guidelines because PLOS One *has not provided credible grounds to suspect misconduct* (as stated above). At the absolute worst, the Journal admittedly has only raised “concerns.” But as you know, scientific “concerns” and “credible grounds to suspect misconduct” are not the same thing. Absent proof of scientific misconduct, there is no basis to contact my employer under COPE guidelines.

F. Conclusion

In conclusion, over my four-decade career, I have engaged in rigorous and scientifically- sound practices of the research community. There is simply no clear evidence to support a finding of research misconduct and no reason why I would jeopardize my 40-year academic career to engage in the conduct that is alleged. Again, I urge you to consider the substantial profit motive of the individuals who initiated the underlying allegations, who are reported to have shared an outrageous \$100 million financial windfall from these allegations. Further, I would encourage you to consider that three journal editors and an independent expert on Western blots have carefully examined my Western blots in four publications and have concluded there is no evidence to support allegations of data manipulation and that the FDA has declined to further investigate the Citizen Petition.

For these reasons, I respectfully request that you *reconsider the retraction notice, or alternatively, consider republication or a corrigendum*, which would be a much more appropriate result given the issues raised. I am available to provide any additional information in person as needed.

Enclosures

Exhibit A



Jordan A. Thomas
Labaton Sucharow
140 Broadway
New York, NY 10005

February 10, 2022

Re: Docket Nos. FDA-2021-P-0930 and FDA-2021-P-0967

Dear Mr. Thomas:

This letter responds to your citizen petition received on August 23, 2021 (August Petition), with supplements dated August 30, 2021, September 9, 2021, November 17, 2021, and December 8, 2021 (Docket No. FDA-2021-P-0930) and your citizen petition received on September 1, 2021 (September Petition), with a supplement dated September 9, 2021 (Docket No. FDA-2021-P-0967) (collectively, your Petitions).

Your August Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that the Food and Drug Administration (FDA or Agency):

- halt the current clinical studies of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [investigational new drug application (IND)] for Simulifam's [sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease...
- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(August Petition at 1-2).

You further state that “[t]he ongoing clinical trials should be paused until the satisfactory completion of these investigations” (August Petition at 2).

Similarly, your September Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that FDA:

- halt the new clinical study of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT05026177), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [IND] for Simulifam's

[sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease; . . .

- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(September Petition at 1-2).

You further state that “[t]he upcoming clinical trial should be paused until the satisfactory completion of these investigations”¹ (September Petition at 2).

On November 17, 2021, you submitted a third supplement to the August Petition (the Third Supplement) stating that based on increasing evidence of purported wrongdoing, “FDA has a duty to immediately halt the simufilam (PT1-125) 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” (Third Supplement at 1).

FDA has carefully considered your Petitions and acknowledges the importance of the issues they raise. But as a threshold matter, by their own terms, your Petitions do not purport to set forth all relevant factual information. Rather, you call on FDA to initiate an investigation and fact-finding process. We are denying your Petitions to the extent that they request, through the citizen petition process, that FDA initiate an investigation. Under § 10.30 (21 CFR 10.30), citizen petitions can request that FDA issue, amend, or revoke a regulation or an order, or take or refrain from taking an administrative action,² and are to be resolved based on information in the administrative record.³ An investigation is not an administrative action, and, as your Petitions implicitly acknowledge, investigations necessarily require fact finding beyond what is presented in the current administrative record.

Moreover, issuing a response to your requests would appear to require FDA to publicly disclose information about an investigational new drug that, by law, FDA generally cannot publicly disclose. The Trade Secrets Act, 18 U.S.C. 1905, prohibits the disclosure of confidential commercial information unless doing so is authorized by law. FDA’s regulations regarding confidential commercial information provide that if the existence of an unapproved application has not previously been publicly disclosed, “no data or information in the application . . . is available for public disclosure.”⁴ In addition, FDA’s regulations provide that “the existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.”⁵ Thus, if the product sponsor has not previously

¹ In your September 9, 2021, supplements to the August Petition and the September Petition, you also “respectfully recommend rescinding the recently announced [Special Protocol Assessment] for Simufilam” (September 9, 2021, supplement at 8).

² See § 10.30(b)(3).

³ See § 10.30(j).

⁴ § 314.430(c) (21 CFR 314.430(c)).

⁵ 21 CFR 312.130(a).


made public the filing of an IND, FDA will not disclose the IND's existence. Nor will FDA disclose any information submitted as part of the IND: the application "includes all data and information submitted with or incorporated by reference in any application or abbreviated application, including investigational new drug applications."⁶ If the sponsor has already disclosed the existence of an IND for a not-yet-approved product, FDA may confirm the existence of the IND.⁷ However, FDA still will not make any "data or information contained in the application . . . available for public disclosure before the agency sends an approval letter," aside from narrow exceptions that are not relevant here.⁸ Accordingly, restrictions on disclosure of nonpublic information contained in an IND file apply both when a sponsor has already disclosed the existence of an IND, and when a sponsor has not.

With respect to your supplemental request that FDA report findings "to interested law enforcement and regulatory authorities," such a request is similarly not amenable to the citizen petition process. Decisions regarding enforcement actions are made on a case-by-case basis and are within the discretion of FDA. Requests for the Agency to initiate enforcement action and related regulatory activity are expressly excluded from the scope of FDA's citizen petition procedures.⁹

We take the issues you raise seriously. Please note that your Petitions are being denied solely on the grounds that your requests are not the appropriate subject of a citizen petition. This response does not represent a decision by the Agency to take or refrain from taking any action relating to the subject matter of your Petitions.

Sincerely,

**Patrizia A.
Cavazzoni -S**

 Digitally signed by Patrizia A.
Cavazzoni -S
Date: 2022.02.09 19:26:42 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

⁶ § 314.430(a).

⁷ § 314.430(b).

⁸ § 314.430(d)(1).

⁹ § 10.30(k).

Exhibit B

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent time: 03/15/2022 04:32:06 PM
To: PLOS Pub Ethics <pub-ethics@plos.org>
Cc: kbakshi@med.cuny.edu; kosciurno@umdnj.edu; nagelero@umdnj.edu; Eitan Friedman; Hoau-yan Wang
Subject: [EXTERNAL] Re: URGENT Please Respond - PLOS ONE: Editorial decision on the publication ethics concerns raised with your article
<https://doi.org/10.1371/journal.pone.0025019>
Attachments: 39788242-v3-Response to Retraction Dr. Zalm-REV BACK-F.pdf Spruck_letter12212021.pdf FDA and Burns letters.pdf
PLOS03142022CS (1).pdf

Dear Dr. Zalm,

I (H-Y W) strongly disagree with retraction and I (H-Y W) stand by the article's findings.

2011 PLOS ONE article, "Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP" (<https://doi.org/10.1371/journal.pone.0025019>).

Please find the enclosed a Response to retraction Dr. Zalm memorandum that states clearly the reasons that the retraction is not warranted as well as a letter by an independent reviewer who indicates there is no manipulation of the data.

Thank you.

Respectfully

Hoau-Yan Wang

*Hoau-Yan Wang, Ph.D.
Medical Professor*

On Tue, Mar 1, 2022 at 11:55 AM PLOS Pub Ethics <pub-ethics@plos.org> wrote:

Dear Dr. Wang and colleagues,

I am writing from the PLOS Publication Ethics team in regard to your 2011 PLOS ONE article, "Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP" (<https://doi.org/10.1371/journal.pone.0025019>). Thank you for engaging with us in the discussion of concerns raised about this article.

We have now completed our editorial assessment of this case and decided to retract the above article. This decision was reached in discussion with the PLOS Publication ethics team and senior members of the journal's Editorial team. Together, we carefully considered the concerns raised, comments you provided, and the implications of the concerns for the reliability of results reported in the article. PLOS ONE abides by guidance of the Committee on Publication Ethics (COPE) in following up on concerns raised to the journal and addressing issues in the published literature. In this case we consider that retraction is warranted due to concerns about results presented in Figures 1, 2, 4 and 6, as well as concerns about the underlying data provided for this article and four other articles mentioned in the retraction notice copied below.

We plan to notify your institution of this issue and editorial decision, per the journal's standard procedure.

The specific issues that underlie this decision are explained in the retraction notice, which is included below my signature and will be posted on your article at the time of retraction. If you have any comments on the issues raised in the notice, or if you see any inaccuracies in the notice, **please reply with your comments no later than 08 March 2022**.

As discussed in COPE's Retraction Guidelines, the purpose of the public retraction notice is to correct the literature and relay the reasons for the editorial decision. Per PLOS' standards we also include standardized statements in retraction notices to indicate authors' positions with regard to the editorial decision. To inform these statements, we ask that each of you **reply individually by 08 March 2022** with your responses to both of the following questions:

1. Please add your initials next to the phrase that indicates your position with regard to the retraction decision:
 - agree with retraction
 - disagree with retraction
2. Add your initials next to the relevant phrase(s) if either of the following applies in your case and you would like a

corresponding statement added to the public retraction notice:

- stand by the article's findings
- apologize for the issues with the published article

Please note that we will not consider requests for custom text in author position statements. We do not consider retraction notices to be an appropriate forum for discussion of items that go beyond the information readers should be provided around the circumstances and basis for the retraction. If you wish to comment publicly on information relayed in the retraction notice you may do so by posting a public Comment on the article or retraction webpage. Please note that any Comment posted on a PLOS webpage must abide by the Good Practice guidelines outlined at <https://journals.plos.org/plosone/s/comments>, and must include a Competing Interests statement which in this case should include your authorship of the retracted article.

After the specified reply deadline the notice text will be finalized and we will not consider further responses or queries regarding the retraction. If we do not receive your reply by **08 March 2022**, or if you do not provide a reply to question 1 by this deadline, we will include a statement in the notice to indicate that you 'did not reply directly or could not be reached'.

If you have questions about this information you may reach me directly by replying to this email. Please reference Case 07282710 in any messages related to this matter.

I realize this will likely be a disappointing outcome and I am sorry I do not have more positive news to relay on this occasion.

Best regards,
Maria

Maria Zalm, Ph.D
Senior Editor Publication Ethics | she, her

PLOS | pub-ethics@plos.org
Empowering researchers to transform science
Carlyle House, Carlyle Road, Cambridge CB4 3DN | United Kingdom

California (U.S.) corporation #C2354500, based in San Francisco

Retraction: Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP

The *PLOS ONE* Editors

Following the publication of this article [1], concerns were raised regarding results presented in Figures 1, 2, 4, and 6. Specifically,

- There appear to be horizontal and vertical irregularities suggestive of splice lines in the following panels:
 - Figure 1C, within lane 4 of the Caspase 3 panel.
 - Figure 2A, just above the 90kDa marker of the GRASP-1 panel
 - Figure 2A, around each individual band in the GRIP1 panel.
 - Figure 6A, between lanes 7-8 of the GluR2 panel.
- Further irregularities have been detected in the background of the following panels:
 - Figure 4A Rap1 panel, near the lower right edge of the panel there appears to be a truncated fragment of a double band.
 - Figure 6A GRASP-1 panel, when levels are adjusted to visualize background, the density of the background noise directly surrounding the bands in lanes 5 and 6 does not appear to match the background noise density elsewhere in the blot.
 - Figure 6A GRIP1 panel, when levels are adjusted to visualize background, there appear to be sharp horizontal and vertical discontinuities in lane 1.

The corresponding author disagreed with the above concerns. They stated that each panel was obtained from a single blot and that the observations are likely the result of image compression artifacts or experimental artifacts such as gel or reagent remnants, or patches intrinsic to the nitrocellulose membranes.

The corresponding author provided image data to support their published western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS' assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. The corresponding author stated that the repetitive features in the background noise of the underlying data are likely the result of scanner artifacts.

The image data provided did not contain any size markers to confirm protein size. The corresponding author explained that the proteins on the blot were verified against pre-stained molecular weight markers.

The data and comments provided to PLOS did not resolve the concerns about the integrity and reliability of the reported data. In light of these issues, the *PLOS ONE* Editors retract this article.

[Author initials] agreed with the retraction. [author initials] either did not respond directly or could not be reached. [author initials]

did not agree with the retraction.

References

1. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP. PLoS ONE 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>
2. Wang H-Y, Frankfurt M, Burns LH (2008) High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence. PLoS ONE 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>
3. Wang H-Y, Burns LH (2009) Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor–Gs Coupling and CREB Activation of Acute Morphine. PLoS ONE 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>
4. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins. PLoS ONE 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>
5. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling. PLoS ONE 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>

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Case Number: 07388476

ref:_00DU0Ifis_5004P1iJ89D:ref

DATE: March 14, 2022
 TO: Dr. Zalm
 Senior Editor Publication Ethics
 FROM: Dr. Hoau-Yan Wang

Re: Response to editorial notice

I write this memorandum in response to PLOS One's retraction notice regarding various articles authored or co-authored by me.¹ I respectfully but unequivocally disagree with your preliminary decision, as it is contrary to the evidence and not supported by COPE's retraction guidelines. As a result, I strongly urge you to reconsider the retraction or, alternatively, to consider a re-publication or corrigendum, for the reasons outlined below.

A. Introduction

In more than four decades as a research scientist, I have been motivated by the desire to help people and society and to pursue curiosity-driven research. My long and stable academic career includes over 120 peer reviewed publications and R&D collaborations with industry. Developing new drugs that help those suffering from debilitating illnesses, like Alzheimer's disease, is how I hope to make a difference. The importance of that work justifies working long days in my lab in New York City, a job that requires a five-hour round-trip daily commute to my home in Philadelphia. I also have a full teaching load as a Tenured Medical Professor at the CUNY School of Medicine that I must balance with my research responsibilities, as I also cherish playing a role in educating the next generation of doctors. Forty years of consistently ethical behavior have earned me a pristine reputation among colleagues, collaborators, and scientists. I value my reputation and would never do anything to jeopardize it. For instance, I run blinded studies where I do not know the treatment parameters and/or diagnoses of any samples, so that neither I nor anyone else in my lab could manipulate data for any improper end. While research scientists are fallible human beings capable of making inadvertent errors, I have always strived to honestly and ethically report methods, procedures, and data.

As you can imagine, the last few months have been absolutely devastating on a personal and

¹ The following five articles are at issue:

1. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) *Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling*. PLOS ONE 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>;
2. Wang H-Y, Frankfurt M, Burns LH (2008) *High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor-Gs Coupling Underlying Opioid Tolerance and Dependence*. PLOS ONE 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>;
3. Wang H-Y, Burns LH (2009) *Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor-Gs Coupling and CREB Activation of Acute Morphine*. PLOS ONE 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>;
4. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) *Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP*. PLOS ONE 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>; and
5. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) *Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins*. PLOS ONE 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>.

professional level. I have been repeatedly and unfairly attacked by people who, at best, do not understand the relevant scientific principles or, at worst, have an admitted financial or competing interest in undermining my research. I urge you to consider the motivations that drive the allegations. The allegations of research misconduct were prompted by a Citizen Petition filed with the FDA by a law firm with no expertise in Western blots, for the financial benefit of two individuals, David Bredt and Geoffrey Pitt. After filing the Citizen Petition, both Bredt and Pitt admitted that they hold short positions in the stock of my industry collaborator, Cassava Sciences, Inc.² A short position means that they can only profit if Cassava's stock price declines, which obviously provides an ample incentive to attack my research for Cassava.³ In December 2021, the DOJ announced "an extensive probe" into "the relationship among the hedge fund [investors] and firms that publish negative reports on certain companies, often with the aim of sending the stock lower."⁴ The short sellers certainly fall within this category that has come under DOJ scrutiny as lacking credibility and improperly motivated. What's more, the FDA has dismissed the Citizen Petition in its entirety and have declined to investigate its allegations further.⁵

In summary, I respectfully disagree with PLOS One's retraction notice for several reasons. First, contrary to COPE guidelines, PLOS One has failed to present "clear evidence" that my publications are unreliable or that any data has been falsified because there is no evidence for such allegations. In fact, none of the allegations are supported by reliable indirect evidence (e.g., a whistleblower, such as a lab technician, co-author, etc.). Second, several independent experts with specific expertise in Western blot imaging as well as editors of prestigious journals who have reviewed the matter have cleared me of wrongdoing.⁶ Third, the FDA has dismissed the Citizen Petition in its entirety, likely recognizing that the short sellers who initially raised allegations of misconduct have significant adverse financial motivations and are not credible. Fourth, PLOS One has not established "credible grounds" to discuss these issues with my employer. These four points are outlined in greater detail below.

B. PLOS ONE has failed to cite "clear evidence" of unreliability, contrary to COPE's retraction guidelines.

² Two days after the announcement of the Citizen Petition, a lawyer at the law firm representing the short sellers issued a press release admitting that his clients have taken a short position on Cassava's stock price. *See* <https://www.businesswire.com/news/home/20210826005765/en/Rebuttal-to-82521-Cassava-Sciences-Press-Release>.

³ According to media reports, after filing the Citizen Petition, short sellers (presumably including Bredt and Pitt) had made **\$100 million in profits** from their short positions in Cassava. *See* "Cassava Short Sellers Reap \$100 Million in August Stock Rout," *Bloomberg* (Aug. 31, 2021), available at: <https://www.bloomberg.com/news/articles/2021-08-31/cassava-short-sellers-reap-100-million-in-august-stock-rout>. Unlike the short sellers, I did not profit in any way from stock price changes in Cassava.

⁴ *See* <https://www.reuters.com/markets/europe/us-doj-launches-expansive-probe-into-short-selling-bloomberg-news-2021-12-10/>

⁵ *See* FDA letter dated February 10, 2022, attached hereto as Exhibit "A."

⁶ *See* findings by the Editor of Journal of Neuroscience, Marina Picciotto, PhD; Editor of Neuroscience, Prof. Juan Lerma, PhD; and Western blot expert, Dr. Charles Spruck.

PLOS One has failed to present “clear evidence” that my publications are unreliable or that I falsified data. COPE guidelines for retraction state editors should consider retraction if:

[T]hey have **clear evidence** that the findings are unreliable, either as a result of major error (e.g., miscalculation or experimental error), or as a result of fabrication (e.g., of data) or falsification (e.g., image manipulation).

COPE Retraction Guidelines, at 2. COPE guidelines also state editors should **state the reason(s)** for retractions and mention the reasons and basis for the retraction to enable readers to understand why the article is unreliable. *Id.* at 4.

Here, PLOS One has provided the following reasons for the retraction:

The corresponding author provided image data to support the contested western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS’ assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. Furthermore, the supporting data files did not contain molecular weight markers or positive controls as needed to verify the reliability of the results. In response to these concerns, the corresponding author stated that the repetitive features in the background noise of the image data are likely the result of scanner artifacts and noted that the protein sizes on the blot were verified against pre-stained molecular weight markers. The explanation given for the background image similarities does not resolve the journal’s concerns in light of PLOS’ assessment of the data files.

This explanation simply states PLOS One has “concerns” with the published data, but it fails to cite “clear evidence” for the retraction other than a summary conclusion or to discount my explanation for the issues other than saying they “do[] not resolve the journal’s concerns.”

As an initial matter, the responses to the inquiries of the five publications were due on a very short notice, often within mere days. I have done my best to gather as many of the original blots that were in my possession as possible. But, as you know, the personnel in a lab fluctuates, with students coming and going as they pursue their degrees. Notably, the oldest of these papers, the PLOS One 2008 paper, was published 14 years ago. However, I was still able to locate most of the original files and provide them to PLOS One. If PLOS One needs additional, specific information for its analysis, I would be happy to discuss how and whether I am able to locate that information.

A major concern of PLOS One appears to be the blot strips and absence of molecular weight markers. I agree with the team at PLOS One that whole blots would be one way to reflect potential cross-reactivity of an antibody with other proteins in a sample. However, I have, as any good scientist would, conducted a control experiment to assess such cross-reactivity before making the decision to cut the blot into strips. This was not indicated in the publication and could be corrected with a republication or corrigendum. Moreover, the decision to cut blots into strips was a budgetary decision. My lab operates on a strict budget, and we simply do not have the resources to process whole blots for all experiments, which would require ordering batch after batch of antibodies. In view of the high specificity of the antibody used, we felt it was justified to cut the blot into strips before probing. This

monetary decision to cut the blots into strips certainly does not indicate “clear evidence” of concerning conduct, as required by the COPE guidelines.

With regard to the molecular weight standards, as is generally known to those in the scientific community, an antibody will not react with the proteins contained in a molecular weight marker sample. Therefore, positions of molecular weight markers in blots are often indicated by pen after protein transfer to the blot. We follow this common practice. In support of this practice, replicated below is an original exemplary blot image that I was able to locate in my files. It shows the blot strips, and the positions of the molecular weight standards indicated with a pen to the right side of the blot strips (**red arrow**). This practice may not have been indicated in the publication and could likewise be corrected with a republication or a corrigendum.

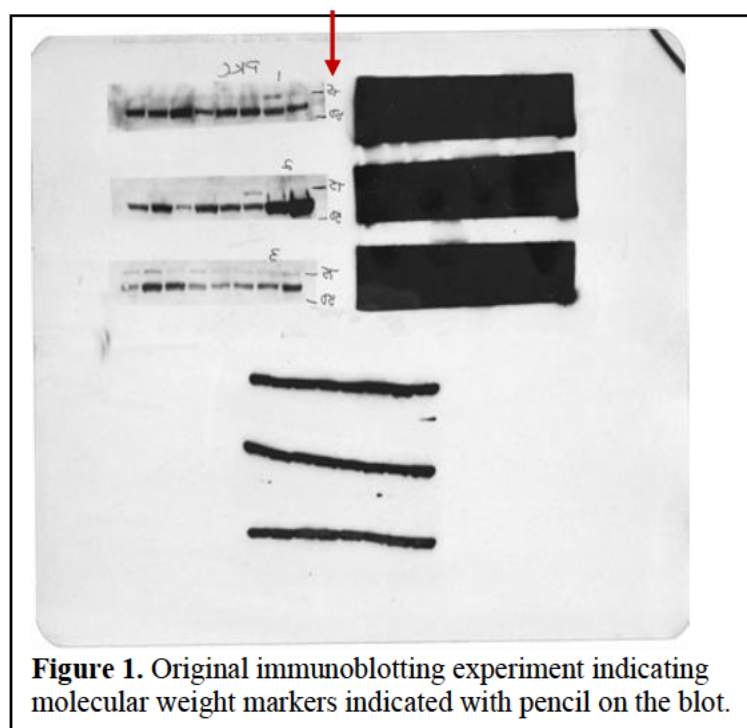


Figure 1. Original immunoblotting experiment indicating molecular weight markers indicated with pencil on the blot.

Some additional concerns relate to similarity in the appearance of bands in a blot. After 40 years of experience and with a steady hand, I am able to load samples in a way that the bands will appear similar in a gel. The original full width blots that I provided illustrate that I did not cut or paste any bands or otherwise commit scientific malpractice.

With regard to similarities in background patterns of the various blots presented, I have provided a very reasonable – and the only – explanation. Before we were able to acquire a more sophisticated scanner, all radiographic images were scanned with a simple scanner (again, due to the limited budget on which my lab operates). The inside of the lid of the scanner is a white sheet that becomes the background of any transparent image that is being scanned, like the blots. Consequently, the same background image is visible on all radiographic images scanned with that same scanner.

I realize PLOS One may have remaining concerns regarding uneven backgrounds, lines, and the like. I have given the best explanations that I have, as some of these visual appearances puzzle me as well. For those images I would urge PLOS One to consider the application of artificial intelligence

(“AI”) as it will prove I did not manipulate any blots. Other journals have applied this technology and have subsequently cleared me. The responses of those journals, and editors in charge, are summarized in section D below.

C. Numerous respected research journals and experts have cleared me of wrongdoing

Faced with similar allegations as PLOS One (presumably raised by the same short sellers), the editors of three respected research journals – Journal of Neuroscience (Marina Picciotto, PhD), Neuroscience (Prof. Juan Lerma, PhD), and Behavioral Pharmacology (Dr. VanderSchuren) – ***have cleared me of all allegations of data manipulation*** made by the short sellers. These clearances are from neutral parties who are experts in the field, all of whom agree I did not engage in data manipulation. The editors’ conclusions followed a thorough examination of raw data, and include the application of AI for Western blots analysis, in four separate papers. For all four papers, the editors-in-chief found “no evidence of data manipulation.” I hope PLOS One will at least consider these editorial decisions in view of its own, follow their lead in applying AI, and reconsider retraction.

Similarly, an independent expert on Western blots, Dr. Charles Spruck, has also examined and refuted the short seller’s allegations of manipulation of my Western blot images across many papers, as shown in the letter by Dr. Spruck attached to this letter. Dr. Spruck is a molecular biologist and researcher at Sanford Burnham, whose academic lab runs approximately 1,000 Western blots each year. After a close examination of the allegations and my data, Dr. Spruck concludes that certain “examples shown as evidence of data manipulation support the opposite.” Dr. Spruck also refutes allegations of scientific misconduct in a letter he wrote to the editors of *Journal of Prevention of Alzheimer’s Disease*:

After objectively reviewing the [Citizen Petition], I have concluded that the vast majority of concerns raised regarding the WB [Western blots] data are baseless and demonstrate a general lack of understanding of the technique and data interpretation. Evidence provided as potentially “altered” or “manipulated” data are effects we see routinely in our WB analyses.

See the letter by Dr. Spruck attached to this letter as Exhibition B. I did not know Dr. Spruck prior to the short sellers’ allegations. Instead, Dr. Spruck is acting independently to ensure that the correct conclusion is reached with respect to the sanctity of this important research. Dr. Spruck’s bio is available at the following link: <https://www.sbpdiscovery.org/our-scientists/charles-spruck-phd>.

D. The individuals who raised these allegations have significant adverse financial motivations.

As discussed above, this investigation was prompted by the reports of financially motivated short sellers of Cassava stock, including Bredt and Pitt. Further, one of the short sellers, Bredt, is first author on a newly issued patent that directly competes with Cassava. Given the short sellers’ goal of destroying the value of Cassava’s stock price, and apparently of favoring the patent Bredt holds over Cassava’s, the short sellers have launched attacks on me, and my entire academic research career based on unfounded claims of data manipulation. While I have conducted work for Cassava over the past ten years, that work has been a very small portion of my entire forty-year career as a research scientist. Moreover, all of the clinical biomarker work I conducted for Cassava was blinded as to all relevant research parameters (treatment group and/or timepoint), meaning that it would have been impossible for me to have

manipulated data in the way the short sellers suggest. In fact, even the FDA has declined to investigate the Citizen Petition, as mentioned above.

COPE retraction guidelines state “retraction notices . . . should specify who is retracting the article and possibly *how the matter came to the Journal’s attention*.” In light of these guidelines, I strongly request that the Journal disclose the identities of the individual(s) and/or entit(ies) who have raised these allegations so the public can evaluate their propriety. This biased sourcing of the report also tips the scale of how much “clear evidence” should be required to conclude that I have engaged in improper conduct: where I can provide an accurate and innocent explanation for my conduct, the financially motivated and biased views of Bredt, Pitt, and others should not be permitted to override that and certainly do not provide “clear evidence” of concerning conduct.

E. PLOS One has no basis to communicate with my employer under COPE guidelines.

PLOS One has neither indicated – let alone proven with “clear evidence” – that I committed scientific misconduct, and therefore no basis exists to contact my employer under COPE guidelines. COPE retraction guidelines state: “When editors have credible grounds to suspect misconduct, this should be brought to the attention of the authors’ institution.” *See* COPE Guidelines, at 6.

Dr. Zalm stated, “We plan to notify your institution of this issue and editorial decision, per the journal’s standard procedure,” which deviates from the COPE retraction guidelines because PLOS One *has not provided credible grounds to suspect misconduct* (as stated above). At the absolute worst, the Journal admittedly has only raised “concerns.” But as you know, scientific “concerns” and “credible grounds to suspect misconduct” are not the same thing. Absent proof of scientific misconduct, there is no basis to contact my employer under COPE guidelines.

F. Conclusion

In conclusion, over my four-decade career, I have engaged in rigorous and scientifically- sound practices of the research community. There is simply no clear evidence to support a finding of research misconduct and no reason why I would jeopardize my 40-year academic career to engage in the conduct that is alleged. Again, I urge you to consider the substantial profit motive of the individuals who initiated the underlying allegations, who are reported to have shared an outrageous \$100 million financial windfall from these allegations. Further, I would encourage you to consider that three journal editors and an independent expert on Western blots have carefully examined my Western blots in four publications and have concluded there is no evidence to support allegations of data manipulation and that the FDA has declined to further investigate the Citizen Petition.

For these reasons, I respectfully request that you *reconsider the retraction notice, or alternatively, consider republication or a corrigendum*, which would be a much more appropriate result given the issues raised. I am available to provide any additional information in person as needed.

Enclosures

Exhibit A



Jordan A. Thomas
Labaton Sucharow
140 Broadway
New York, NY 10005

February 10, 2022

Re: Docket Nos. FDA-2021-P-0930 and FDA-2021-P-0967

Dear Mr. Thomas:

This letter responds to your citizen petition received on August 23, 2021 (August Petition), with supplements dated August 30, 2021, September 9, 2021, November 17, 2021, and December 8, 2021 (Docket No. FDA-2021-P-0930) and your citizen petition received on September 1, 2021 (September Petition), with a supplement dated September 9, 2021 (Docket No. FDA-2021-P-0967) (collectively, your Petitions).

Your August Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that the Food and Drug Administration (FDA or Agency):

- halt the current clinical studies of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [investigational new drug application (IND)] for Simulifam's [sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease...
- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(August Petition at 1-2).

You further state that “[t]he ongoing clinical trials should be paused until the satisfactory completion of these investigations” (August Petition at 2).

Similarly, your September Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that FDA:

- halt the new clinical study of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT05026177), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [IND] for Simulifam's

[sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease; . . .

- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(September Petition at 1-2).

You further state that “[t]he upcoming clinical trial should be paused until the satisfactory completion of these investigations”¹ (September Petition at 2).

On November 17, 2021, you submitted a third supplement to the August Petition (the Third Supplement) stating that based on increasing evidence of purported wrongdoing, “FDA has a duty to immediately halt the simufilam (PT1-125) 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” (Third Supplement at 1).

FDA has carefully considered your Petitions and acknowledges the importance of the issues they raise. But as a threshold matter, by their own terms, your Petitions do not purport to set forth all relevant factual information. Rather, you call on FDA to initiate an investigation and fact-finding process. We are denying your Petitions to the extent that they request, through the citizen petition process, that FDA initiate an investigation. Under § 10.30 (21 CFR 10.30), citizen petitions can request that FDA issue, amend, or revoke a regulation or an order, or take or refrain from taking an administrative action,² and are to be resolved based on information in the administrative record.³ An investigation is not an administrative action, and, as your Petitions implicitly acknowledge, investigations necessarily require fact finding beyond what is presented in the current administrative record.

Moreover, issuing a response to your requests would appear to require FDA to publicly disclose information about an investigational new drug that, by law, FDA generally cannot publicly disclose. The Trade Secrets Act, 18 U.S.C. 1905, prohibits the disclosure of confidential commercial information unless doing so is authorized by law. FDA’s regulations regarding confidential commercial information provide that if the existence of an unapproved application has not previously been publicly disclosed, “no data or information in the application . . . is available for public disclosure.”⁴ In addition, FDA’s regulations provide that “the existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.”⁵ Thus, if the product sponsor has not previously

¹ In your September 9, 2021, supplements to the August Petition and the September Petition, you also “respectfully recommend rescinding the recently announced [Special Protocol Assessment] for Simufilam” (September 9, 2021, supplement at 8).

² See § 10.30(b)(3).

³ See § 10.30(j).

⁴ § 314.430(c) (21 CFR 314.430(c)).

⁵ 21 CFR 312.130(a).

made public the filing of an IND, FDA will not disclose the IND's existence. Nor will FDA disclose any information submitted as part of the IND: the application "includes all data and information submitted with or incorporated by reference in any application or abbreviated application, including investigational new drug applications."⁶ If the sponsor has already disclosed the existence of an IND for a not-yet-approved product, FDA may confirm the existence of the IND.⁷ However, FDA still will not make any "data or information contained in the application . . . available for public disclosure before the agency sends an approval letter," aside from narrow exceptions that are not relevant here.⁸ Accordingly, restrictions on disclosure of nonpublic information contained in an IND file apply both when a sponsor has already disclosed the existence of an IND, and when a sponsor has not.

With respect to your supplemental request that FDA report findings "to interested law enforcement and regulatory authorities," such a request is similarly not amenable to the citizen petition process. Decisions regarding enforcement actions are made on a case-by-case basis and are within the discretion of FDA. Requests for the Agency to initiate enforcement action and related regulatory activity are expressly excluded from the scope of FDA's citizen petition procedures.⁹

We take the issues you raise seriously. Please note that your Petitions are being denied solely on the grounds that your requests are not the appropriate subject of a citizen petition. This response does not represent a decision by the Agency to take or refrain from taking any action relating to the subject matter of your Petitions.

Sincerely,

**Patrizia A.
Cavazzoni -S**

Digitally signed by Patrizia A.
Cavazzoni -S
Date: 2022.02.09 19:26:42 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

⁶ § 314.430(a).

⁷ § 314.430(b).

⁸ § 314.430(d)(1).

⁹ § 10.30(k).

Exhibit B

From: Hoau-Yan Wang <[REDACTED]@gmail.com>
Sent time: 03/15/2022 04:39:30 PM
To: PLOS Pub Ethics <pub-ethics@plos.org>
Cc: astucky@usc.edu; [REDACTED]@hotmail.com; Eitan Friedman; Hoau-yan Wang
Subject: [EXTERNAL] Re: URGENT Please Respond - PLOS ONE: Editorial decision on the publication ethics concerns raised with your article
<https://doi.org/10.1371/journal.pone.0160585>
Attachments: 39788242-v3-Response to Retraction Dr. Zalm-REV BACK-F.pdf Spruck_letter12212021.pdf PLOS03142022CS (1).pdf FDA and Burns letters.pdf

Dear Dr. Zalm,

I (H-Y W) strongly disagree with retraction and I (H-Y W) stand by the article's findings.

2016 PLOS ONE article, "Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling"
(<https://doi.org/10.1371/journal.pone.0160585>).

Please find the enclosed a Response to retraction Dr. Zalm memorandum that states clearly the reasons that the retraction is not warranted as well as a letter by an independent reviewer who indicates there is no manipulation of the data.

Thank you.

Respectfully

Hoau-Yan Wang

*Hoau-Yan Wang, Ph.D.
Medical Professor*

On Tue, Mar 1, 2022 at 11:18 AM PLOS Pub Ethics <pub-ethics@plos.org> wrote:

Dear Dr. Wang and colleagues,

I am writing from the PLOS Publication Ethics team in regard to your 2016 PLOS ONE article, "Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling" (<https://doi.org/10.1371/journal.pone.0160585>). Thank you for engaging with us in the discussion of concerns raised about this article.

We have now completed our editorial assessment of this case and decided to retract the above article. This decision was reached in discussion with the PLOS Publication ethics team and senior members of the journal's Editorial team. Together, we carefully considered the concerns raised, comments and data you provided, and the implications of the concerns for the reliability of results reported in the article. PLOS ONE abides by guidance of the Committee on Publication Ethics (COPE) in following up on concerns raised to the journal and addressing issues in the published literature. In this case we consider that retraction is warranted due to concerns about results presented in Figures 1, 5, 6, 8, 9, 10, and 11, as well as concerns about the underlying data provided for this article and four other articles mentioned in the retraction notice copied below.

We plan to notify your institution of this issue and editorial decision, per the journal's standard procedure.

The specific issues that underlie this decision are explained in the retraction notice, which is included below my signature and will be posted on your article at the time of retraction. If you have any comments on the issues raised in the notice, or if you see any inaccuracies in the notice, **please reply with your comments no later than 08 March 2022**. In addition, please note that the retraction notice includes two items that you have not yet had the opportunity to comment on, namely the concerns pertaining to irregularities in the Fig. 8B Prefrontal cortex panel and irregularities in the Fig. 11B Prefrontal cortex tPA panel. Please note that the editorial decision still holds in absence of these items, but we will consider updating the retraction notice to include your response to these specific items, should you wish to comment on them.

As discussed in COPE's Retraction Guidelines, the purpose of the public retraction notice is to correct the literature and relay the reasons for the editorial decision. Per PLOS' standards we also include standardized statements in retraction notices to indicate authors' positions with regard to the editorial decision. To inform these statements, we ask that each of you **reply individually by 08 March 2022** with your responses to both of the following questions:

1. Please add your initials next to the phrase that indicates your position with regard to the retraction decision:

- agree with retraction
- disagree with retraction

2. Add your initials next to the relevant phrase(s) if either of the following applies in your case and you would like a corresponding statement added to the public retraction notice:

- stand by the article's findings
- apologize for the issues with the published article

Please note that we will not consider requests for custom text in author position statements. We do not consider retraction notices to be an appropriate forum for discussion of items that go beyond the information readers should be provided around the circumstances and basis for the retraction. If you wish to comment publicly on information relayed in the retraction notice you may do so by posting a public Comment on the article or retraction webpage. Please note that any Comment posted on a PLOS webpage must abide by the Good Practice guidelines outlined at <https://journals.plos.org/plosone/s/comments>, and must include a Competing Interests statement which in this case should include your authorship of the retracted article.

After the specified reply deadline the notice text will be finalized and we will not consider further responses or queries regarding the retraction. If we do not receive your reply by **08 March 2022**, or if you do not provide a reply to question 1 by this deadline, we will include a statement in the notice to indicate that you 'did not reply directly or could not be reached'.

If you have questions about this information you may reach me directly by replying to this email. Please reference Case 7308904 in any messages related to this matter.

I realize this will likely be a disappointing outcome and I am sorry I do not have more positive news to relay on this occasion.

Maria Zalm, Ph.D

Senior Editor Publication Ethics | she, her

PLOS | pub-ethics@plos.org

Empowering researchers to transform science

Carlyle House, Carlyle Road, Cambridge CB4 3DN | United Kingdom

California (U.S.) corporation #C2354500, based in San Francisco

Retraction: Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling

The PLOS ONE Editors

Following the publication of this article [1], concerns were raised regarding results presented in Figures 1, 2, 5, 6, 8, 9, 10, and 11. Specifically,

1. The following panels appear similar:
 - The Fig. 2A Hippocampus and Prefrontal Cortex β -actin panels and the Fig. 2C Hippocampus and Prefrontal Cortex β -actin panels respectively.
 - The Fig. 5A Hippocampus and Prefrontal Cortex TrkB panels and the Fig. 6A Hippocampus and Prefrontal Cortex TrkB panels respectively.
 - The Fig. 9A Hippocampus β -actin panel and the Fig. 11A Hippocampus β -actin panel.
 - The Fig. 10A Prefrontal cortex β -actin panel and the Fig. 11B Prefrontal cortex β -actin panel.
2. When levels are adjusted to visualize background, the following panels appear to partially overlap:
 - The Fig. 1B Hippocampus P75NTR panel and the Fig. 1D Hippocampus ERK2 panel.
 - The Fig. 1E Prefrontal cortex N-Shc panel and the Fig. 1F Prefrontal cortex NR1 panel.
3. When levels are adjusted to visualize background, there appear to be vertical irregularities suggestive of splice lines in:
 - The Fig. 5B Hippocampus pS⁴⁷³-Act1 panel, between lanes 2 and 3.
 - The Fig. 6A Hippocampus NR1 panel, between lanes 2 and 3.
4. When levels are adjusted to visualize background, there appear to be horizontal and/or vertical irregularities in the background around bands presented in:
 - The Fig. 8B Prefrontal cortex panel, between the two bands in lane 2.
 - The Fig. 9A Hippocampus BDNF panel, between the BDNF bands in lanes 1-2, and around the BDNF bands in lanes 4-6.
 - The Fig. 10A β -actin panel, around lane 3
 - The Fig. 10A Prefrontal cortex Pro-BDNF panel, around the area presented below the 15kDa marker in lanes 2-6.
 - The Fig. 11B Prefrontal cortex tPA panel, around the bands presented in lanes 5-6.

Regarding point 1, the corresponding author confirmed the duplications and explained that results in the indicated pairs of figure panels (Figs. 2A and 2C, Figs 9A and 11A, Figs 10A and 11B, and Figs 5A and 6A) originated from the same blots, which were re-probed with different antibodies.

The corresponding author disagreed with point 2, and stated that the results presented in these panels were obtained from separate blots.

Regarding points 3 and 4, the corresponding author indicated that the Fig. 5B Hippocampus pS473-Act1 panel was spliced during

figure preparation. The corresponding author disagreed with the concerns about irregularities in Figures 6A, 9A and 10A suggesting that the observations are likely the result of image artefacts or experimental artefacts such as gel or reagent remnants or protein degradation products.

The corresponding author provided image data to support their western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS' assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. The corresponding author stated that the repetitive features in the background noise of the underlying data are likely the result of scanner artifacts.

In addition, the data provided did not present complete blots for all data and did not contain any size markers to confirm protein size. The corresponding author explained that the proteins on the blot were verified against pre-stained molecular weight markers, and that the blots were cut into separate strips before probing.

With the exception of point 1, the data and comments provided to PLOS did not resolve the concerns about the integrity and reliability of the reported data. Therefore, the *PLOS ONE* Editors retract this article.

[Author initials] agreed with the retraction. [author initials] either did not respond directly or could not be reached. [author initials] did not agree with the retraction.

References

1. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling. *PLoS ONE* 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>
2. Wang H-Y, Frankfurt M, Burns LH (2008) High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor–Gs Coupling Underlying Opioid Tolerance and Dependence. *PLoS ONE* 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>
3. Wang H-Y, Burns LH (2009) Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor–Gs Coupling and CREB Activation of Acute Morphine. *PLoS ONE* 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>
4. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP. *PLoS ONE* 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>

Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins. *PLoS ONE* 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>

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Case Number: 07308904

ref:_00DU0Ifis_5004P1eeyIG ref

DATE: March 14, 2022
 TO: Dr. Zalm
 Senior Editor Publication Ethics
 FROM: Dr. Hoau-Yan Wang

Re: Response to editorial notice

I write this memorandum in response to PLOS One's retraction notice regarding various articles authored or co-authored by me.¹ I respectfully but unequivocally disagree with your preliminary decision, as it is contrary to the evidence and not supported by COPE's retraction guidelines. As a result, I strongly urge you to reconsider the retraction or, alternatively, to consider a re-publication or corrigendum, for the reasons outlined below.

A. Introduction

In more than four decades as a research scientist, I have been motivated by the desire to help people and society and to pursue curiosity-driven research. My long and stable academic career includes over 120 peer reviewed publications and R&D collaborations with industry. Developing new drugs that help those suffering from debilitating illnesses, like Alzheimer's disease, is how I hope to make a difference. The importance of that work justifies working long days in my lab in New York City, a job that requires a five-hour round-trip daily commute to my home in Philadelphia. I also have a full teaching load as a Tenured Medical Professor at the CUNY School of Medicine that I must balance with my research responsibilities, as I also cherish playing a role in educating the next generation of doctors. Forty years of consistently ethical behavior have earned me a pristine reputation among colleagues, collaborators, and scientists. I value my reputation and would never do anything to jeopardize it. For instance, I run blinded studies where I do not know the treatment parameters and/or diagnoses of any samples, so that neither I nor anyone else in my lab could manipulate data for any improper end. While research scientists are fallible human beings capable of making inadvertent errors, I have always strived to honestly and ethically report methods, procedures, and data.

As you can imagine, the last few months have been absolutely devastating on a personal and

¹ The following five articles are at issue:

1. Stucky A, Bakshi KP, Friedman E, Wang H-Y (2016) *Prenatal Cocaine Exposure Upregulates BDNF-TrkB Signaling*. PLOS ONE 11(8): e0160585. <https://doi.org/10.1371/journal.pone.0160585>;
2. Wang H-Y, Frankfurt M, Burns LH (2008) *High-Affinity Naloxone Binding to Filamin A Prevents Mu Opioid Receptor-Gs Coupling Underlying Opioid Tolerance and Dependence*. PLOS ONE 3(2): e1554. <https://doi.org/10.1371/journal.pone.0001554>;
3. Wang H-Y, Burns LH (2009) *Naloxone's Pentapeptide Binding Site on Filamin A Blocks Mu Opioid Receptor-Gs Coupling and CREB Activation of Acute Morphine*. PLOS ONE 4(1): e4282. <https://doi.org/10.1371/journal.pone.0004282>;
4. Bakshi K, Kosciuk M, Nagele RG, Friedman E, Wang H-Y (2011) *Prenatal Cocaine Exposure Increases Synaptic Localization of a Neuronal RasGEF, GRASP-1 via Hyperphosphorylation of AMPAR Anchoring Protein, GRIP*. PLOS ONE 6(9): e25019. <https://doi.org/10.1371/journal.pone.0025019>; and
5. Bakshi K, Parihar R, Goswami SK, Walsh M, Friedman E, Wang H-Y (2014) *Prenatal Cocaine Exposure Uncouples mGluR1 from Homer1 and Gq Proteins*. PLOS ONE 9(3): e91671. <https://doi.org/10.1371/journal.pone.0091671>.

professional level. I have been repeatedly and unfairly attacked by people who, at best, do not understand the relevant scientific principles or, at worst, have an admitted financial or competing interest in undermining my research. I urge you to consider the motivations that drive the allegations. The allegations of research misconduct were prompted by a Citizen Petition filed with the FDA by a law firm with no expertise in Western blots, for the financial benefit of two individuals, David Bredt and Geoffrey Pitt. After filing the Citizen Petition, both Bredt and Pitt admitted that they hold short positions in the stock of my industry collaborator, Cassava Sciences, Inc.² A short position means that they can only profit if Cassava's stock price declines, which obviously provides an ample incentive to attack my research for Cassava.³ In December 2021, the DOJ announced "an extensive probe" into "the relationship among the hedge fund [investors] and firms that publish negative reports on certain companies, often with the aim of sending the stock lower."⁴ The short sellers certainly fall within this category that has come under DOJ scrutiny as lacking credibility and improperly motivated. What's more, the FDA has dismissed the Citizen Petition in its entirety and have declined to investigate its allegations further.⁵

In summary, I respectfully disagree with PLOS One's retraction notice for several reasons. First, contrary to COPE guidelines, PLOS One has failed to present "clear evidence" that my publications are unreliable or that any data has been falsified because there is no evidence for such allegations. In fact, none of the allegations are supported by reliable indirect evidence (e.g., a whistleblower, such as a lab technician, co-author, etc.). Second, several independent experts with specific expertise in Western blot imaging as well as editors of prestigious journals who have reviewed the matter have cleared me of wrongdoing.⁶ Third, the FDA has dismissed the Citizen Petition in its entirety, likely recognizing that the short sellers who initially raised allegations of misconduct have significant adverse financial motivations and are not credible. Fourth, PLOS One has not established "credible grounds" to discuss these issues with my employer. These four points are outlined in greater detail below.

B. PLOS ONE has failed to cite "clear evidence" of unreliability, contrary to COPE's retraction guidelines.

² Two days after the announcement of the Citizen Petition, a lawyer at the law firm representing the short sellers issued a press release admitting that his clients have taken a short position on Cassava's stock price. *See* <https://www.businesswire.com/news/home/20210826005765/en/Rebuttal-to-82521-Cassava-Sciences-Press-Release>.

³ According to media reports, after filing the Citizen Petition, short sellers (presumably including Bredt and Pitt) had made **\$100 million in profits** from their short positions in Cassava. *See* "Cassava Short Sellers Reap \$100 Million in August Stock Rout," *Bloomberg* (Aug. 31, 2021), available at: <https://www.bloomberg.com/news/articles/2021-08-31/cassava-short-sellers-reap-100-million-in-august-stock-rout>. Unlike the short sellers, I did not profit in any way from stock price changes in Cassava.

⁴ *See* <https://www.reuters.com/markets/europe/us-doj-launches-expansive-probe-into-short-selling-bloomberg-news-2021-12-10/>

⁵ *See* FDA letter dated February 10, 2022, attached hereto as Exhibit "A."

⁶ *See* findings by the Editor of Journal of Neuroscience, Marina Picciotto, PhD; Editor of Neuroscience, Prof. Juan Lerma, PhD; and Western blot expert, Dr. Charles Spruck.

PLOS One has failed to present “clear evidence” that my publications are unreliable or that I falsified data. COPE guidelines for retraction state editors should consider retraction if:

[T]hey have **clear evidence** that the findings are unreliable, either as a result of major error (e.g., miscalculation or experimental error), or as a result of fabrication (e.g., of data) or falsification (e.g., image manipulation).

COPE Retraction Guidelines, at 2. COPE guidelines also state editors should **state the reason(s)** for retractions and mention the reasons and basis for the retraction to enable readers to understand why the article is unreliable. *Id.* at 4.

Here, PLOS One has provided the following reasons for the retraction:

The corresponding author provided image data to support the contested western blot results in this [1] and other PLOS ONE articles [2-5]. Per PLOS’ assessment of the data files, the pixel patterns in background areas of blot images provided for multiple panels in [1-5] appear more similar than would be expected for data obtained in independent experiments. Furthermore, the supporting data files did not contain molecular weight markers or positive controls as needed to verify the reliability of the results. In response to these concerns, the corresponding author stated that the repetitive features in the background noise of the image data are likely the result of scanner artifacts and noted that the protein sizes on the blot were verified against pre-stained molecular weight markers. The explanation given for the background image similarities does not resolve the journal’s concerns in light of PLOS’ assessment of the data files.

This explanation simply states PLOS One has “concerns” with the published data, but it fails to cite “clear evidence” for the retraction other than a summary conclusion or to discount my explanation for the issues other than saying they “do[] not resolve the journal’s concerns.”

As an initial matter, the responses to the inquiries of the five publications were due on a very short notice, often within mere days. I have done my best to gather as many of the original blots that were in my possession as possible. But, as you know, the personnel in a lab fluctuates, with students coming and going as they pursue their degrees. Notably, the oldest of these papers, the PLOS One 2008 paper, was published 14 years ago. However, I was still able to locate most of the original files and provide them to PLOS One. If PLOS One needs additional, specific information for its analysis, I would be happy to discuss how and whether I am able to locate that information.

A major concern of PLOS One appears to be the blot strips and absence of molecular weight markers. I agree with the team at PLOS One that whole blots would be one way to reflect potential cross-reactivity of an antibody with other proteins in a sample. However, I have, as any good scientist would, conducted a control experiment to assess such cross-reactivity before making the decision to cut the blot into strips. This was not indicated in the publication and could be corrected with a republication or corrigendum. Moreover, the decision to cut blots into strips was a budgetary decision. My lab operates on a strict budget, and we simply do not have the resources to process whole blots for all experiments, which would require ordering batch after batch of antibodies. In view of the high specificity of the antibody used, we felt it was justified to cut the blot into strips before probing. This

monetary decision to cut the blots into strips certainly does not indicate “clear evidence” of concerning conduct, as required by the COPE guidelines.

With regard to the molecular weight standards, as is generally known to those in the scientific community, an antibody will not react with the proteins contained in a molecular weight marker sample. Therefore, positions of molecular weight markers in blots are often indicated by pen after protein transfer to the blot. We follow this common practice. In support of this practice, replicated below is an original exemplary blot image that I was able to locate in my files. It shows the blot strips, and the positions of the molecular weight standards indicated with a pen to the right side of the blot strips (**red arrow**). This practice may not have been indicated in the publication and could likewise be corrected with a republication or a corrigendum.

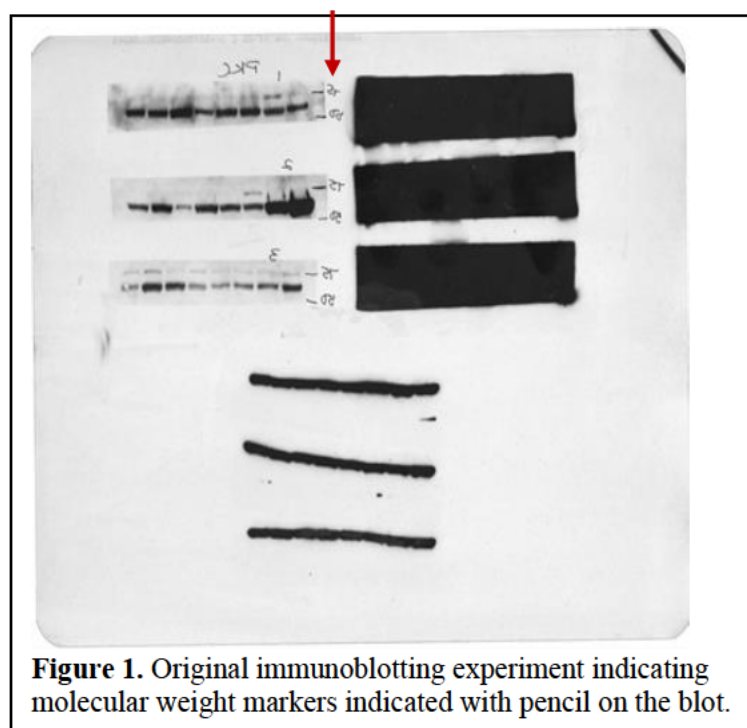


Figure 1. Original immunoblotting experiment indicating molecular weight markers indicated with pencil on the blot.

Some additional concerns relate to similarity in the appearance of bands in a blot. After 40 years of experience and with a steady hand, I am able to load samples in a way that the bands will appear similar in a gel. The original full width blots that I provided illustrate that I did not cut or paste any bands or otherwise commit scientific malpractice.

With regard to similarities in background patterns of the various blots presented, I have provided a very reasonable – and the only – explanation. Before we were able to acquire a more sophisticated scanner, all radiographic images were scanned with a simple scanner (again, due to the limited budget on which my lab operates). The inside of the lid of the scanner is a white sheet that becomes the background of any transparent image that is being scanned, like the blots. Consequently, the same background image is visible on all radiographic images scanned with that same scanner.

I realize PLOS One may have remaining concerns regarding uneven backgrounds, lines, and the like. I have given the best explanations that I have, as some of these visual appearances puzzle me as well. For those images I would urge PLOS One to consider the application of artificial intelligence

(“AI”) as it will prove I did not manipulate any blots. Other journals have applied this technology and have subsequently cleared me. The responses of those journals, and editors in charge, are summarized in section D below.

C. Numerous respected research journals and experts have cleared me of wrongdoing

Faced with similar allegations as PLOS One (presumably raised by the same short sellers), the editors of three respected research journals – Journal of Neuroscience (Marina Picciotto, PhD), Neuroscience (Prof. Juan Lerma, PhD), and Behavioral Pharmacology (Dr. VanderSchuren) – ***have cleared me of all allegations of data manipulation*** made by the short sellers. These clearances are from neutral parties who are experts in the field, all of whom agree I did not engage in data manipulation. The editors’ conclusions followed a thorough examination of raw data, and include the application of AI for Western blots analysis, in four separate papers. For all four papers, the editors-in-chief found “no evidence of data manipulation.” I hope PLOS One will at least consider these editorial decisions in view of its own, follow their lead in applying AI, and reconsider retraction.

Similarly, an independent expert on Western blots, Dr. Charles Spruck, has also examined and refuted the short seller’s allegations of manipulation of my Western blot images across many papers, as shown in the letter by Dr. Spruck attached to this letter. Dr. Spruck is a molecular biologist and researcher at Sanford Burnham, whose academic lab runs approximately 1,000 Western blots each year. After a close examination of the allegations and my data, Dr. Spruck concludes that certain “examples shown as evidence of data manipulation support the opposite.” Dr. Spruck also refutes allegations of scientific misconduct in a letter he wrote to the editors of *Journal of Prevention of Alzheimer’s Disease*:

After objectively reviewing the [Citizen Petition], I have concluded that the vast majority of concerns raised regarding the WB [Western blots] data are baseless and demonstrate a general lack of understanding of the technique and data interpretation. Evidence provided as potentially “altered” or “manipulated” data are effects we see routinely in our WB analyses.

See the letter by Dr. Spruck attached to this letter as Exhibition B. I did not know Dr. Spruck prior to the short sellers’ allegations. Instead, Dr. Spruck is acting independently to ensure that the correct conclusion is reached with respect to the sanctity of this important research. Dr. Spruck’s bio is available at the following link: <https://www.sbpdiscovery.org/our-scientists/charles-spruck-phd>.

D. The individuals who raised these allegations have significant adverse financial motivations.

As discussed above, this investigation was prompted by the reports of financially motivated short sellers of Cassava stock, including Bredt and Pitt. Further, one of the short sellers, Bredt, is first author on a newly issued patent that directly competes with Cassava. Given the short sellers’ goal of destroying the value of Cassava’s stock price, and apparently of favoring the patent Bredt holds over Cassava’s, the short sellers have launched attacks on me, and my entire academic research career based on unfounded claims of data manipulation. While I have conducted work for Cassava over the past ten years, that work has been a very small portion of my entire forty-year career as a research scientist. Moreover, all of the clinical biomarker work I conducted for Cassava was blinded as to all relevant research parameters (treatment group and/or timepoint), meaning that it would have been impossible for me to have

manipulated data in the way the short sellers suggest. In fact, even the FDA has declined to investigate the Citizen Petition, as mentioned above.

COPE retraction guidelines state “retraction notices . . . should specify who is retracting the article and possibly *how the matter came to the Journal’s attention*.” In light of these guidelines, I strongly request that the Journal disclose the identities of the individual(s) and/or entit(ies) who have raised these allegations so the public can evaluate their propriety. This biased sourcing of the report also tips the scale of how much “clear evidence” should be required to conclude that I have engaged in improper conduct: where I can provide an accurate and innocent explanation for my conduct, the financially motivated and biased views of Bredt, Pitt, and others should not be permitted to override that and certainly do not provide “clear evidence” of concerning conduct.

E. PLOS One has no basis to communicate with my employer under COPE guidelines.

PLOS One has neither indicated – let alone proven with “clear evidence” – that I committed scientific misconduct, and therefore no basis exists to contact my employer under COPE guidelines. COPE retraction guidelines state: “When editors have credible grounds to suspect misconduct, this should be brought to the attention of the authors’ institution.” *See* COPE Guidelines, at 6.

Dr. Zalm stated, “We plan to notify your institution of this issue and editorial decision, per the journal’s standard procedure,” which deviates from the COPE retraction guidelines because PLOS One *has not provided credible grounds to suspect misconduct* (as stated above). At the absolute worst, the Journal admittedly has only raised “concerns.” But as you know, scientific “concerns” and “credible grounds to suspect misconduct” are not the same thing. Absent proof of scientific misconduct, there is no basis to contact my employer under COPE guidelines.

F. Conclusion

In conclusion, over my four-decade career, I have engaged in rigorous and scientifically- sound practices of the research community. There is simply no clear evidence to support a finding of research misconduct and no reason why I would jeopardize my 40-year academic career to engage in the conduct that is alleged. Again, I urge you to consider the substantial profit motive of the individuals who initiated the underlying allegations, who are reported to have shared an outrageous \$100 million financial windfall from these allegations. Further, I would encourage you to consider that three journal editors and an independent expert on Western blots have carefully examined my Western blots in four publications and have concluded there is no evidence to support allegations of data manipulation and that the FDA has declined to further investigate the Citizen Petition.

For these reasons, I respectfully request that you *reconsider the retraction notice, or alternatively, consider republication or a corrigendum*, which would be a much more appropriate result given the issues raised. I am available to provide any additional information in person as needed.

Enclosures

Exhibit A



Jordan A. Thomas
Labaton Sucharow
140 Broadway
New York, NY 10005

February 10, 2022

Re: Docket Nos. FDA-2021-P-0930 and FDA-2021-P-0967

Dear Mr. Thomas:

This letter responds to your citizen petition received on August 23, 2021 (August Petition), with supplements dated August 30, 2021, September 9, 2021, November 17, 2021, and December 8, 2021 (Docket No. FDA-2021-P-0930) and your citizen petition received on September 1, 2021 (September Petition), with a supplement dated September 9, 2021 (Docket No. FDA-2021-P-0967) (collectively, your Petitions).

Your August Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that the Food and Drug Administration (FDA or Agency):

- halt the current clinical studies of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT04388254 and NCT04994483), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [investigational new drug application (IND)] for Simulifam's [sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease...
- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(August Petition at 1-2).

You further state that “[t]he ongoing clinical trials should be paused until the satisfactory completion of these investigations” (August Petition at 2).

Similarly, your September Petition describes “grave concerns about the quality and integrity of the laboratory-based studies surrounding this drug candidate and supporting the claims for its efficacy,” and requests that FDA:

- halt the new clinical study of Simufilam (PTI-125) sponsored by Cassava Sciences (NCT05026177), pending audits of (1) the publications relied on by Cassava in support of its scientific claims concerning Simufilam; (2) the [IND] for Simulifam's

[sic] use in Alzheimer's Disease; and (3) all clinical biomarker studies of Simufilam in Alzheimer's Disease; . . .

- oversee third party reanalysis of all clinical biomarker studies of Simufilam in Alzheimer's disease

(September Petition at 1-2).

You further state that “[t]he upcoming clinical trial should be paused until the satisfactory completion of these investigations”¹ (September Petition at 2).

On November 17, 2021, you submitted a third supplement to the August Petition (the Third Supplement) stating that based on increasing evidence of purported wrongdoing, “FDA has a duty to immediately halt the simufilam (PT1-125) 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” (Third Supplement at 1).

FDA has carefully considered your Petitions and acknowledges the importance of the issues they raise. But as a threshold matter, by their own terms, your Petitions do not purport to set forth all relevant factual information. Rather, you call on FDA to initiate an investigation and fact-finding process. We are denying your Petitions to the extent that they request, through the citizen petition process, that FDA initiate an investigation. Under § 10.30 (21 CFR 10.30), citizen petitions can request that FDA issue, amend, or revoke a regulation or an order, or take or refrain from taking an administrative action,² and are to be resolved based on information in the administrative record.³ An investigation is not an administrative action, and, as your Petitions implicitly acknowledge, investigations necessarily require fact finding beyond what is presented in the current administrative record.

Moreover, issuing a response to your requests would appear to require FDA to publicly disclose information about an investigational new drug that, by law, FDA generally cannot publicly disclose. The Trade Secrets Act, 18 U.S.C. 1905, prohibits the disclosure of confidential commercial information unless doing so is authorized by law. FDA’s regulations regarding confidential commercial information provide that if the existence of an unapproved application has not previously been publicly disclosed, “no data or information in the application . . . is available for public disclosure.”⁴ In addition, FDA’s regulations provide that “the existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.”⁵ Thus, if the product sponsor has not previously

¹ In your September 9, 2021, supplements to the August Petition and the September Petition, you also “respectfully recommend rescinding the recently announced [Special Protocol Assessment] for Simufilam” (September 9, 2021, supplement at 8).

² See § 10.30(b)(3).

³ See § 10.30(j).

⁴ § 314.430(c) (21 CFR 314.430(c)).

⁵ 21 CFR 312.130(a).

made public the filing of an IND, FDA will not disclose the IND's existence. Nor will FDA disclose any information submitted as part of the IND: the application "includes all data and information submitted with or incorporated by reference in any application or abbreviated application, including investigational new drug applications."⁶ If the sponsor has already disclosed the existence of an IND for a not-yet-approved product, FDA may confirm the existence of the IND.⁷ However, FDA still will not make any "data or information contained in the application . . . available for public disclosure before the agency sends an approval letter," aside from narrow exceptions that are not relevant here.⁸ Accordingly, restrictions on disclosure of nonpublic information contained in an IND file apply both when a sponsor has already disclosed the existence of an IND, and when a sponsor has not.

With respect to your supplemental request that FDA report findings "to interested law enforcement and regulatory authorities," such a request is similarly not amenable to the citizen petition process. Decisions regarding enforcement actions are made on a case-by-case basis and are within the discretion of FDA. Requests for the Agency to initiate enforcement action and related regulatory activity are expressly excluded from the scope of FDA's citizen petition procedures.⁹

We take the issues you raise seriously. Please note that your Petitions are being denied solely on the grounds that your requests are not the appropriate subject of a citizen petition. This response does not represent a decision by the Agency to take or refrain from taking any action relating to the subject matter of your Petitions.

Sincerely,

**Patrizia A.
Cavazzoni -S**

Digitally signed by Patrizia A.
Cavazzoni -S
Date: 2022.02.09 19:26:42 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

⁶ § 314.430(a).

⁷ § 314.430(b).

⁸ § 314.430(d)(1).

⁹ § 10.30(k).

Exhibit B

From: Pubpeer <alerts@pubpeer.com>
Sent time: 03/15/2022 06:15:28 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau-Yan Wang,

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Subject: [EXTERNAL] Suzanne Craft published an article

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Article Aug 2008 · Neurobiology of Aging

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Hoau-Yan, are these your publications?



H-Y Wang

Article: PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients

The Journal of Prevention of Alzheimer s Disease 09/2020; 7(4):256-264.

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Hoau-Yan Wang *(Correspondence)

Article: Hyper-activated Insulin Signaling Cascade in Human Glioblastoma Cells

Critical Reviews in Oncogenesis 01/2019; 24(3).

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Your publication has a new achievement:
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Dear Hoau-Yan Wang,

There's a new comment on your article entitled: **PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis, Neurobiology of Aging**

This link will log you in so that you can respond to the comment; please do not share the link with anyone else

See comment and respond

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From: Pubpeer <alerts@pubpeer.com>
Sent time: 03/19/2022 03:07:18 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau-Yan Wang,

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From: Pubpeer <alerts@pubpeer.com>
Sent time: 03/22/2022 02:45:58 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

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From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent time: 03/22/2022 04:48:55 PM
To: Maria Agosto; Hoau-yan Wang
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Hi Dr. Wang,
Were you able to get a carryover approval or year 2 agreement with Cassava?
Yan

Yan Bing Li
Project Administrator
Grants & Contracts
212-417-8473
Yan_Bing_Li@rfcuny.org

From: Li, Yan
Sent: Wednesday, January 5, 2022 11:43 AM
To: Maria Agosto <magosto@med.cuny.edu>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: RE: 72587-0002-Cassava

OK. Thanks Maria for confirming!

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Yan_Bing_Li@rfcuny.org

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Sent: Wednesday, January 5, 2022 11:11 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>; Hoau-yan Wang <hywang@med.cuny.edu>
Subject: RE: 72587-0002-Cassava

Hello Yan,

No pending e-pays for this project.

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Maria

From: Li, Yan <Yan_Bing_Li@rfcuny.org>
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To: Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Maria Agosto <magosto@med.cuny.edu>
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212-417-8473

Yan_Bing_Li@rfcunyu.org

From: Hoau-yan Wang <hywang@med.cuny.edu>

Sent: Monday, October 4, 2021 7:42 PM

To: Li, Yan <Yan_Bing_Li@rfcunyu.org>

Cc: Maria Agosto <magosto@med.cuny.edu>

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212-417-6473 Fax
Yan_Bing_Li@rfcuny.org
<http://www.rfcuny.org>



From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 03/24/2022 01:47:26 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Rosalia Crupi published an article

ResearchGate



This week's research from your network



Suggested for you

Effect of pharmacological manipulations on Arc function

Article Dec 2020

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[Rosalia Crupi](#) · one of your co-authors
published an article

Sensitivity of Zebrafish Embryogenesis to Risk of Fotemustine Exposure

Article Mar 2022 · Fishes

[View article](#)



[Andrei Blasko](#) · one of your co-authors
answered this question **How to adjust pH?**

"Add close to 1:1 mole ratio of NaOH to lactic acid and adjust to the desired pH"

[View answer](#)

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Hoau-Yan, are these your publications?



[H-Y Wang](#)

Article: PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients

The Journal of Prevention of Alzheimer s Disease 09/2020; 7(4):256-264.

[Confirm authorship](#)

[Not me](#)



Hoau-Yan Wang *(Correspondence)

Article: Hyper-activated Insulin Signaling Cascade in Human Glioblastoma Cells
Critical Reviews in Oncogenesis 01/2019; 24(3).

[Confirm authorship](#)

[Not me](#)



Yun Wang

Article: The presynaptic particle web: Ultrastructure, composition, dissolution,
and reconstitution
Neuron 11/2001; 32(1):63-77.

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From: 3258093297 <3258093297@qq.com>
Sent time: 03/24/2022 02:09:36 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] a question

Dear Professor Wang^o

Sorry to be a bother. I am a first year master student in the department of hygiene toxicology from SiChuan University. I read your paper titled as "PTI-125 binds and reverses an altered conformation of filamin A to reduce Alzheimer's disease pathogenesis" and met a problem.

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I will be appreciated for your reply, thank you very much!

RuiQian

86-18220522502

SiChuan University

From: Hoau-yan Wang
Sent time: 03/24/2022 10:22:59 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] a question

POL 87(2)(a)

Hoau

From: 3258093297 <3258093297@qq.com>
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To: Hoau-yan Wang
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SiChuan University

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent time: 03/24/2022 10:25:33 AM
To: Hoau-yan Wang
Subject: RE: [EXTERNAL] a question

POL 87(2)(a)

[REDACTED]

Jennifer L. Beidel | 215.972.7850 | jennifer.beidel@saul.com

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Thursday, March 24, 2022 10:23 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] a question

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[REDACTED]

[REDACTED]

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From: Hoau-yan Wang
Sent time: 03/24/2022 10:51:19 AM
To: Li, Yan <Yan_Bing_Li@rfcuny.org>; Maria Agosto
Subject: Re: 72587-0002-Cassava

Hi Yan,

Can you please tell me the title of the account. I will do my best to see whether it is possible to get a carryover approval on year 2 with Cassava.

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OK. Thanks Maria for confirming!

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New York, NY 10036
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212-417-6473 Fax
Yan_Bing_Li@rfcunv.org
<http://www.rfcunv.org>

From: Hoau-yan Wang
Sent time: 03/24/2022 10:52:28 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Re: [EXTERNAL] a question

POL 87(2)(a)

Hoau

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent: Thursday, March 24, 2022 10:25 AM
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Subject: RE: [EXTERNAL] a question

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From: Li, Yan <Yan_Bing_Li@rfcuny.org>
Sent time: 03/24/2022 10:59:45 AM
To: Hoau-yan Wang; Maria Agosto
Subject: [EXTERNAL] RE: 72587-0002-Cassava

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Sent time: 03/25/2022 09:06:26 AM
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Cc: [REDACTED]@gmail.com
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To: Hoau-yan Wang <hywang@med.cuny.edu>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Hi Dr. Wang,
Sure. Title is: *Analyzing Patient Samples from a 1-Year Open-Label Extension Study of PTI-125 Using SavaDx and Other Biomarkers*
Yan

Maria,
Any epays for this project? End date must be prior to 12/31/21
Yan

Yan Bing Li
Project Administrator
Grants & Contracts
Office Hours Mon – Tues
Remote Hours Wed – Fri
212-417-8473
Yan_Bing_Li@rfcunyu.org

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Wednesday, January 5, 2022 10:40 AM
To: Li, Yan <Yan_Bing_Li@rfcunyu.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

Hi Yan,

Can you please let me know of the title of the account (grant). I am not sure whether I can ask for extension as there were a lot of things going on I have no control over, but I will do my best.

Thanks. Stay safe!

Hoau

From: Li, Yan <Yan_Bing_Li@rfcunyu.org>
Sent: Tuesday, January 4, 2022 11:52 AM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] RE: 72587-0002-Cassava

Dr. Wang,
Acct# 72587-0002 had ended back in December. Do you have any pending invoices on this account? In addition, there is about \$31k on direct, will you be asking for an extension? I'm not sure if that is possible, but please let me know.

Thanks,
Yan

Yan Bing Li
Project Administrator
Grants & Contracts
Office Hours Mon – Tues
Remote Hours Wed – Fri
212-417-8473
Yan_Bing_Li@rfcunv.org

From: Hoau-yan Wang <hywang@med.cuny.edu>
Sent: Monday, October 4, 2021 7:42 PM
To: Li, Yan <Yan_Bing_Li@rfcunv.org>
Cc: Maria Agosto <magosto@med.cuny.edu>
Subject: Re: 72587-0002-Cassava

will do.

Thanks.

Hoau

From: Li, Yan <Yan_Bing_Li@rfcunv.org>
Sent: Monday, October 4, 2021 3:13 PM
To: Hoau-yan Wang
Cc: Maria Agosto
Subject: [EXTERNAL] 72587-0002-Cassava

Hi Prof. Wang

Please note that your account with Cassava will be ending in two months (12/31/2021) & I see you have over \$30k to spend. Please try to spend it down as best you can. Otherwise, try to request an extension. I wanted to send this to you early in case Cassava denies any extension requested late in the budget period.

Best,

Yan

Yan Bing Li
Project Administrator
Grants & Contracts

230 West 41st Street
New York, NY 10036
212-417-8473
212-417-6473 Fax
Yan_Bing_Li@rfcunv.org
<http://www.rfcunv.org>

From: Pubpeer <alerts@pubpeer.com>
Sent time: 03/27/2022 03:11:02 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] New comment

PubPeer

Dear Hoau- Yan Wang,

There's a new comment on your article entitled: **SavaDx, a novel plasma biomarker to detect Alzheimer's disease, confirms mechanism of action of simufilam, Alzheimer s & Dementia**

This link will log you in so that you can respond to the comment; please do not share the link with anyone else

See comment and respond

Regards,
PubPeer

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From: ResearchGate <no-reply@researchgatemail.net>
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To: Hoau-yan Wang
Subject: [EXTERNAL] Ian A Blair published an article

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Hoau-Yan, are these your publications?



H-Y Wang

Article: PTI-125 Reduces Biomarkers of Alzheimer's Disease in Patients

The Journal of Prevention of Alzheimer s Disease 09/2020; 7(4):256-264.

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[Not me](#)



Hoau-Yan Wang *(Correspondence)

Article: Hyper-activated Insulin Signaling Cascade in Human Glioblastoma Cells

Critical Reviews in Oncogenesis 01/2019; 24(3).

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From: Hoau-yan Wang
Sent time: 03/28/2022 10:18:00 AM
To: [REDACTED]@gmail.com
Subject: Fw: [EXTERNAL] Fwd: Book chapter revision required
Attachments: Chapter 11-FF 197-215-HYW_edited20220228.docx

From: Hoau-yan Wang
Sent: Monday, February 28, 2022 10:55 AM
To: Khosrow Kashfi
Cc: [REDACTED]@hotmail.com
Subject: Re: [EXTERNAL] Fwd: Book chapter revision required

Dear Kho,

Enclosed is the finalized book chapter that had been edited according to the comments you sent. As suggested, I eliminated most systemic insulin resistance (and associated references) so that the book chapter is more focused on brain insulin resistance. Please note, this book chapter is one page less than the original. (197-214)

Please lead us know if you have any questions.

Thanks.

Best,

Hoau

From: Khosrow Kashfi <drkho@verizon.net>
Sent: Sunday, February 20, 2022 8:03 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Fwd: Book chapter revision required

Dear Hoau-Yan

Hope all is well. Please see below.

Thanks
Kho

Khosrow Kashfi, PhD, FRSC, FRSB
Guest Editor: Biochemical Pharmacology
Associate Editor: Onco Therapeutics
Associate Editor: Frontiers in Redox Physiology
Associate Editor: Frontiers in Pharmacology
Editor: International Journal of Molecular Sciences
Associate Medical Professor
Department of Molecular, Cellular & Biomedical Sciences
City University of New York School of Medicine
160 Convent Avenue, New York, NY 10031
Tel: (212) 650-6641
Fax: (212) 650-7692
[Email: kashfi@med.cuny.edu](mailto:kashfi@med.cuny.edu)
Website: www.avicennatherapeutics.com

CHAPTER 11

Brain Insulin Resistance, Nitric Oxide and Alzheimer's Disease Pathology

Zhe Pei¹, Kuo-Chieh Lee¹, Amber Khan^{1,2}, Hoau-Yan Wang^{1,2*}

¹*Department of Molecular, Cellular and Biomedical Sciences, City University of New York School of Medicine, 160 Convent Avenue, New York, New York 10031, USA.*

²*Department of Biology, Neuroscience Program, Graduate School of The City University of New York, 365 Fifth Avenue, New York, New York 10061, U.S.A.*

Abstract: Alzheimer's disease (AD) is a devastating age-related neurodegenerative disease characterized by progressive pathological changes and functional and cognitive impairments. Among several pathological mechanisms, brain insulin resistance appears to contribute significantly to the pathology and cognitive deficits. Brain insulin resistance has been demonstrated in animal models of AD and postmortem human brain tissue from patients with AD dementia. Studies conducted in AD models and in humans suggest that attenuating brain insulin resistance by agents such as glucagon-like peptide1 (GLP-1) analogs and small molecule drug candidate PTI-125 also reduces many AD pathologic features and symptoms. Insulin affects NO levels by activating endothelial and neuronal nitric oxide synthase (eNOS, nNOS), and systemic insulin resistance has been linked to reduced nitric oxide (NO) bioavailability. Increasing NO availability reduces systemic insulin resistance, and the insulin signaling pathway is associated with activation of eNOS, implying a causal relationship. This chapter explores this relationship and the role of impaired NO availability in brain insulin resistance in AD dementia.

Keywords: CaMKII (calcium-calmodulin-dependent kinase II), gamma-Aminobutyric acid (GABA) receptor, glutamate, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, insulin resistance, NADPH oxidase 2 (Nox2), NADPH oxidase subunit NOX2, NG-monomethyl-L-arginine (L-NMMA), nitric oxide synthase (NOS), N-methyl-D-aspartate (NMDA) receptor, reactive oxygen species (ROS), type-2 diabetes (T2D)

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that includes many underlying pathophysiological changes that gradually lead to dementia [1-4].

***Corresponding author Hoau-Yan Wang:** Department of Molecular, Cellular and Biomedical Sciences, City University of New York School of Medicine, 160 Convent Avenue, New York, NY 10031, USA. Email: hywang@med.cuny.edu

The lack of effective treatments for AD dementia and the enormous socioeconomic impact to society underscores the urgent need to develop effective treatments for this devastating disease [5, 6]. Many promising therapeutic agents in development for AD aim to reduce brain insulin resistance, a common early pathological feature of AD dementia with or without diabetes [7-10]. The pathological factors that contribute to brain insulin resistance are not fully understood. Nitric oxide (NO) is one of several biological molecules that interact with the insulin signaling pathway bi-directionally. In this chapter, we discuss the role of the NO system in the development of brain insulin resistance and explore the possibility that manipulating NO might be therapeutic for AD dementia.

INSULIN RECEPTOR SIGNALING AND ITS INTERACTION WITH NO SYSTEM

Insulin, a peptide secreted by the beta (β) cells in pancreas, crosses the blood-brain barrier in a regulated and saturable manner to enter the central nervous system (CNS). Although de novo synthesis of insulin in the brain is still debated, support for local brain insulin synthesis includes the detection of C-peptide and insulin mRNA in various brain regions in humans with the mRNA levels were especially high in hippocampus, striatum, and thalamus [11-15]. Insulin expression is decreased in AD compared to normal controls [14].

Insulin produces its cellular actions by binding its cognate insulin receptors (IRs) present on all cells including neurons and glia in brain regions such as olfactory bulb, cerebral cortex, hippocampus, hypothalamus and amygdala [8, 16, 17]. IRs are more concentrated in neurons relative to glial cells and are particularly highly expressed in post-synaptic densities [8, 16-18]. Upon insulin binding to the extracellular α -subunit domains of IRs, the intracellular IR β -subunit domains dimerize, leading to activation of their intrinsic tyrosine kinase to cause autophosphorylation. Insulin-like growth factor-1 (IGF-1) also binds and activates IRs, although with lower affinity, leading to the same trophic and metabolic actions as insulin, including neuronal plasticity [19, 20].

In addition to regulation of glucose utilization and homeostasis, insulin activates PI3K-Akt (Phosphoinositide 3-kinase - Protein kinase B/Akt) and mTOR (Mechanistic target of rapamycin) signaling via recruitment of insulin receptor substrate family (IRS) proteins such as IRS-1 and IRS-2. This insulin-stimulated PI3K/Akt/mTOR pathway has many other functions in cells throughout the body including the neuronal and vascular systems. Insulin activates Akt via IRS1-PI3K to directly phosphorylate serine1177 residues and activate vascular endothelial NO

synthase (eNOS), leading to NO production and consequent vasodilation and increased capillary blood flow [21, 22]. Insulin signaling promoting NO-mediated vasodilation in the brain is supported by increased blood flow in the insular cortex following intranasal insulin in men, independent of cortisol manipulation [23]. Expression of eNOS has been shown not only in endothelium of the cerebrovasculature, but more importantly, in dendritic spines [24]. Innate eNOS activity confers protection against secondary neuronal injury; thus, impaired eNOS due to insufficient insulin signaling in the brain can conceivably contribute to pathologies in AD leading to cognitive impairments [25].

Insulin has been shown to modulate a wide range of neuronal function. Insulin regulates 1) trafficking of ligand-gated ion channels, 2) expression and localization of GABA (γ -Aminobutyric acid), NMDA (N-Methyl-D-aspartic acid or N-Methyl-D-aspartate), and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, 3) catecholamine release and uptake, and 4) synaptic plasticity shown by long-term potentiation (LTP) and depression (LTD) in a NMDA receptor and PI3K dependent manner [26-29]. Insulin also promotes dendritic spine formation and excitatory synaptic development, and insulin regulates the development and health of excitatory synapses by activating PI3K/Akt/mTOR and Rac1/Cdc42 signaling [30].

Activation of the NMDA receptor recruits and activates neuronal NO synthase (nNOS) via Akt- and CaMKII (Ca^{2+} /calmodulin-dependent protein kinase II) - mediated phosphorylation of nNOS to promote production of NO in the postsynaptic field [31, 32]. The activation of nNOS was also found to elevate AMPA receptor levels [32]. Thus, insulin can increase NO production in postsynaptic neurons by stimulating nNOS via activation of NMDA receptors. Increased NO promotes NADPH oxidase 2 (NOX2)-dependent ROS production postsynaptically, which may damage the dendritic field. Dendritic field destruction is one of the pathological changes in AD [33].

The importance of NO in modulating insulin receptor activity has also been illustrated by blockade of the phosphatases SHP-1 (Src homology region 2 domain-containing phosphatase-1), SHP-2 (SH2 domain-containing protein tyrosine phosphatase-2), and PTP1B (Protein Tyrosine Phosphatase 1B) by S-nitrosylation of the cysteine residue at the enzyme's active sites concomitantly with a burst of NO production in response to insulin [34, 35]. Inhibition of the PTP1B, SHP-1, SHP-2 by S-nitrosylation release inhibition of tyrosine phosphatases on insulin signaling. Hence, increased NO levels can promote NO-dependent tyrosine-

phosphorylated insulin receptor and its downstream effectors IRS-1, thereby facilitating insulin signaling [35, 36]. Such potentiation of the insulin signaling could offset insulin resistance and related pathologies in AD.

In contrast to the positive action of NO on insulin signaling in the endothelial cells, intracerebroventricular infusion of the NO donor S-nitrosoglutathione (GSNO) impairs insulin signaling and induces inducible NO synthase (iNOS) expression in the hypothalamus. This impaired insulin signaling (insulin resistance) and induction of iNOS recapitulates the food consumption pattern of obese individuals [37]. This NO-mediated suppression of insulin signaling was linked to S-nitrosylation of IR and its downstream signaling molecule, Akt in the hypothalamus [37].

In accord, inhibition of iNOS or blocking S-nitrosylation of insulin signaling pathway reduces hypothalamic insulin resistance and normalizes energy homeostasis. However, the effects of intraventricular infusion of GSNO on levels of insulin signaling in other brain regions, especially the cognition-relevant hippocampus and cortex remain unclear. Moreover, although these studies highlight the reciprocal interactions between the NO system and the insulin signaling pathways that are important for maintaining functionality of a cell or of the much more complex brain, especially in the presence of diseases such as Alzheimer's disease (Figure 1), these studies also indicate that NO's influence on insulin signaling is cell-type-dependent, such that the functional output of diverse organs and brain regions are differentially affected.

THE INTER-RELATIONSHIP BETWEEN BRAIN INSULIN SIGNALING AND MEMORY/COGNITIVE PERFORMANCE

Brain insulin signaling is an important regulator of food intake, body weight, reproduction, and learning and memory [10, 38]. Among the many physiological activities regulated by brain insulin signaling, memory is the most relevant to AD pathogenesis. Several lines of evidence support the notion that brain insulin signaling plays a critical role in modulating cognitive function. Intranasal insulin administration improves cognition, including short- and long-term objective memory and working memory in both animals and humans [38-43].

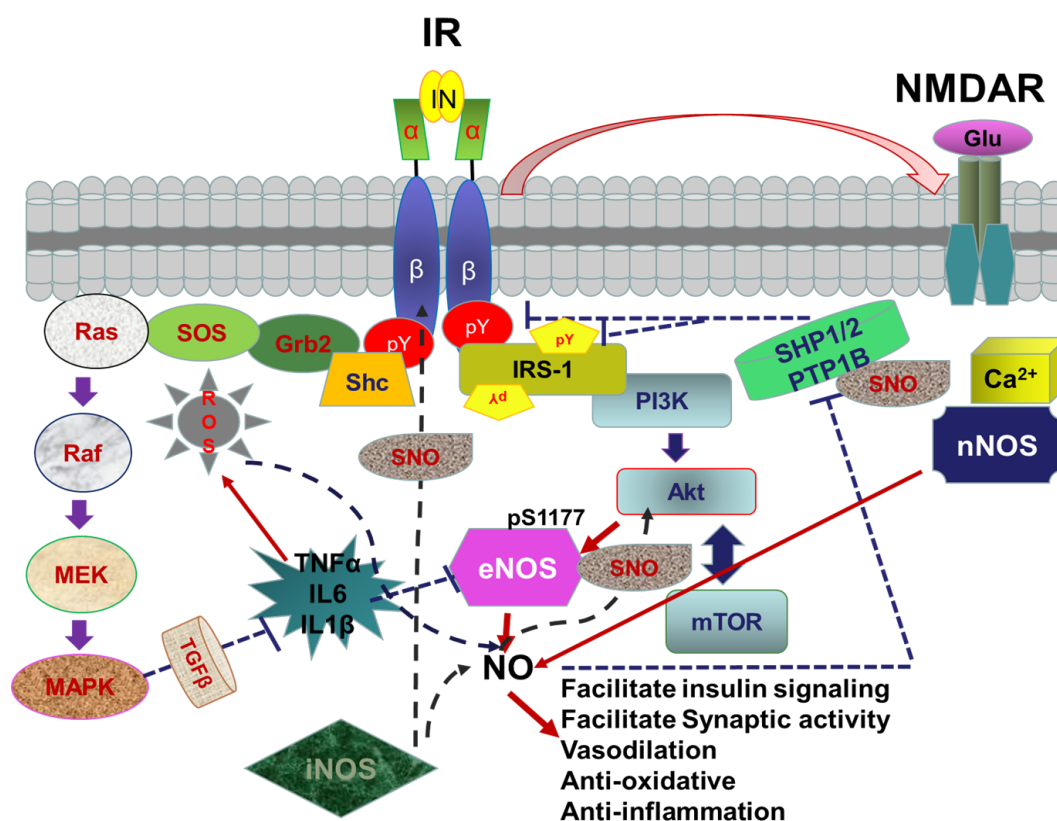


Figure 1: Reciprocal interactions between insulin signaling cascades and nitric oxide (NO) system in the brain. Insulin signaling is initiated by the binding of insulin (IN) to its cognate receptor, insulin receptors (IRs). This leads to autophosphorylation on tyrosine residues (pY) and activation of the IRs. The activation of IRs recruits (and tyrosine-phosphorylated) IRS-1 and the adaptor, Shc leading to the activation of two parallel downstream PI3K/Akt/mTOR and Ras/Raf/MEK/MAPK pathways, respectively. Activation of PI3K/Akt/mTOR pathway can activate eNOS expressed in endothelium of the cerebrovasculature and dendritic field by triggering phosphorylation on serine¹¹⁷⁷ residue of endothelial NO synthase (eNOS) thereby increase NO production. IR activation can also potentiate NMDA receptors (NMDARs) activities to increase intracellular Ca²⁺ as well as recruitment and activation of the neuronal NO synthase (nNOS) resulting in increased NO production. The increase in NO production facilitates insulin-induced IR signaling and synaptic activation by inhibiting phosphatases including PTP1B, SHIP1 and SHIP2 by promoting S-nitrosylation of these molecules, cause direct vasodilation and promote anti-oxidative and -inflammatory activities under physiological conditions. Insulin signaling through activation of the Ras/Raf/MEK/MAPK cascade can suppress production of proinflammatory cytokines such as tumor necrotic factor α (TNF α) via activation of transforming growth factor β (TGF β) thereby reduces ROS production. Conversely, the aberrantly elevated proinflammatory cytokines in the brain of neurodegenerative diseases such as Alzheimer's disease can disrupt the redox balance and increase reactive oxygen species (ROS) leading to brain insulin resistance, NMDAR impairments and endothelial dysfunction by reducing eNOS expression, thereby reduces NO availability. In contrast to the positive effects of NO on insulin signaling, inducible NO synthase (iNOS), a mediator of inflammation, plays an important role in stress-induced insulin resistance probably by promoting S-nitrosylation of the IR and its downstream signaling molecule, Akt. Lastly, the heightened inflammatory processes in neurodegeneration can

increase NO levels and the potential for brain insulin resistance, thereby ~~accelerate~~ pathology and cognitive impairment in Alzheimer's disease. IRS-1: insulin receptor substrate-1; PI3 kinase: phosphatidylinositol 3 kinase; NMDAR: N-methyl-D-aspartate receptors; MAPK: mitogen-activated protein kinase; PTP1B: protein tyrosine phosphatase 1B; SHIP1: SH-2 containing inositol 5' polyphosphatase 1; SHIP2: SH-2 containing inositol 5' polyphosphatase 2; IL-6: Interleukin 6; IL-1 β : Interleukin 1 β . positive contributor, indicates a minor or potential positive contributor, indicates a prominent positive contributor, indicates a negative contributor.

Intraventricular insulin administration improves memory and reduces chronic neuroinflammation in young but not old rats [44]. Intracerebroventricular administration of insulin improves passive avoidance task performance [45].

Similarly, direct intra-hippocampal administration enhances spatial learning and memory [46-48]. In addition, increased IR mRNA and protein levels in the hippocampal CA1 region after a spatial memory task correlates with short-term memory formation [49]. The critical role of brain insulin signaling in facilitating cognition is also supported by genetic modulation of the insulin signaling cascade. Selective disruption of insulin signaling by antisense knockdown of the IR gene in hippocampi of rats impairs synaptic plasticity and spatial learning [50].

After learning-induced long-term memory consolidation, gene expression of IR in the hippocampal CA1 and CA3 regions was increased and decreased, respectively, together with reduction in IR protein levels [51]. Learning experience and long-term memory formation also results in specific increases in levels of downstream molecules such as IRS-1 and Akt, together with decreases in Akt activation (phosphorylation), recruitment of adaptor Shc and activation of ERK1/2 (Extracellular signal - regulated protein kinase1/2) [51]. These studies imply that activation of the brain insulin signaling facilitates cognitive function and that learning and memory formation reciprocally promotes neuronal insulin signaling. The notion that brain insulin signaling is critical to cognition was however not supported by a report showing that mice that had lost 95% of IRs and downstream signaling due to neuron-specific insulin receptor knockout (NIRKO) show unimpaired learning and memory or behavior in various cognitive tests [52].

Accumulating evidence also supports the notion that insulin positively influences neuronal activities in brain and cognition in humans. Activation of brain insulin signaling by acute intranasal insulin administration promotes various neuroelectrophysiological activities such as event-related and transcortical direct current shift [53, 54]. Similarly, intranasal insulin application also positively influences neuroimaging measurements [55, 56]. Acute and chronic intranasal administration of insulin improve memory and cognitive performance in healthy young adults, obese or type-2 diabetic older subjects and even memory-impaired

subjects ([38, 39, 57-63]. In contrast, no cognitive or functional benefits were observed with 12-month intranasal insulin administration to mild cognitive impairment and AD dementia patients in a randomized (1:1) double-blind clinical trial [64].

In contrast to the positive role of brain insulin signaling on cognitive performance, disruption of insulin signaling makes neurons more vulnerable to metabolic stress and accelerates neuronal dysfunction, leading to cognitive decline and dementia, including AD [8, 65-69]. Severity-correlated reduction in cognitive performance in type-2 diabetes (T2D) and AD are associated with a decrease in brain IR expression and the phosphorylation of the insulin signaling molecules with lower CSF (Cerebrospinal fluid) insulin levels in both AD and T2D patient brains [70].

Decreased insulin signaling, including altered IR kinase activity and IRS expression, and increased basal (non-stimulated) activation (indicated by IRS-1 phosphorylation) become more prominent as AD progresses [8, 71-73]. Although IR protein levels were comparable in AD and control brains, the IR was distributed throughout the cell soma and dendrites of neurons in controls but was predominantly intracellular in AD neurons [8, 9, 72, 74]. The reduced insulin signaling in AD brain was correlated with decreased IRS-1 and IRS-2 levels as well as the robust co-localization of the elevated phosphorylated S312- and S616- IRS-1 with neurofibrillary tangles [72].

Impaired brain insulin signaling indicated by an increased basal AKT phosphorylation and implied compromised insulin-driven AKT activation, is associated with AD neuropathology and lower cognitive function [75]. Resonating with the concept that decreased brain insulin signaling is a key pathogenic event in AD, the brain areas with the highest IR levels such as the hippocampus and temporal lobe have the greatest neuronal vulnerability and neurodegenerative pathology in AD [76, 77]. Together, the data reviewed here suggest that impaired insulin signaling is a key contributor to cognitive decline and the neuropathology of AD. Hence, failure to improve cognition by the 12-month intranasal insulin administration to mild cognitive impairment and AD dementia patients may be due to the insulin resistance is too severe in these trial subjects [64].

THE ROLE OF NO IN BRAIN INSULIN RESISTANCE AND COGNITIVE PERFORMANCE

Brain insulin resistance refers to a reduced or failed response to insulin of brain cells. It may be caused by reduced IR protein levels, reduced binding affinity, or

inability to recruit adaptor proteins and activate downstream signaling cascades such as PI3K-Akt. Reduced insulin responsiveness contributes to impaired neuroplasticity, neurotransmission with aberrant receptor regulation and/or neurotransmitter release, glucose uptake into GLUT4 (Glucose transporter type 4)-expressing neurons and altered insulin-elicited homeostatic or inflammatory responses in glial cells. Ultimately, brain insulin resistance can disturb systemic metabolism, impair cognition, and cause psychiatric problems. Brain insulin resistance in AD can occur without apparent systemic insulin resistance or metabolic syndromes such as T2D [8, 9, 74]. Although the causal factors of brain insulin resistance are clearly diverse and not yet fully elucidated, studies on systemic insulin resistance suggest that changes in the NO system interacting with IR signaling may contribute. Table 1 summarizes the reports regarding cause-effect relationship between NOS changes and insulin resistance and/or cognitive performance.

Table 1: Studies examine the cause-and-effect relationship between altered NO availability and insulin receptor signaling, cognition and/or Alzheimer's disease pathology.

NOS	Species/manipulation	NO Level	IR	Cognitive Effects/AD Pathology	Ref.
nNOS	Hu. None	↑	-	None	[78]
nNOS	APP23 mice	↑	-	associate astrocytic APP	[79]
nNOS eNOS	NOS-KO Mice ICV L-NMMA	↓	+	None	[80]
nNOS	Rat ICV L-NMMA	↓	+	None	[81]
nNOS	Rat/Rabbit L-NMMA	↓	-	Impaired learning	[82]
nNOS	Rat L-NMMA	↓	-	NO contributes spatial memory	[83]
nNOS	Hu. None	↑	-	AD Dementia Rate 0-3	[84]
nNOS	Mice NOS-KO 7-NI	↓	-	Increase reactive oxygen species and NMDAR activation in brain	[33]
nNOS	Rat TRIM/7-NI	↓	-	Impaired learning and memory	[85]
nNOS	Mice 7-NI	↓	-	nNOS/eNOS both affect memory	[86]
nNOS	Rat 7-NI	↓	-	Impaired learning and memory formation	[87]

nNOS	Rat L-arginine/ 7-NI	↓	-	NO positively affects working memory	[88]
iNOS	Hu. None	↑	-	iNOS and eNOS were highly expressed in astrocytes in AD	[78]
iNOS	Hu. None	↑	-	iNOS expression increases in temporal cortical neurons and astrocytes	[84]
iNOS	Mice Tg2576 APP	↑	-	Calcium-dependent NOS enzymatic activity decreases; iNOS increases (neuron, microglia) in AD model	[89]
iNOS	Rat 1400W/PGE2/Aminoguanidine	↑	-	iNOS inhibition changes retinal glial activation	[90]
iNOS	Mice/Rat iNOS KO ICV GSNO	↑	+	Not determined	[37]
iNOS	Mice iNOS shRNA ICV L-NIL /L-NAME	↓	+	Not determined	[91]

Table 1: cont.

eNOS	Mice eNOS+/-	↓	+	Early cerebral infarctions at 3-6 months, amyloid angiopathy and cognitive impairment	[92]
eNOS	Mice SweArc tg AD mice	↓	-	AD model	[93]
eNOS	Mice eNOS+/-	↓	-	Increased cerebrovascular beta amyloid	[94]
eNOS	Mice eNOS KO	↓	-	Increased APP, BACE1, amyloid beta in brains	[95]
eNOS	Mice eNOS KO; APP/PS1/eNOS KO	↓	-	Increased tau phosphorylation, p25/p35 ratio, CDK5 activity	[96]
eNOS	Cell line/Mice eNOS KO L-NAME	↓	-	Increased APP, amyloid beta and BACE1 levels	[97]
eNOS	Hu. eNOS T-786C	↓	-	metabolic syndrome is associated with worse cognition only in the presence of the eNOS-786C allele	[98]
eNOS	Rat shRNA	↑	-	eNOS affects neuronal survival and functional	[24]

1400W, N-[[3-(aminomethyl)phenyl]methyl]-ethanimidamide, dihydrochloride; 7-NI, 7-Nitroindazole; AD, Alzheimer's disease; APP23 mouse, an Alzheimer mouse model with an overexpression of mutant human APP/Amyloid Beta Precursor Protein (Swedish mutation); BACE1, Beta-secretase 1/beta-site APP cleaving enzyme 1; CDK5, Cyclin-dependent kinase 5; eNOS, Endothelial Nitric Oxide Synthase; GSNO, S-Nitrosoglutathione; Hu., Human; ICV, Intracerebroventricular injection; iNOS, Inducible nitric oxide synthase; IR, Insulin resistance; IHC, Immunohistochemistry; KO, knock-out; L-NAME, N(ω)-nitro-L-arginine methyl ester; L-

NIL, L-N6-(1-iminoethyl)-lysine; L-NMMA, L-NG-monomethyl Arginine acetate; NMDAR, N-methyl-D-aspartate receptor; nNOS, Neuronal nitric oxide synthase; PGE₂, 9-oxo-11 α ,15S-dihydroxy-prosta-5Z,13E-dien-1-oic acid; TRIM, 1-(α,α,α -trifluoro-o-tolyl)-Imidazole.

The availability of NO is regulated by enzymatic activity and levels of NOS isoforms as well as by levels of reactive species such as superoxide that can quench and reduce NO. NO is generated by three NOS isoforms that are expressed in tissue-specific expression patterns [99-101]. While nNOS (NOS1) is predominantly found in neuronal tissue, NOS2 or inducible NOS (iNOS) is upregulated in activated macrophages, and NOS3 (eNOS) is abundantly expressed in endothelium and also found in dendritic spines [24, 101]. eNOS and nNOS, which catalyze the Ca²⁺-dependent constitutive NO production, occur predominantly in blood vessels and neural tissues, respectively. NO is also rapidly elevated during inflammation and may be a primary mediator of the inflammatory injury that occurs in neurodegenerative disorders such as AD [101, 102]. Thus, elevated NO levels, directly resulting from inflammatory processes in neurodegeneration, likely increase potential for insulin resistance, and accelerate pathology and cognitive impairment in AD.

Interestingly, systemic and presumably brain insulin resistance together with insulin secretory defects are observed when NOS activity in the brain is inhibited by intracerebroventricular (ICV) injection of L-NMMA in free-moving rats [81]. In contrast, ICV infusion of S-nitrosoglutathione (GSNO), a NO donor in mice impaired insulin signaling in hypothalamus and replicated the food intake pattern of obese individuals by causing nitrosation of IR and its downstream Akt [37]. Further, S-nitrosation of the IR, IRS-1, and Akt (protein kinase B) can lead to insulin resistance [103, 104]. Genetically eliminating iNOS (iNOS null) or inhibiting iNOS using iNOS targeting antisense oligonucleotides both reduce hypothalamic insulin resistance and normalize energy homeostasis [37]. Thus, selective manipulation of brain NO system can lead to systemic and brain insulin signaling defects but the role of NO in brain insulin resistance remains controversial.

Modulation of NOS can also affect cognitive performance. Systemic administration of the NO synthase inhibitor nitro-L-arginine methyl ester (L-NAME) in rats and rabbits impairs maze (spatial) learning in rats [82, 105] as well as the conditioned eye-blink response in rabbits [82]. Inhibition of NOS by 7-nitroindazole, L-NAME or N-MMA, impairs passive-avoidance and elevated pulse-maze memory performance [106], T-maze [107] and memory of shock

avoidance [108]. Conversely, administration of the NO precursor L-arginine or NO donors such as sodium nitroprusside, S-nitroso-N-acetylpenicillamine (SNAP), and molsidomine improves learning and memory including avoidance memory, maze performance and objective recognition [108-111] and prevents age-related memory deficits [108].

While these data collectively suggest that chemical manipulation of the NO system can lead to systemic and brain region-specific insulin resistance as well as changes in cognitive performance, whether brain insulin resistance is induced by perturbing brain NOS was not explicitly demonstrated in the cognitive tests. Furthermore, effects on cognitive performance were not assessed together with insulin signaling changes. Thus, the contribution to altered cognition and dementia by altered NO availability caused by insulin signaling changes is still unclear.

To further elucidate the inter-relationship between brain insulin signaling and cognitive performance, genetic manipulations of the NO system have been employed and polymorphisms of the NOS have been examined. Emerging data from animal models and humans indicates that polymorphisms in the eNOS gene influence susceptibility to systemic insulin resistance and metabolic disturbances leading to T2D [112-115]. In contrast, eNOS T786C and E298D mutations do not increase the risk of sporadic AD [116, 117]. Similarly, NOS gene polymorphisms do not alter disease risk in the majority of late-onset AD and Lewy body dementia cases [118]. Further analysis of the E298 allele reveals its association with higher risk of AD in the MIRAGE African American but not Caucasian population [119]. Although these studies suggest a causative role of reduced eNOS levels and sensitivity in the development of systemic insulin resistance, metabolic disturbance, and blood vessel resistance in animal models, eNOS polymorphisms in humans do not appear to affect brain insulin signaling and play a minor role in the AD progression. In addition to eNOS, iNOS activity is considerably higher in the hippocampus of AD patients compared to controls [120]. Together with the demonstration that decreased NO availability leads to many features of the diabetic state [121], the modulation of NO availability including genetic or polymorphism-induced changes in the NOS system appears to influence insulin signaling in peripheral tissues and may be an important molecular mechanism underlying the development of insulin resistance in the peripheral tissues. However, such changes in NO availability have little impact on brain insulin signaling and cognition.

Moreover, the impact on cognitive performance of altered NO availability resulting from compromised brain insulin signaling remains unclear. NO has long been regarded as a part of neurotoxic insult derived from neuroinflammation driven in part by elevation of pro-inflammatory cytokines including TNF α , IL-6 and IL-1 β

in the AD brain. Proinflammatory cytokines such as $\text{TNF}\alpha$ disrupt gene expression to reduce eNOS protein levels in endothelium and probably in dendritic spines by decreasing eNOS mRNA stability [122-125]. Thus, by reducing eNOS levels, proinflammatory cytokines such as $\text{TNF}\alpha$ can interfere with insulin signaling to evoke tissue-specific insulin resistance. Since AD is associated with sustained neuroinflammation with elevated proinflammatory cytokines in the brain, especially in areas important for cognition such as hippocampus and cortical regions [8, 9, 74], the insulin resistance induced by proinflammatory cytokines may be intertwined with neurodegeneration and dementia.

Conversely, stimulation of insulin signaling via PI3K-Akt can activate eNOS by phosphorylating the enzyme on the serine1177 residue. Insulin signaling can also potentiate adiponectin signaling to activate AMP kinase that in turn activates eNOS through phosphorylation of S1177 to promote glucose uptake in GluT4 expression neurons [101, 126]. Activation of eNOS also requires its localization in the caveolae and linkage with heat shock protein 90 (HSP90). Obesity-associated insulin resistance can decrease eNOS activity by reducing caveolin-1 in caveolae and disrupting eNOS interaction with HSP90 and insulin signaling cascade [127, 128]. Hence, elevated proinflammatory cytokines and reactive oxygen species (ROS) in AD brain can lead to reduced eNOS phosphorylation and activation, resulting in decreased NO availability and insulin resistance in endothelium as well as impaired vasodilation [129, 130]. Finally, superoxide rapidly reacts with NO to produce the more potent oxidant peroxynitrite, leading to endothelial dysfunction, reduced NO availability, exacerbating brain insulin resistance and promoting AD pathogenesis. Although these data point to the possible contribution of reduced NO by the elevated proinflammatory cytokines to insulin resistance in AD brain, the inter-relationships among proinflammatory cytokines, NO system and insulin resistance needs to be more clearly defined.

CONCLUDING REMARKS

In conclusion, ample of evidence from animal models and humans illustrates that impairments in the NO system contribute to the development of insulin resistance and associated metabolic disturbance in peripheral tissues. However, the direct contribution of reduced NO availability to brain insulin resistance is much less clear. Insulin is a critical regulator of multiple brain functions, including synaptic plasticity, learning and memory. Importantly, impaired insulin signaling (insulin resistance) in AD brain can occur without apparent systemic insulin signaling defects. Thus, clarifying the causal relationship of changes in the NO system to insulin signaling perturbations might increase our understanding of AD pathogenic

mechanisms and identify new therapeutic approaches such as modulating NO availability in brain to slow progression of the disease.

CONFLICT OF INTEREST

None Declare

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None

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From: Alzforum <alzforum@alzforum.org>
Sent time: 03/28/2022 10:53:10 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Weekly Newsletter

The latest from [Alzforum.org](https://www.alzforum.org) - March 28, 2022

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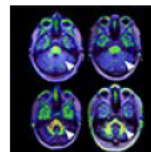
WEEKLY NEWSLETTER

March 28, 2022

NEWS

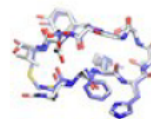
[In First for the Field, \$\alpha\$ -Synuclein PET. Only for Multiple System Atrophy](#)

A new tracer detects α -synuclein aggregates in people with multiple system atrophy. Binding is weak, and undetectable in people with other synucleinopathies.



[TAPAS Anyone? PyroGlu-A \$\beta\$ Vaccine Shrinks Plaques in Mice](#)

The new vaccine stalled neurodegeneration and improved learning. An antibody that binds the same epitope had similar effects, and only binds soluble oligomers.



[Gantenerumab Prevention Trial in Sporadic Alzheimer's Begins](#)

Taking a stab at secondary prevention, the four-year Phase 3 trial will assess the antibody's ability to slow slippage in 1,200 cognitively healthy, amyloid-positive people.

[Field Loses GSM Developer Steven Wagner, 64](#)

Wagner pioneered γ -secretase modulators to treat Alzheimer's disease, with a candidate slated to enter Phase 1 this year. Read tributes from [Rudy Tanzi](#), [William Van Nostrand](#), [Barry Greenberg](#), [Graham Johnson](#), [Patrick May](#), [Grant Krafft](#), [Kumar Sambamurti](#), and [Xulun Zhang](#).



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COMMENTS

[Gil Rabinovici](#) on [In First for the Field, \$\alpha\$ -Synuclein PET. Only for Multiple System Atrophy](#)

[Cynthia Lemere](#) on [TAPAS Anyone? PyroGlu-A \$\beta\$ Vaccine Shrinks Plaques in Mice](#)

[Pierre Tariot](#) on [Gantenerumab Prevention Trial in Sporadic Alzheimer's Begins](#)

[Jeffrey Cummings](#) on [Gantenerumab Prevention Trial in Sporadic Alzheimer's Begins](#)

[Paul Aisen](#) on [Gantenerumab Prevention Trial in Sporadic Alzheimer's Begins](#)

[Frédéric Checler](#) on A η - α and A η - β peptides impair LTP ex vivo within the low nanomolar range and impact neuronal activity in vivo.

[Johnathan Cooper-Knock](#) and [Winston Hide](#) on Robust TREM2 Expression May Delay Alzheimer's Disease

[Emrah Düzel](#) on Like GWAS, BWAS Need Thousands of Participants

[Sarah Genon](#) on Like GWAS, BWAS Need Thousands of Participants

[Brian Gordon](#) on Like GWAS, BWAS Need Thousands of Participants

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DATABASES

Mutations

Added

[PSEN1 L418W](#)

[PSEN1 G78G](#)

[PSEN1 V151V](#)

[PSEN1 T281T](#)

[PSEN1 c.*9C>T](#)

Therapeutics

Updated

[Donepezil](#)

[Nicotinamide Riboside](#)

[Simufilam](#)

CONFERENCE CALENDAR

Conferences

[The Leuven Protein Aggregation Meeting](#)
21 – 23 September 2022

[EMBO/FEBS Lecture Course: Mitochondria in Life, Death, and Disease](#)
27 September – 1 October 2022

Webinars

[Microglial Extracellular Vesicles](#)
4 April 2022

[Microglial Origins, States, and Fates](#)
9 May 2022

Training Programs / Courses

[Novel Mechanisms, Tools, and Therapies in Neuroinflammation](#)
8 – 9 September 2022

Due to the COVID-19 pandemic, many upcoming meetings have been postponed, canceled, or rescheduled as virtual meetings. We have updated our conference calendar and will continue to monitor and update as necessary.

[VIEW ALL CONFERENCES](#)

JOBS

[Postdoctoral Fellow](#)

Mayo Clinic
Jacksonville, Florida

[Postdoctoral Scholar in Data Science Methodology for AD Research](#)

National Alzheimer's Coordinating Center / University of Washington
Seattle, Washington

[Postdoctoral Fellow - Genetics, Epigenetics and Therapeutic Innovation in Neurodegenerative Diseases](#)

Van Andel Institute
Grand Rapids, Michigan

[Postdoctoral Fellow](#)

Indiana University School of Medicine
Fort Wayne, Indiana

[Postdoctoral Associate](#)

Cornell University
Ithaca, New York

[UCSF Postdoctoral Fellowship Position](#)

University of California, San Francisco

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GRANTS

Prospective Observational Comparative Effectiveness Research in Clinical Neurosciences (UG3/UH3 Clinical Trial Not Allowed) (PAR-22-076)

Technology Development Research for Establishing Feasibility and Proof of Concept (R21 - Clinical Trial Not Allowed) (PAR-22-126)

Focused Technology Research and Development (R01 Clinical Trial Not Allowed) (PAR-22-127)

BRAIN Initiative: Integration and Analysis of BRAIN Initiative Data (R01 Clinical Trial Not Allowed) (RFA-MH-22-220)

Notice of Intent to Publish a Funding Opportunity Announcement for Impact of the Microbiome Gut-Brain Axis on ADRD (R01 Clinical Trial Not Allowed) (NOT-NS-22-088)

Catalyst for a Cure Initiative to Prevent & Cure Neurodegeneration

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From: The Scientist <newsletters@the-scientist.com>
Sent time: 04/01/2022 09:02:07 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Can these fish do math?

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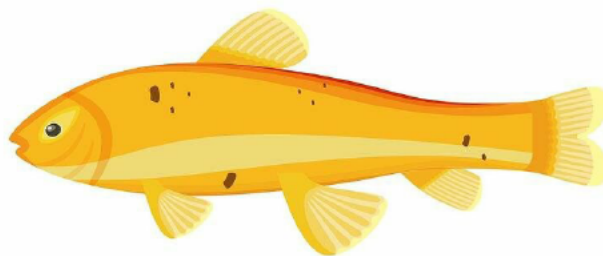
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Can These Fish Do Math?

By Sophie Fessl

Scientists find that two species can be trained to distinguish quantities that vary by one.




PLOS ONE Pulls Five Papers Tied to Alzheimer's Drug Controversy

By Jef Akst

The retracted studies were coauthored by a scientist who worked on an Alzheimer's therapy in development by Cassava Sciences, a company reportedly under investigation for providing falsified data to the FDA.

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Keep Reading



Sunflowers' Bee-Attracting Ultraviolet Also Helps Retain Moisture

By Natalia Mesa

The dual purposes of the plants' hidden colors may conflict as the climate warms, authors of a new study suggest.

Convalescent Plasma for COVID-19 Cuts Hospitalizations

Infographic: Putting Cancer's Unique Microbiomes to Use

On the Trail of the Jackalope



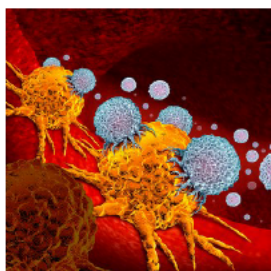
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Research Resources



Symposium: Identifying Biomarkers to Guide Cancer Immunotherapy

By *The Scientist* Creative Services Team

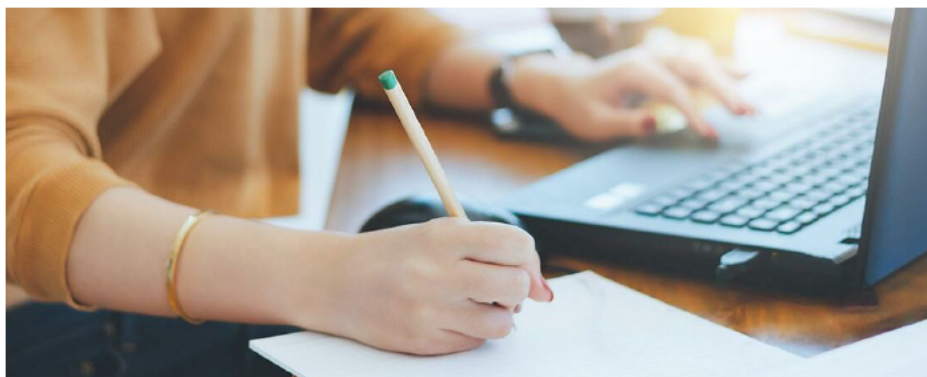
An expert panel will discuss their efforts to identify new biomarkers for various cancers, including non-small cell lung cancer and clear cell renal cell carcinoma. They will also highlight the cutting-edge technologies they use to develop clinical applications for these biomarkers.



Video: Optimizing Assay Optics

By Tecan

Researchers produce reliable data when they choose the correct tools for their needs. Watch this video from Tecan to learn about the optical options found within microplate readers.



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From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 04/04/2022 04:12:16 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Congratulations Hoau-Yan, you achieved top stats last week

ResearchGate



Your publication has a new achievement:
**Effects of simuflam on cerebrospinal fluid
biomarkers in Alzheimer's disease: A randomized
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From: Apoorva Mandavilli <apoorva.mandavilli@nytimes.com>
Sent time: 04/10/2022 11:43:42 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Time-sensitive: Request for comment for New York Times article on Cassava

Hello Dr. Wang,

I'm a reporter for *The New York Times*. I'm writing an article about Cassava, and the recent retractions of your papers.

Please respond to the following questions. I would appreciate a response by **Tuesday 10 am ET**.

1. Are you still a member of Cassava's scientific advisory board?
2. What is the status of CUNY's investigation into the allegations against you? Please comment.
3. Please comment on the recent retractions of five of your papers in PLoS One, as well as the other retraction and expressions of concern over the past three months.
4. I understand you did not agree with the retractions. Please comment on the concerns about the work, as well as the charges of image manipulation.
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9. Cassava initially said the re-analysis of results from the phase 2b trial were done by an independent lab, but later revealed it was done by you. Please explain how you can be considered to be independent when you receive money from the company, and lead all of its lab work.

Happy to clarify any questions that are unclear.

Thanks,
Apoorva

--

Reporter, Science & Global Health
~~The New York Times~~
Twitter: @apoorva_nyc

From: Hoau-yan Wang
Sent time: 04/11/2022 08:24:44 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] Time-sensitive: Request for comment for New York Times article on Cassava

POL 87(2)(a)

From: Apoorva Mandavilli <apoorva.mandavilli@nytimes.com>
Sent: Sunday, April 10, 2022 11:43 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Time-sensitive: Request for comment for New York Times article on Cassava

Hello Dr. Wang,

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Apoorva

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Reporter, Science & Global Health
The New York Times
Twitter: @apoorva_nyc

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent time: 04/11/2022 09:37:15 AM
To: Hoau-yan Wang
Subject: Re: [EXTERNAL] Time-sensitive: Request for comment for New York Times article on Cassava

POL 87(2)(a)

Jennifer Beidel
Jennifer.beidel@saul.com
(215) 470-0667

On Apr 11, 2022, at 8:24 AM, Hoau-yan Wang wrote:

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From: Apoorva Mandavilli
Sent: Sunday, April 10, 2022 11:43 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Time-sensitive: Request for comment for New York Times article on Cassava

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Apoorva
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Reporter, Science & Global Health
[The New York Times]
Twitter: @apoorva_nyc

"Saul Ewing Arnstein & Lehr LLP (saul.com) " made the following annotations:

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From: Hoau-yan Wang
Sent time: 04/11/2022 10:14:53 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Re: [EXTERNAL] Time-sensitive: Request for comment for New York Times article on Cassava

POL 87(2)(a)

[REDACTED]

Hoau

From: Beidel, Jennifer L.
Sent: Monday, April 11, 2022 9:37 AM
To: Hoau-yan Wang
Subject: Re: [EXTERNAL] Time-sensitive: Request for comment for New York Times article on Cassava

[REDACTED]

Jennifer Beidel
jennifer.beidel@saul.com
(215) 470-0667

On Apr 11, 2022, at 8:24 AM, Hoau-yan Wang wrote:

****EXTERNAL EMAIL**** - This message originates from outside our Firm. Please consider carefully before responding or clicking links/attachments.

[REDACTED]

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From: Apoorva Mandavilli <apoorva.mandavilli@nytimes.com>
Sent time: 04/12/2022 09:01:21 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Time-sensitive: Request for comment for New York Times article on Cassava

Hello, I'm following up on this to request a response.

Best,
Apoorva

On Sun, Apr 10, 2022 at 11:43 PM Apoorva Mandavilli <apoorva.mandavilli@nytimes.com> wrote:

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Twitter: @apoorva_nyc

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From: Hoau-yan Wang
Sent time: 04/12/2022 09:55:51 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] Re: Time-sensitive: Request for comment for New York Times article on Cassava

POL 87(2)(a)

From: Apoorva Mandavilli <apoorva.mandavilli@nytimes.com>
Sent: Tuesday, April 12, 2022 9:01 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Time-sensitive: Request for comment for New York Times article on Cassava

Hello, I'm following up on this to request a response.

Best,
Apoorva

On Sun, Apr 10, 2022 at 11:43 PM Apoorva Mandavilli <apoorva.mandavilli@nytimes.com> wrote:
Hello Dr. Wang,

I'm a reporter for *The New York Times*. I'm writing an article about Cassava, and the recent retractions of your papers.

Please respond to the following questions. I would appreciate a response by **Tuesday 10 am ET**.

1. Are you still a member of Cassava's scientific advisory board?
2. What is the status of CUNY's investigation into the allegations against you? Please comment.
3. Please comment on the recent retractions of five of your papers in PLoS One, as well as the other retraction and expressions of concern over the past three months.
4. I understand you did not agree with the retractions. Please comment on the concerns about the work, as well as the charges of image manipulation.
5. One expert on biomarkers noted that the reported biomarker values in your Simufilam work are out of range for the ELISA used and better match those expected from Luminex. Please respond.
6. Some experts noted that the drug restoring the shape of 100% of filamin A did not seem believable given filamin A's distribution in the body. Please respond.
7. Some experts said the improvement in cognition did not seem believable because the patients' scores after treatment took them out of Alzheimer's disease range entirely. Please respond.
8. Some experts said that the results from the clinical trial were difficult to interpret because there was no placebo arm, and the patients were not followed long enough to confirm that the results were real. Please respond.
9. Cassava initially said the re-analysis of results from the phase 2b trial were done by an independent lab, but later revealed it was done by you. Please explain how you can be considered to be independent when you receive money from the company, and lead all of its lab work.

Happy to clarify any questions that are unclear.
Thanks,
Apoorva

--

Reporter, Science & Global Health
The New York Times
Twitter: @apoorva_nyc

--

Reporter, Science & Global Health
The New York Times
Twitter: @apoorva_nyc

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>

Sent time: 04/12/2022 09:55:57 AM

To: Hoau-yan Wang

Subject: [REDACTED] [EXTERNAL] Re: Time-sensitive: Request for comment for New York Times article on Cassava

POL 87(2)(a)

[REDACTED]

"Saul Ewing Arnstein & Lehr LLP (saul.com) " made the following annotations:

+~~~~~+

This e-mail may contain privileged, confidential, copyrighted, or other legally protected information. If you are not the intended recipient (even if the e-mail address is yours), you may not use, copy, or retransmit it. If you have received this by mistake please notify us by return e-mail, then delete.

+~~~~~+

From: Hoau-yan Wang
Sent time: 04/12/2022 12:13:22 PM
To: [REDACTED]@gmail.com
Subject: Fw: [EXTERNAL] Re: Time-sensitive: Request for comment for New York Times article on Cassava

From: Apoorva Mandavilli <apoorva.mandavilli@nytimes.com>
Sent: Tuesday, April 12, 2022 9:01 AM
To: Hoau-yan Wang
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Apoorva

--

Reporter, Science & Global Health
The New York Times
Twitter: @apoorva_nyc

--

Reporter, Science & Global Health
The New York Times
Twitter: @apoorva_nyc

From: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Sent time: 04/12/2022 04:15:07 PM
To: Hoau-yan Wang
Cc: Bollinger, Andrew E. <Andrew.Bollinger@saul.com>; Helmerhorst, Eva J. <eva.helmerhorst@saul.com>
Subject: Re: [EXTERNAL] Re: Time-sensitive: Request for comment for New York Times article on Cassava

POL 87(2)(a)

[REDACTED]

Jennifer Beidel
Jennifer.beidel@saul.com
(215) 470-0667

On Apr 12, 2022, at 9:55 AM, Hoau-yan Wang wrote:

****EXTERNAL EMAIL**** - This message originates from outside our Firm. Please consider carefully before responding or clicking links/attachments.

[REDACTED]

[REDACTED]

From: Apoorva Mandavilli
Sent: Tuesday, April 12, 2022 9:01 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Re: Time-sensitive: Request for comment for New York Times article on Cassava

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Reporter, Science & Global Health
[The New York Times]
Twitter: @apoorva_nyc

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Reporter, Science & Global Health
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Twitter: @apoorva_nyc

"Saul Ewing Arnstein & Lehr LLP (saul.com) " made the following annotations:

+~~~~~+

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+~~~~~+

From: Hoau-yan Wang
Sent time: 04/14/2022 01:29:16 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: FW: Time-sensitive: Request for comment for New York Times article on Cassava

POL 87(2)(a)

From: Remi Barbier <remi@cassavasciences.com>
Sent: Tuesday, April 12, 2022 4:52 PM
To: Guy D. Singer (gsinger@orrick.com)
Cc: Hoau-yan Wang; Lindsay Burns; Rick Barry (rick@rickbarry.net); Sandy Robertson - Francisco Partners (robertson@franciscopartners.com)
Subject: [EXTERNAL] FW: FW: Time-sensitive: Request for comment for New York Times article on Cassava

More from NYT, below.

Remi Barbier
President & CEO



From: [Remi Barbier](#)
Sent: Tuesday, April 12, 2022 3:50 PM
To: [Apoorva Mandavilli](#)
Cc: [Mike Sitrick](#); [Eric Schoen](#)
Subject: RE: FW: Time-sensitive: Request for comment for New York Times article on Cassava

Yes they are. That should be its own story. By this low-bar from PLOS, many, if not most, Western blots with hand poured gels and traditional x-ray film may qualify for retraction. Science editors are supposed to follow COPE guidelines for retraction (COPE is an independent org that assists science journal editors, see <https://publicationethics.org/guidance/Guidelines>). There are open questions about whether PLOS editor followed COPE guidelines in retracting Prof. Wang's five paper.

We stand by Prof. Wang 100%.

Remi Barbier
President & CEO



From: [Apoorva Mandavilli](#)
Sent: Tuesday, April 12, 2022 3:36 PM
To: [Remi Barbier](#)
Cc: [Mike Sitrick](#); [Eric Schoen](#)
Subject: Re: FW: Time-sensitive: Request for comment for New York Times article on Cassava

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Sorry, I think there is some miscommunication here. Per my previous email, I am asking how you feel about ALL of the retractions from Dr. Wang's lab and whether you are concerned about the quality of the lab's work. Those retractions are not all because of approx 6 pixels.

On Tue, Apr 12, 2022 at 4:27 PM Remi Barbier <remi@cassavasciences.com> wrote:

Pls see below.

Remi Barbier
President & CEO

From: [Apoorva Mandavilli](#)
Sent: Tuesday, April 12, 2022 3:11 PM
To: [Remi Barbier](#)
Cc: [Mike Sitrick](#); [Eric Schoen](#)
Subject: Re: FW: Time-sensitive: Request for comment for New York Times article on Cassava

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Thank you.

So no comment on the 5 PLoS retractions? **We did comment. See prior email regarding PLOS:**

4. Please comment on the recent retractions of papers in PLoS One from Dr. Wang's lab, including those related to Cassava's work. **The specific allegation involves approx. 6 pixels out of thousands or possibly millions that appear to be visual artifacts in the background only, and that are visible only under extremely manipulated conditions. These background pixels have no impact on the data or its interpretation.**

6. The comment was not that your blot showed 100% of filamin A in the body but that the idea of it shifting all filamin A in the brain *given the protein's distribution in the body* does not seem rational. Thanks for sharing the email from the editor. However, it does not say no evidence, it says they do not find compelling evidence, and also says they are adding an expression of concern, so it is not resolved yet. **Lack of evidence is lack of evidence, however worded. As a reminder, this is spoken by a neutral, expert in the field.**

As I said below: "Expressions of concerns" are placeholders to recognize CUNY's pending investigation into allegations. If CUNY clears, the expressions of concerns are expected to clear.

8. Where you say: **"That said, mild-to-moderate Alzheimer's disease is an irreversible, chronic disease. It's a one-way street in that patients inevitably decline over time"** In your press releases, you have said the drug improved cognition and decreased neuropsychiatric behaviors -- doesn't that mean you're saying your drug does reverse aspects of the disease and that decline is not inevitable?

We have no further comment beyond what is in the press release.

On Tue, Apr 12, 2022 at 4:03 PM Remi Barbier <remi@cassavasciences.com> wrote:

Pls see below.

Remi Barbier
President & CEO



From: [Apoorva Mandavilli](#)
Sent: Tuesday, April 12, 2022 1:31 PM
To: [Remi Barbier](#)
Cc: [Mike Sitrick](#); [Eric Schoen](#)
Subject: Re: FW: Time-sensitive: Request for comment for New York Times article on Cassava

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Thank you. A couple of follow ups based on your responses:

4. Re: the retractions, I am not asking about one specific allegation in one specific paper. I am asking for comment on the number of retractions and expressions of concern by now. Dr. Wang now has 6 retractions and 2 expressions of concern, even if not all of them are related to Cassava. Does that not concern you? **Five of the six retractions are from PLOS. The**

sixth retraction was voluntary by all authors due to a faint visual artifact in a single blot. The authors are repeating the experiment and are expected to resubmit results to the journal. "Expressions of concerns" are placeholders to recognize CUNY's pending investigation into allegations. If CUNY clears, the expressions of concerns are expected to clear.

6. I'm referring to Fig 2A in this paper, where all of the misshapen protein seems to have shifted by PTI-125 binding : <https://www.sciencedirect.com/science/article/pii/S0197458017300878>

One prominent Alzheimer's researcher said there was "no rational way this could happen." (1) This paper refers to measurement of an altered conformation of filamin A in the brain that normalizes with drug treatment, and not with all filamin A in the body which would clearly and obviously not be rational. This is a distinction with a difference. (2) This paper went through peer-review prior to publication, indicating there are neutral experts in the field who believe the methods and the data. (3) More recently, this paper went through another examination by neutral, expert parties as a result of allegations. In response to these allegations, the journal editor requested raw data for the article, including images of original, uncropped Western blots. Having received that data and completed its review, the editors found no evidence for the allegations. In fact, below is a reprint of the email from Peter Rapp, PhD, Editor-in-Chief, Neurobiology of Aging:

"We have now completed our evaluation of concerns regarding your 2017 report in Neurobiology of Aging (Wang et al. (2017) Neurobiol Aging, 55:99-114), including issues identified in your own review of the manuscript. To recap the evaluation, we considered input from several independent sources: 1) all of the available material was evaluated by a senior, highly-cited NIH scientist who has no conflicts or competing interests, but who has extensive relevant methodological expertise, 2) the paper was scanned using AI-based, automated image proofing software available through NBA's publisher (i.e., Proofing), and 3) the Editor who handled your original and revised submissions and I both reviewed the concerns, your responses, and the other available input. Our joint conclusion is that the number and nature of errors identified in the published report are legitimate concerns that might cause reasonable readers to question the reliability of the results. That said, we did not find compelling evidence of deliberate data manipulation intended to misrepresent the findings. In the interest of NBA readers, our consensus decision is to publish an 'Expression of Concern' in connection with the report, with final action pending the outcome of the ongoing inquiry at the sponsoring institution (i.e., similar to the recent notice published at J Neurosci). If the outcome of that inquiry does not recommend otherwise, we would anticipate lifting the Expression of Concern and publishing a corrigendum.

8. I'm not following your response to this question. The experts were not saying that an open-label trial should have a placebo arm. What they were saying is that an open-label placebo arm cannot be interpreted as showing positive results *because* there is no placebo, and you cannot rule out a placebo effect, especially in the 9-month range of the results reported. **To be clear, FDA does not accept cognition data from an open-label study as statutory evidence of efficacy. No one will argue this point.** That said, mild-to-moderate Alzheimer's disease is an irreversible, chronic disease. It's a one-way street in that patients inevitably decline over time. We are not aware of a placebo effect going out 9 months in an open-label study in patients with mild-to-moderate Alzheimer's disease.

9. Please respond to the question asked -- Dr. Wang is not independent if he is on your scientific advisory board, so why was he described as such? As to your response, the alternative would be to hire a truly independent lab, one that is not linked to Cassava as Dr. Wang is. Why did you choose not to go that route?

(1) Either way, we pay.

(2) I don't see Dr Wang -- or any medical doctor -- selling out his/her reputation for \$2,000 per month.

(3) In biotech, SAB members are independent if they are (i) non-employees (ii) whose compensation is not based on results and (ii) who perform their work independently in their own facilities at their discretion. Prof. Wang clearly meets this definition.

Thanks,
Apoorva

On Tue, Apr 12, 2022 at 2:10 PM Remi Barbier <remi@cassavasciences.com> wrote:

Apoorva -

Specific responses to your specific questions are provided in **red BOLD** below. Please acknowledgment receipt of this email.

Do you know when your article will print?

Thank you,

Remi

Remi Barbier
President & CEO



From: Apoorva Mandavilli <apoorva.mandavilli@nytimes.com>

Sent: Sunday, April 10, 2022 10:38 PM

To: Eric Schoen <eschoen@cassavasciences.com>

Subject: Time-sensitive: Request for comment for New York Times article on Cassava

CAUTION: This email originated from outside the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

I'm a reporter for The New York Times. I am writing about your company, and specifically about some of the questions raised about your work. Please respond to the following questions. I would appreciate a response by **Tuesday 10 am ET**.

1. How many employees does the company now have? **Approx. 25 fulltime.**
2. Is your lab work done only at Dr. Wang's lab at CUNY, as you have previously stated? Or do you also rely on other labs now? **We work with and rely on multiple labs.**
3. Is Dr. Wang still a member of your scientific advisory board? **Yes.**
4. Please comment on the recent retractions of papers in PLoS One from Dr. Wang's lab, including those related to Cassava's work. **The specific allegation involves approx. 6 pixels out of thousands or possibly millions that appear to be visual artifacts in the background only, and that are visible only under extremely manipulated conditions. These background pixels have no impact on the data or its interpretation.**
5. One expert on biomarkers noted that your reported biomarker values are out of range for the ELISA you used and better match those expected from Luminex. Please respond. **Other experts may disagree.**
6. Some experts noted that the drug restoring the shape of 100% of filamin A did not seem believable given filamin A's distribution in the body. Please respond. **We don't make this claim.**
7. Some experts said the improvement in cognition did not seem believable because the patients' scores after treatment took them out of Alzheimer's disease range entirely. Please respond. **The data is the data.**
8. Some experts said that the results from the clinical trial were difficult to interpret because there was no placebo arm, and the patients were not followed long enough to confirm that the results were real. Please respond. **An open-label study has no placebo arm by definition. Cognition measurements in randomized trials can be difficult to interpret (see Biogen data) and cognition measurement in open-label studies are even harder to interpret. However, safety data is safety data.**
9. You initially said the re-analysis of results from your phase 2b trial were done by an independent lab, but later revealed it was done by Dr. Wang. Please explain how Dr. Wang can be considered to be independent when he receives money from the company and leads all of your lab work.
(1) Prof. Wang does not conduct all of our lab work.
(2) We are not aware of any medical professor who consults for free on an ongoing basis. We pay him \$2,000/month.
(3) We have many external advisors, consultants, directors and auditors who are both compensated and independent.
(4) The alternative would be to conduct the bioanalysis in house, which some might argue is non-independent.
10. Your phase 3 trial has only 60 participants per the fireside chat last week. How do you plan to step up the recruitment? **Biotech companies do not generally disclose details of their patient recruitment plans to the public. We are confident we will achieve our goals.**

Happy to clarify any questions that are unclear.

Thanks,
Apoorva

From: Thoburn Freeman <[REDACTED]@gmail.com>
Sent time: 04/20/2022 09:56:44 AM
To: Hoau-yan Wang
Subject: [EXTERNAL]

Hello Sir,

Apologies if these questions are inappropriate however i was wondering if you knew when the university's investigation report relating to cassava sciences of you will be released? Also what's your opinion of cassava sciences? I hope you're having a good week.

Kind regards,
Concerned investor.

From: Hoau-yan Wang
Sent time: 04/20/2022 11:28:09 AM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL]

POL 87(2)(a)

From: Thoburn Freeman <[REDACTED]@gmail.com>
Sent: Wednesday, April 20, 2022 9:56 AM
To: Hoau-yan Wang
Subject: [EXTERNAL]

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Concerned investor.

From: 이호준 <korearise@naver.com>
Sent time: 04/20/2022 10:16:35 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] hi

Hello? My name is Lee Hojun.

I am an investor in Korea.

I'm afraid you won't answer, but I have to ask because My economic life is at stake

If you don't mind, I'd like to ask you a few questions.

1. When does the cuny investigation related to simufilem paper end?

2. I would like to ask what your honest opinion is about the allegation that your paper was fabricated.

I'd appreciate it if you could answer my question.

May your future be full of happiness.

From: Hoau-yan Wang
Sent time: 04/21/2022 12:04:07 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: [EXTERNAL] hi

POL 87(2)(a)

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May your future be full of happiness.

From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 04/25/2022 04:27:04 AM
To: Hoau-yan Wang
Subject: [EXTERNAL] Congratulations Hoau-Yan, you achieved top stats last week

ResearchGate



Your publication has a new achievement:
**Effects of simuflam on cerebrospinal fluid
biomarkers in Alzheimer's disease: A randomized
clinical trial**

[View achievement](#)

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From: [REDACTED] <[REDACTED]@citymail.cuny.edu>
Sent time: 05/03/2022 01:32:00 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Newspaper Reporter Asking For Comments Over Simufilam Research

FERPA/Privacy

Dear Dr. Wang,

My name is [REDACTED], and I am a reporter for the Macaulay Messenger – a student run publication for the Macaulay Honors College of CUNY.

I am reaching out to ask for your response to recent allegations questioning the integrity of your research on simufilam and filamin A. I would appreciate your insight into both the allegations as well as the science behind the drug and why you view filamin A as a key target for Alzheimer's research.

Thank you for your time, and I look forward to hearing back from you.

Sincerely,

[REDACTED]
[REDACTED] at the Macaulay Messenger
Macaulay Honors Student at the City College of New York

From: Hoau-yan Wang
Sent time: 05/03/2022 01:54:04 PM
To: Beidel, Jennifer L. <jennifer.beidel@saul.com>
Subject: Fw: Newspaper Reporter Asking For Comments Over Simufilam Research

POL 87(2)(a)

From: [REDACTED] <[REDACTED]@citymail.cuny.edu>
Sent: Tuesday, May 3, 2022 1:32 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Newspaper Reporter Asking For Comments Over Simufilam Research

FERPA/Privacy

Dear Dr. Wang,

My name is [REDACTED], and I am a reporter for the Macaulay Messenger – a student run publication for the Macaulay Honors College of CUNY.

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Sincerely,

[REDACTED]
[REDACTED] at the Macaulay Messenger
Macaulay Honors Student at the City College of New York

From: ResearchGate <no-reply@researchgatemail.net>
Sent time: 05/05/2022 11:24:10 PM
To: Hoau-yan Wang
Subject: [EXTERNAL] Hoau-Yan, you have 26 mentions of your research

ResearchGate



Hoau-Yan, we found 26 mentions of your research last week

See all your mentions and other stats about your work in your weekly stats report.

W From the page: Cassava Sciences

... ..ound as PTI-609 (PTI for Pain Therapeutics, Inc.).[20] In 2012, Burns and Wang's team reintroduced t... ..

Publication mentioned

PTI-609: A Novel Analgesic that Binds Filamin A to Control Opioid Signaling

[View stats report](#)

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