: 4150-31)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Findings of Research Misconduct

AGENCY: Office of the Secretary, HHS.

ACTION: Notice.

SUMMARY: Findings of research misconduct have been made against Gian-Stefano Brigidi, Ph.D. (Respondent), who was a Postdoctoral Fellow, Department of Neurobiology, University of California San Diego (UCSD), and was an Assistant Professor, Department of Neurobiology, University of Utah (UU). Respondent engaged in research misconduct in research supported by U.S. Public Health Service (PHS) funds, specifically National Institute of Mental Health (NIMH), National Institutes of Health (NIH), grant F32 MH110141, National Human Genome Research Institute (NHGRI), NIH, grant T32 HG000044, National Institute of Neurological Disorders and Stroke (NINDS), NIH, grant P30 NS047101, and National Library of Medicine (NLM), NIH, grant T15 LM011271. The research was included in grant applications submitted for PHS funds, specifically R01 NS131809-01, R01 NS133405-01, DP2 NS127276-01, and R01 NS111162-01A1 submitted to NINDS, NIH, and R21 MH121860-01, R21 MH121860-01A1, F32 MH110141-01, F32 MH110141-01A1, and F32 MH110141-01AS1 submitted to NIMH, NIH. The administrative actions, including supervision for a period of five (5) years, were implemented beginning on March 24, 2024, and are detailed below.

FOR FURTHER INFORMATION CONTACT:

Sheila Garrity, JD, MPH, MBA
Director
Office of Research Integrity
1101 Wootton Parkway, Suite 240
Rockville, MD 20852
(240) 453-8200

SUPPLEMENTARY INFORMATION: Notice is hereby given that the Office of Research Integrity (ORI) has taken final action in the following case:

Gian-Stefano Brigidi, Ph.D., University of California San Diego (UCSD) and University of Utah (UU): Based on the report of an assessment conducted by UU, and inquiry conducted by UCSD, the Respondent's admission, and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Gian-Stefano Brigidi, former Postdoctoral Fellow in the Department of Neurobiology, UCSD, and former Assistant Professor, Department of Neurobiology, UU, engaged in research misconduct in research supported by PHS funds, specifically NIMH, NIH, grant F32 MH110141, NHGRI, NIH, grant T32 HG000044, NINDS, NIH, grant P30 NS047101, and NLM, NIH, grant T15 LM011271. The research was included in grant applications submitted for PHS funds, specifically R01 NS131809-01, R01 NS133405-01, DP2 NS127276-01, and R01 NS111162-01A1 submitted to NINDS, NIH, and R21 MH121860-01, R21 MH121860-01A1, F32 MH110141-01, F32 MH110141-01A1, and F32 MH110141-01AS1 submitted to NIMH, NIH.

ORI found that Respondent engaged in research misconduct by knowingly or intentionally falsifying and/or fabricating data and results by manipulating primary data values to falsely increase the n-value, manipulating fluorescence micrographs and their quantification graphs to augment the role of ITFs in murine hippocampal neurons, and/or manipulating confocal images that were obtained through different experimental conditions in twenty (20) figures of one (1) published paper and four (4) PHS grant applications, one (1) panel of one (1) poster, and seven

(7) slides of one (1) presentation:

- Genomic Decoding of Neuronal Depolarization by Stimulus-Specific NPAS4 Heterodimers. *Cell*. 2019 Oct 3;179(2):373-391.e27. doi: 10.1016/j.cell.2019.09.004 (hereafter referred to as "*Cell* 2019").

- Genomic mechanisms linking neuronal activity history with present and future functions. Poster for "The Brigidi Lab – a neuronal activity lab in the Department of Neurobiology at the University of Utah" (hereafter referred to as the "UU Department of Neurobiology poster").

- Decoding neural circuit stimuli into spatially organized gene regulation. Presentation presented to the UU Department of Neurobiology & Anatomy on January 23, 2020 (hereafter referred to as "UU Department of Neurobiology presentation").

- DP2 NS127276-01, "Decoding neuronal activity history at the genome through the spatially segregated inducible transcription factors," submitted to NINDS, NIH, on August 20, 2020, Awarded Project Dates: September 15, 2021-August 1, 2023.

- F32 MH110141-01, "Regulation of excitatory-inhibitory balance by the local translation of the immediate early gene Npas4," submitted to NIMH, NIH, on August 10, 2015.

- F32 MH110141-01A1, "Regulation of Excitatory-Inhibitory Balance by Local Translation of the Immediate Early Gene Npas4," submitted to NIMH, NIH, on December 8, 2015, Awarded Project Dates: August 1, 2016-July 31, 2018.

- F32 MH110141-01A1S1, “Regulation of Excitatory-Inhibitory Balance by Local Translation of the Immediate Early Gene Npas4,” submitted to NIMH, NIH, on December 8, 2016, Awarded Project Dates: December 1, 2016-July 31, 2017.

The falsified and/or fabricated data also were included in twenty-three (23) figures in the following five (5) PHS grant applications:

- R01 NS131809-01, “Regulation and function of dendritic mRNA that encodes the neuronal transcription factor Npas4,” submitted to NINDS, NIH, on June 6, 2022.

- R01 NS133405-01, “Assessing the impact of the inducible transcription factor NPAS4 on spatial tuning in the mouse hippocampus,” submitted to NINDS, NIH, on October 5, 2022.

- R01 NS111162-01A1, “Molecular and cellular mechanisms underlying activity dependent gene regulation in neurons,” submitted to NINDS, NIH, on March 5, 2019, Awarded Project Dates: December 15, 2019-November 30, 2024.

- R21 MH121860-01, “Identification of dendritically-localized transcription factor mRNAs as a mechanism for conveying multiple streams of information to the nucleus,” submitted to NIMH, NIH, on February 19, 2019.

- R21 MH121860-01A1, “Identification of dendritically-localized transcription factor mRNAs,” submitted to NIMH, NIH, on March 16, 2020.

Specifically, ORI found that:

1. Respondent knowingly or intentionally combined two to three real data sets and two to five fabricated data sets to falsely increase the n-values reported in:

   - Figures 1B, 1D, 1E, 1G, 1I, 1J, 1M-1O, 1Q-1T, S2B-S2D, S2F-S2H, S3I, S3L, S3M, and S6H of *Cell* 2019 and Slides 6-10, 13, and 28 of the UU Department of Neurobiology presentation representing the quantification of NPAS4 immunohistofluorescence

   - Figures 2H, 2I, 2K, 2P, 3C, 3E, 4D-4G, 4K-4N, 4P-4Q, S3G, S5B, and S5C of *Cell* 2019 representing the quantification of *Npas4* mRNA or puro-PLA puncta

   - Figures S1E, S1G, and S1H of *Cell* 2019 representing the quantification of whole-cell clamp recordings of CA1 PN

   - Figures 2 (lower panel) and 3c of F32 MH110141-01, Figures 1g, 2b, 2d, and 4 of F32 MH110141-01A1S1, and Figures 1g, 2b, 2d, and 4 of F32 MH110141-01A1 representing time points of NPAS4 quantification after no stimulation or post-stimulation in the alveus or radiatum SR, SO, SP, SLM, with or without the addition of an inhibitor

2. Respondent knowingly or intentionally manipulated confocal images that were obtained through different experimental conditions in:

   - Figures 1A, 1C, and 1F of *Cell* 2019 and Slides 6-9 of the UU Department of Neurobiology presentation representing confocal images of hippocampal slices immunostained for NPAS4 and Neu

- Figures S2A and S2E of *Cell* 2019 by manipulating and misrepresenting the GFP signals as NPAS4 signals in wildtype mice

- Figures 1H, 1L, 1P, S3K, S6F, and S6G of *Cell* 2019 and Slides 9 and 28 of the UU Department of Neurobiology presentation by manipulating the raw images of hippocampal slices immunostained with NPAS4 and Neu and/or ARNT1 or ARNT2 by generating a mask of NPAS4 immunofluorescent signal through GFP signal from tissue obtained from Thy1-GFP mice to intentionally enhance the appearance of the dendritic NPAS4 signal

- Figures S6F and S6G of *Cell* 2019 by manipulating the raw images of hippocampus slices by overlaying a GFP channel over ARNT1 channel and using the multiply feature in Photoshop to restrict ARNT1 signal through GFP to enhance the ARNT1 signal in three panels

- Slides 7, 9, and 28 of the UU Department of Neurobiology presentation by manipulating six images representing post-stimulation with different time points by using a GFP mask overlaid on top of raw NPAS4 immunofluorescence

- Figure 4 of DP2 NS127276-01 and panel 1 of the UU Department of Neurobiology poster representing twelve images in columns 2-4 labeled EGR, FOS, ATF4 by mislabeling the microscope images as immunofluorescent stained with antibodies against EGR, FOS, and ATF4 when they actually were stained with anti-NPAS4 and selected images to support the immunofluorescence data in the ITF induction graphs

- Figure 5 of DP2 NS127276-01 representing two confocal images in the far-right column by intentionally and selectively enhancing the brightness of the anti-NPAS4 immunofluorescent channel within the dashed box and left brightness unchanged in surrounding areas of the images

- Figure 6 of DP2 NS127276-01 in twelve images in columns 2-5 labeled *Egr2*, *Fos*, and *Atf4* by intentionally mislabeling the microscope images as RNA in situ hybridization with probes against Egr2, Fos, and Atf4 when they actually were stained with NPAS4 probes and intentionally selecting and quantifying images in the quantification graphs to support the conclusions of the grant application

3. Respondent knowingly or intentionally manipulated the fluorescence micrographs and their quantification graphs to augment the role of ITFs in murine hippocampal neurons in Figures 2B-2G, 2J, 2L-2O, 3B, 3D, 3F-3H, 4C, 4J, 4O, S1A-S1D, S1F, S1I-S1J, S3A-S3F, S3H, S3J, S3N-S3T, S5D-S5G, and S6A-S6E of *Cell* 2019; the falsified/fabricated data also were included in Figures 2B-2H, 3, 4B-4E, and 5C-5G of R21 MH121860-01, Figures 2, 3B-3E, 4B-4C, 4E-4I, and 5B-5E of R21 MH121860-01A1, Figures 3, 5, 6B, 7, 8, 10B-10D, 11A-11C, and 11E-11F in R01 NS131809-01, Figure 8 of R01 NS133405-01, and Figures 3B-3C, 3E-3I, 4B-4I, 5, 9, 10B-10E, and 11-12 of R01 NS111162-01A1.

Respondent entered into a Voluntary Settlement Agreement (Agreement) and voluntarily agreed to the following:

(1) Respondent will have his research supervised for a period of five (5) years beginning on March 24, 2024 (the "Supervision Period"). Prior to the submission of an application for PHS support for a research project on which Respondent's participation is proposed and prior to

Respondent's participation in any capacity in PHS-supported research, Respondent will submit a plan for supervision of Respondent's duties to ORI for approval. The supervision plan must be designed to ensure the integrity of Respondent's research. Respondent will not participate in any PHS-supported research until such a supervision plan is approved by ORI. Respondent will comply with the agreed-upon supervision plan.

(2) The requirements for Respondent's supervision plan are as follows:

i. A committee of 2-3 senior faculty members at the institution who are familiar with Respondent's field of research, but not including Respondent's supervisor or collaborators, will provide oversight and guidance for a period of five (5) years from the effective date of the Agreement. The committee will review primary data from Respondent's laboratory on a quarterly basis and submit a report to ORI at six (6) month intervals setting forth the committee meeting dates and Respondent's compliance with appropriate research standards and confirming the integrity of Respondent's research.

ii. The committee will conduct an advance review of each application for PHS funds, or report, manuscript, or abstract involving PHS-supported research in which Respondent is involved. The review will include a discussion with Respondent of the primary data represented in those documents and will include a certification to ORI that the data presented in the proposed application, report, manuscript, or abstract are supported by the research record.

(3) During the Supervision Period, Respondent will ensure that any institution employing him submits, in conjunction with each application for PHS funds, or report, manuscript, or

abstract involving PHS-supported research in which Respondent is involved, a certification to ORI that the data provided by Respondent are based on actual experiments or are otherwise legitimately derived and that the data, procedures, and methodology are accurately reported and not plagiarized in the application, report, manuscript, or abstract.

(4) If no supervision plan is provided to ORI, Respondent will provide certification to ORI at the conclusion of the Supervision Period that his participation was not proposed on a research project for which an application for PHS support was submitted and that he has not participated in any capacity in PHS-supported research.

(5) During the Supervision Period, Respondent will exclude himself voluntarily from serving in any advisory or consultant capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee.

(6) Respondent will request that the following paper be corrected or retracted:

- *Cell.* 2019 Oct 3;179(2):373-391.e27. doi: 10.1016/j.cell.2019.09.004

Respondent will copy ORI and the Research Integrity Officer at UCSD on the correspondence with the journal.

Dated: April 4, 2024.

Sheila Garrity,

Director, Office of Research Integrity,

Office of the Assistant Secretary for Health.

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