: 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 Carlo Spirli, Ph.D. (Respondent), who was an Assistant Professor of Medicine, Department of Digestive Diseases, Yale University (YU). Respondent engaged in research misconduct in research supported by U.S. Public Health Service (PHS) funds, specifically National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), grants R01 DK079005 and P30 DK034989. The administrative actions, including debarment for a period of four (4) years, were implemented beginning on March 28, 2023, 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:

Carlo Spirli, Ph.D., Yale University: Based on the report of an investigation conducted by YU and additional analysis conducted by ORI in its oversight review, ORI found that Carlo Spirli, Ph.D., former Assistant Professor of Medicine, Department of Digestive Diseases, YU, engaged in research misconduct in research supported by PHS funds, specifically NIDDK, NIH, grants R01 DK079005 and P30 DK034989.

ORI found that Respondent engaged in research misconduct by knowingly, intentionally, or recklessly falsifying and/or fabricating data included in the following four (4) published papers, two (2) presentations, and three (3) grant applications submitted for PHS funds:

- Cyclic AMP/PKA-dependent Paradoxical Activation of Raf/MEK/ERK Signaling in Polycystin-2 Defective Mice Treated with Sorafenib. *Hepatology.* 2012 Dec;56(6):2363-74. doi: 10.1002/hep.25872 (hereafter referred to as "*Hepatology* 2012a").
- Altered Store Operated Calcium Entry Increases Cyclic 3',5'-Adenosine Monophosphate Production and Extracellular Signal-Regulated Kinases 1 and 2 Phosphorylation in Polycystin-2-Defective Cholangiocytes. *Hepatology.* 2012 Mar;55(3):856-68. doi: 10.1002/hep.24723 (hereafter referred to as "*Hepatology* 2012b").
- Protein Kinase A-Dependent pSer(675)-β-catenin, a Novel Signaling Defect in a Mouse Model of Congenital Hepatic Fibrosis. *Hepatology.* 2013 Nov;58(5):1713-23. doi:10.1002/hep.26554 (hereafter referred to as "*Hepatology* 2013").
- Posttranslational Regulation of Polycystin-2 Protein Expression as a Novel Mechanism of Cholangiocyte Reaction and Repair from Biliary Damage. *Hepatology.* 2015 Dec; 62(6):1828-39. doi: 10.1002/hep.28138 (hereafter referred to as "*Hepatology* 2015"). Retraction in: *Hepatology.* 2022 Dec;76(6):1904. doi: 10.1002/hep.32595.
- PKA-Dependent p-SER675-b-Catenin Phosphorylation Increases Cholangiocyte Motility in Pkhd1del4/del4 Mouse, a Model of Fibropolycystic Liver Diseases Caused by Defective Fibrocystin Function. Presented at the European Association for the Study of the Liver (EASL) (hereafter referred to as "EASL Presentation 2011").
- Cyclic-AMP-Dependent, Rac1-Mediated Nuclear Translocation Of P-Ser-675β-Catenin, A Novel Signaling Defect in Congenital Hepatic Fibrosis (CHF) and Caroli's Disease (CD). Presented at the American Association for the Study of Liver Diseases (AASLD) Annual Meeting, Boston, MA, in November 2012 (hereafter referred to as "AASLD Presentation 2011").
- R01 DK079005-11A1, "Epithelial Angiogenic Signaling in Biliary Pathophysiology and in Polycystic Disease," submitted to NIDDK, NIH, on December 13, 2018. Administratively withdrawn by the funding agency on March 1, 2021.

- R01 DK090021-01 “Mechanisms of fibrosis in fibrocystin-deficiency associated cholangiopathies” submitted to NIDDK, NIH, on February 2, 2010. Administratively withdrawn by the funding agency on July 1, 2012.
- R01 DK090021-01A1 “Mechanisms of fibrosis in fibrocystin-deficiency associated cholangiopathies” submitted to NIDDK, NIH, on November 11, 2010. Administratively withdrawn by the funding agency on July 1, 2015.

Respondent knowingly, intentionally, or recklessly falsified and/or fabricated Western blot image data for cholangiopathies in a murine model of Congenital Hepatic Fibrosis (CHF) by reusing blot images, with or without manipulating them to conceal their similarities, and falsely relabeling them as data representing different experiments or proteins and falsifying quantitative data in associated graphs purportedly derived from those images in twenty-one (21) figures included in four (4) papers, two (2) presentations, and three (3) grant applications. In the absence of reliable image and numerical data, the figures, statistical analyses, and related text also are false.

Specifically, the respondent reused Western blot images from the same source and falsely relabeled them to represent different proteins and/or experimental results in:

- *Hepatology* 2012a:
  - Figure 3, representing different concentrations of sorafenib treatment in:
    - pERK blot panel, lanes 1-2 and 3-4 are the same
    - pERK blot panel, lanes 2, 4, and 5 are the same
  - Figure 4C and Figure 6C (left), representing different concentrations of sorafenib treatment in:
    - CC3 blot panel, lanes 1 and 2 are the same
  - Figure 4C, representing different concentrations of sorafenib treatment in:
    - Actin blot panel, lanes 3-7 for wild type (WT) and lanes 8-12 for Pkd2cKO cholangiocytes are the same

  - Figure 5A (left), representing B-Raf kinase activity with different concentrations of sorafenib treatment in WT:
    - ERK1/2 blot panel, lanes 1-2 and lanes 3-4 are the same
  - Figure 5A (right), representing and Raf-1 kinase activity with different concentrations of sorafenib treatment in WT:
    - ERK1/2 blot panel, lanes 1-2 and lanes 3-4 are the same
- *Hepatology* 2012b:
  - Figure 6A, representing thapsigargin treatment in WT and Pkd2KO cholangiocytes:
    - ERK blot panel, lanes 1-3 WT and lanes 4-6 Pkd2KO are the same
- *Hepatology* 2013:
  - Figure 1A in:
    - pSer^{675}-β-Cat blot panel, lanes 1-3 for WT are a mirror image of lanes 4-6 for PC-KO
    - pSer^{675}-β-Cat blot panel, lane 1 for WT control and lane 9 for Pkhd1$^{del4/del4}$, PKA inhibitor are the same
  - Figure 5A:
    - Actin blot panel, lanes 1-4 for WT and lanes 6-9 for Pkhd1$^{del4/del4}$ are the same
- *Hepatology* 2015:
  - Figure 2A:
    - PC2 blot panel, lane 4 for "TNFα" and lane 5 for "Mix" are the same
    - PC2 blot panel, lane 6 for "DETA" and lane 7 for "Thapsi" are the same
    - Actin blot panel, lane 6 for "DETA" and lane 7 for "Thapsi" are the same
  - Figure 4A:
    - PC2 blot panel, lane 1 for "Ctrl" and lane 8 for "Mix+MG+GHX" are the same
    - PC2 blot panel, lane 3 for "Mix," lane 4 for "Mix+CHX," and lane 5 for "MG" are the same
  - Figure 4C:

- NEK1 blot panel, lane 6 for “Thapsi” and lane 7 for “DETA” are the same

- Figure 5 (left):
  - PC2, blot panel, lane 1 for “Ctrl” and lane 2 for “MG” are the same
  - PC2 blot panel, lanes 3-4 for “TNFα” and “TNFα+MG” and lanes 7-8 for “Mix,” and “Mix+MG” are the same
  - Actin blot panel, lanes 1-4 for “Ctrl,” “MG,” “TNFα,” and “TNFα+MG” and lanes 5-8 for “INFγ,” “INFγ+MG,” “Mix,” and “Mix+MG” are the same
- Figure 5 (right):
  - Actin blot panel, lanes 5-6 for “INFγ” and “INFγ+MG” and lanes 7-8 for “Mix” and “Mix+MG” are the same
- Figure 6D:
  - LC3-II blot panel, lane 2 for “Thapsi” and lane 8 for “Chloroq” are the same
- Figure 7B:
  - PC2 blot panel, lanes 11-12, 13-14, and 15-16 are the same representing six repeat experiments of “DDC” mice
  - PC2 blot panel, lanes 5-6, 7-8, and 9-10 are the same representing six repeat experiments of “DDC+Bort” mice
  - Actin blot panel, lanes 1-4 for “Ctrl,” lanes 5-8 for “DDC,” and lanes 11-14 for “DDC+Bort” are the same
  - Actin blot panel, lanes 9-10 for “DDC” and lanes 15-16 for “DDC+Bort” are the same
- Figure 8B:
  - Actin blot panel, lanes 1-5 for “WT” and lanes 6-10 for *Mdr2*$^{-/-}$ are the same

- AASLD Presentation 2012:
  - Slide 7:

- pSer^{675} β-Cat blot panel, lanes 1-3 WT are the same as pSer^{675} β-Cat blot panel, lanes 4-6 PC-KO in Figure 1A of *Hepatology* 2013
- pSer^{675} β-Cat blot panel, lanes 4-6 WT are the same as pSer^{675} β-Cat blot panel, lanes 7-9 Pkhd1$^{del4/del4}$ in Figure 1A of *Hepatology* 2013
- β-Cat blot panel, lanes 1-3 WT are the same as β-Cat blot panel, lanes 4-6 Pkhd1$^{del4/del4}$ in Figure 1A of *Hepatology* 2013
- β-Cat blot panel, lanes 4-6 WT are the same as β-Cat blot panel, lanes 7-9 Pkhd1$^{del4/del4}$ in Figure 1A of *Hepatology* 2013

- R01 DK090021-01 and R01 DK090021-01A1:
  - Figure 8 (and Slide 9 of EASL Presentation 2011):
    - p^{675}-β-Cat blot panel, lanes 8 and 9 are spliced in over the bands from unrelated sources
    - H3 Hyst blot, lane 8 is spliced in over the bands from unrelated sources
- R01 DK079005-11A1:
  - Figure 12A:
    - VEGFR2 blot panel, lanes 5 and 6-8 are spliced in from unrelated sources
  - Figure 12B:
    - VEGFR2 blot panel, lanes 7 and 8 are spliced in from unrelated sources

Dr. Spirli entered into a Voluntary Exclusion Agreement (Agreement) and voluntarily agreed to the following:

(1) Respondent will exclude himself voluntarily for a period of four (4) years beginning on March 28, 2023 (the "Exclusion Period") from any contracting or subcontracting with any agency of the United States Government and from eligibility for or involvement in nonprocurement or procurement transactions referred to as "covered transactions" in 2 CFR parts 180 and 376 (collectively the "Debarment Regulations").

(2) During the Exclusion 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.

(3) Respondent will request that the following papers be corrected or retracted:

- *Hepatology* 2012;56:2363-74. doi: 10.1002/hep.25872
- *Hepatology* 2012;55(3):856-68. doi:10.1002/hep.24723
- *Hepatology* 2013;58(5):1713-23. doi: 10.1002/hep.26554

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

Dated: April 10, 2023.

Sheila Garrity,
Director, Office of Research Integrity,
Office of the Assistant Secretary for Health.
[FR Doc. 2023-07850 Filed: 4/12/2023 8:45 am; Publication Date: 4/13/2023]