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

Li Chen, Ph.D., Mount Sinai School of Medicine: Based on evidence and findings of an investigation report by Mount Sinai School of Medicine (MSSM) transmitted to the United States Department of Health and Human Services (HHS), Office of Research Integrity (ORI), in April 2010 and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Li Chen, former Postdoctoral Fellow, Department of Gene and Cell Medicine, MSSM, engaged in research misconduct in research that was supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), grant R01 DK062972 and National Institute of General Medical Sciences (NIGMS), NIH, grant P20 GM075019 and was submitted in grant applications R01 DK074695 and R01 DK083286 to NIDDK, NIH, P20 GM075019 to NIGMS, NIH, and R01 NS062054 to the National Institute of Neurological Disorders and Stroke (NINDS), NIH.

ORI found that the Respondent intentionally, knowingly, and recklessly fabricated and falsified data reported in four (4) publications, one (1) submitted manuscript, and four (4) grant applications:

- Chen, L., & Woo, S.L.C. "Complete and persistent phenotypic correction of phenylketonuria in mice by site-specific genome integration of murine phenylalanine hydroxylase cDNA." *Proc. Natl. Acad. Sci. U.S.A.* 102(43):15581-15586, October 2005 (hereafter referred to as "*PNAS* 2005")

- Chen, L., Thung, S.N., & Woo, S.L.C. "Metabolic Basis of Sexual Dimorphism in PKU Mice After Genome-targeted PAH Gene Therapy." *Mol. Ther*. 15:1079-1085, June 2007; Retracted in December 2010 (hereafter referred to as "*Mol. Ther*. June 2007")

- Chen, L., & Woo, S.L.C. "Correction in Female PKU Mice by Repeated Administration of mPAH cDNA Using phiBT1 Integration System." *Mol. Ther*. 15:1789-1795, October 2007; Retracted in December 2010 (hereafter referred to as "*Mol. Ther*. Oct. 2007")

- Chen, L., & Woo, S.L.C. "Site-Specific Transgene Integration in the Human Genome Catalyzed by ÖBT1 Phage Integrase." *Hum. Gene Ther.* 19:143-151, February 2008; Retracted in August 2010 (hereafter referred to as "*HGT* 2008")

- Chen, L., Roy, I., Prasad, P.N., & Woo, S.L.C. "Nanoparticle-Based Gene Therapy for Metabolic Disorders: Hepatic Delivery of Minicircle DNA for Complete Correction of Phenylketonuria." Submitted for publication in *Proc. Natl. Acad. Sci. U.S.A.* (hereafter referred to as the "*PNAS* 2008 manuscript")

- R01 DK074695, "Genome-targeted PAH Gene Integration in PKU Mice and Sexual Dimorphism," Savio L.C. Wood, Ph.D., Principal Investigator (P.I.) (hereafter referred to as "R01 DK074695")

- P20 GM075019, "Growth, Differentiation & Genetic Alteration of Human ES Cells," Gordon M. Keller, Ph.D., P.I. (hereafter referred to as "P20 GM075019")

- R01 NS062054, "Nanoparticle-medicated Gene Therapy for PKU," Savio L. Woo, Ph.D., P.I. (hereafter referred to as "R01 NS062054")

- R01 DK083285, "Nanoparticle-Mediated Gene Therapy PKU," Savio L. Woo, Ph.D., P.I. (hereafter referred to as "R01 DK083285")

The Respondent fabricated figures reporting the chromosomal locations of integration sites, fabricated data reporting the use of polymerase chain reaction (PCR) to determine integration frequencies, falsified data representing the detection of chromosomal translocations in human cells, and fabricated figures by falsely reporting the results of High-Performance Liquid

Chromatography (HPLC) assays. The Respondent also falsified experimental data for LacZ stained liver sections and for hematoxylin and eosin (H&E) stained liver sections.

Specifically, ORI finds by a preponderance of the evidence that the Respondent engaged in misconduct in science and research misconduct by intentionally, knowingly, and recklessly:

1. fabricating and/or falsifying nineteen (19) figures by falsely reporting that phenylketonuria (PKU) gene therapy experiments were successfully completed, when the available evidence shows the experiments were not performed; specifically the Respondent:

    (a) fabricated figures where DNA sequencing was purportedly used to identify the chromosomal locations of integration sites for the PAH gene in mouse and human cells, reported in seven (7) figures:

    - *PNAS* 2005, Figure 2A
    - *HGT* 2008, Figures 3b and 3c
    - R01 NS062054, Figures 3 and 20
    - R01 DK074695, Figure 6
    - R01 DK083286, Figure 17
    - P20 GM075019, Figure 4

(b) fabricated data purportedly representing the use of PCR to determine integration frequencies for the phenylalanine hydroxylase (PAH) gene and the secreted embryonic alkaline phosphatase (SEAP) reporter gene, in mouse and human cells, reported in eleven (11) figures:

- *PNAS* 2005, Figures 2C and 3B
- *Mol. Ther*. June 2007, Figures 2a and 5a
- *Mol. Ther*. Oct. 2007, Figures 2d and 5a
- *HGT* 2008, Figure 4
- R01 NS062054, Figure 4b and 10a
- R01 DK074695, Figure 7b
- R01 DK083286, Figure 2b

(c) falsified figures representing the detection of chromosomal tranlocations in human cells, purportedly determined by PCR in two (2) figures:

- *HGT* 2008, Figure 5a
- R01 NS062054, Figure 21a

2. fabricating the results of HPLC assays to show generally lowered blood levels of phenylalanine after PKU gene therapy and to show liver levels of BH_4 when the Respondent did not have the HPLC data needed to support those claims; specifically the Respondent:

(a) fabricated serum phenylalanine graphs in:

- *PNAS* 2005, Figure 4B; this false data also is presented in R01 DK074695, Figure 10b
- *Mol. Ther*. June 2007, Figure 1a; this false data also is presented in R01 DK074695, Figure 11
- R01 DK083286, Figure 3; this false data also is presented in *Mol. Ther*. June 2007, Figure 3, and R01 NS062054, Figure 7
- *Mol. Ther*. Oct. 2007, Figure 4a; this false data also is presented in R01 NS062054, Figure 9a
- *PNAS* 2008 manuscript, Figure 4

(b) fabricated graphs for BH_4 levels in:

- *Mol. Ther*. June 2007, Figure 5c; this false data also is presented in R01 NS062054, Figure 8c

3. falsely reporting the results of LacZ stained liver sections by reusing and relabeling an image and claiming that it represents different experiments; specifically, the same image was used to represent mice treated with a nanoplex gene delivery system in R01 NS062054, Figure 14b (right panel), and also to represent a wholly different experiment for mice treated with 10 injections of the phiBT1 integrase system alone in R01 NS062054, Figure 4c (right panel), and *Mol. Ther*. Oct. 2007, Figure 2b (D panel)

4. falsely reporting the results of H&E stained liver sections in R01 NS062054, Figure 6, by using the identical image to represent four (4) different experimental treatments of H&E stained liver sections; specifically the Respondent reused and relabeled one image to represent liver sections form mice that received either 1 or 10 injections, with or without the phiBT1 integrase plasmid.

The Respondent failed to take responsibility for the fabrication and falsification described in ORI's findings.

The following administrative actions have been implemented for a period of three (3) years, beginning on April 11, 2014:

(1) Respondent is debarred from any contracting or subcontracting with any agency of the United States Government and from eligibility for, or involvement in, nonprocurement programs of the United States Government referred to as "covered transactions" pursuant to HHS' Implementation (2 CFR part 376 *et seq*) of Office of Management and Budget (OMB) Guidelines to Agencies on Governmentwide Debarment and Suspension, 2 CFR part 180 (collectively the "Debarment Regulations"); and

(2) Respondent is prohibited from serving in any advisory capacity to PHS, including but not limited to service on any PHS advisory committee, board, and/or peer review committee, or as a consultant.

FOR FURTHER INFORMATION CONTACT:

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Donald Wright,
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