DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive - MSC 7982
Bethesda, Maryland 20892-7982
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

February 6, 2017

Re: Animal Welfare Assurance
A3714-01 [OLAW Case H]

Dr. Shlomo Melmed
Senior Vice President for Academic Affairs
Cedars-Sinai Medical Center
North Tower Plaza 2015
8700 Beverly Blvd.
Los Angeles, CA 90048-1865

Dear Dr. Melmed,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your February 1, 2017 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the Cedars-Sinai Medical Center, following up on an initial December 23, 2016 notification by telephone. According to the information provided, OLAW understands that on November 9, 2016 three mice died and an additional nine mice experienced prolonged anesthetic recovery following administration of diluted dexmedetomidine. The study team attributed the adverse effects to the newly opened dexmedetomidine and on the following day performed an unapproved experiment on eight mice to test their hypothesis. One mouse died and seven mice exhibited prolonged recovery as a result of the unauthorized procedure. After further review of the procedures conducted by the study team, the Principal Investigator (PI) determined that the newly opened bottle of dexmedetomidine was erroneously diluted and the dosing error may have contributed to the observed prolonged recovery and mortalities. The associated animal activity was not PHS funded.

The corrective actions consisted of the following:

1. Imposing a six month probation on the relevant protocol during which time the IACUC and Comparative Medicine will monitor the animals and clinical outcomes of all procedures approved on the protocol. The PI is also required to provide advanced notice to the IACUC of the dates of all scheduled studies involving surgical anesthesia and submit anesthetic monitoring records for all surgical procedures to the IACUC within a week of performance.

2. Counseling of laboratory staff by the PI on protocol compliance, submission and approval of protocol amendments prior to implementation and prompt reporting of unanticipated adverse events.

3. Retraining of the PI and research personnel on the IACUC CITI module.

4. Prompt reporting of unanticipated adverse events to Comparative Medicine for guidance.

5. Consulting with Comparative Medicine regarding appropriate anesthetics, dosages and dilutions and submission of protocol amendments, if warranted.

Based on the information provided, OLAW is satisfied that appropriate actions have been taken to investigate, correct and prevent recurrence of the noncompliance. We appreciate having been informed about this matter and find no cause for further action by this Office.

Sincerely,

Neera V. Gopee, DVM, PhD, DACLAM, DABT
Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Chair

CEDARS-SINAI

Shlomo Melmed, MB, ChB, MACP, FRCP
Executive Vice President and Dean of the Medical Faculty
Helene A. and Philip E. Hixon Distinguished Chair in Investigative Medicine
Director, Burns & Allen Research Institute

Transmit via E-mail

February 1, 2017

Axel Wolff, M.S., D.V.M.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare (OLAW)
National Institutes of Health
RKL 1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

RE: Follow-up report of noncompliance regarding National Cancer Institute Grants R01 CA188743 and R01 CA206220 (CSMC IACUC Study Title: New Nanoconjugates for Human Glial Tumors and Metastatic Brain Tumors; CSMC IACUC #5289; Animal Species: Mice)

Dear Dr. Wolff:

In my capacity as the Institutional Official at Cedars-Sinai Medical Center (CSMC) (Assurance #D16-00420, Legacy #A3714-01), and in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals (Policy) IV.F.3, I am writing this letter to provide a follow-up report regarding an incident of noncompliance and deviation from the provisions of the *Guide* related to the above-referenced NCI Grant. This case was previously reported to Dr. Neera Gopee by Secondary Individu Assistant Dean, Research Compliance and Quality Improvement at CSMC in a telephone conversation on December 23, 2016.

On November, 9, 2016, the study team had experienced prolonged anesthetic recovery and deaths of 3 of 12 mice following stereotactic brain tumor cell implantation. The mice received ketamine + dexmedetomidine IP injectable anesthesia that had been reversed with atipamezole. The study team theorized that the mortality was due to faulty manufacture of a newly-opened bottle of dexmedetomidine and performed an unapproved experiment the following day (Nov 10) to test this theory. Eight test mice were anesthetized and reversed with atipamezole after 15 minutes; five mice received the anesthetics dilution from the day prior and three mice received a freshly prepared dilution. This experiment led to atypically prolonged recovery in all mice and the death of one mouse. The adverse event was reported

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to the manufacturer which in turn filed an FDA report. Other labs having been dispensed the same lot of drug were polled and reported no adverse events.

The study team reported these findings to Comparative Medicine on November 10, 2016. After investigating with the lab, on November 15, 2016, the CSMC Department of Comparative Medicine notified the IACUC Leadership of the unanticipated adverse outcome on IACUC005289. During the investigation, it was determined that the study team had modified the approved anesthetic dosing regimen described in their protocol without prior IACUC approval and had performed the unapproved experiment. The laboratory staff was promptly informed by Comparative Medicine that they must use the anesthesia dose as listed on the approved protocol and that it was inappropriate to conduct the unapproved experiment.

This incident of noncompliance was discussed by the IACUC at the December 19, 2016 IACUC meeting, at which time the Committee determined that the unapproved experiments constitute a serious noncompliance with the PHS Policy and deviation from the provisions of the *Guide*. On December 21, 2016, on behalf of the Committee, the IACUC Chair reiterated in writing that the PI must perform experiments according to the approved protocol, and that if changes are desired or necessary, a modification must be submitted and approved before implementing the proposed changes. Additionally, the IACUC Chair informed the PI that she was required to attended the January 16, 2017 IACUC meeting to discuss this incident with the IACUC. At the convened IACUC meeting on January 16, 2017, the IACUC Chair reminded her that as PI she is held responsible for the conduct of the work; it is her responsibility to ensure that study staff follow the protocol and understand what is in the protocol. The PI accepted responsibility for this incidence of noncompliance. The PI also reported that she had further reviewed lab staff procedures and subsequently determined that the anesthetic drugs had been incorrectly diluted, likely leading to the prolonged recoveries and mortality.

The IACUC placed the protocol on probation for a six-month period. During this time, the IACUC and Comparative Medicine staff will monitor the animals and clinical outcomes of all procedures on this protocol. The PI is required to provide any requested data or updates. Should further problems occur, the PI and protocol may be subject to additional corrective actions. Furthermore, the IACUC required that the PI implement additional corrective actions as described below:

1. During the probation period, the PI is required to submit to the IACUC, in advance, the dates of all planned experiments involving administration of surgical anesthesia. The PI is required to submit anesthesia monitoring records for all surgical experiments to the IACUC office within one week of conducting them.
2. The PI must counsel all laboratory staff within the lab, educating them on the following:
    a. Perform only the approved procedures described in the protocol adhering to the approved procedures exactly,

   b. the need for prior approval from the IACUC before implementing changes to the approved procedures, and
   c. the importance of promptly reporting unanticipated adverse outcomes (UAO).
3. The PI and study staff involved with the incident are required to repeat the IACUC CITI training module.
4. If any future UAO should arise, the PI or study staff must promptly report the UAO to Comparative Medicine and attempt to solve the cause of the problem after consulting with Comparative Medicine.
5. The PI must further consult with Comparative Medicine regarding dilutions, dosages and types of anesthesia to be used. If changes to the approved protocol are determined to be warranted, a modification must be submitted and approved prior to making those changes.

As of this date, the PI is complying with all stipulations mandated by the IACUC. The 6-month probationary period for the PI and the affected protocol will end on July 17, 2017.

The study team verified that expenditures on the associated NCI grants related to the unapproved procedures were negligible (less than $20).

Please be assured that the institution considers the protection of laboratory animals to be of utmost importance. Please contact me at Phone Number Dr. Denis Magoffin, IACUC Chair, at hone Numb ne Numpr condary Individ Assistant Dean, Research Compliance at Phone Number with any questions or concerns about this matter.

Sincerely,

Shlomo Melmed, M.D.

cc: Robert Maydwell, Grant Management Specialist, NCI
Secondary Individual Global Director, AAALAC Int.
Secondary Individual Vice President of Research, CSMC
Department Chair for PI of Record, CSMC
Denis Magoffin, Ph.D., IACUC Chair, CSMC
John D. Young, V.M.D., M.S., Assistant Dean, Comparative Medicine, CSMC
Secondary Individual Assistant Dean, Research Compliance & QI, CSMC
Secondary Individual Assistant Dean, Sponsored Research & Funds Administration, CSMC
Principal Investigator of Record, CSMC

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Thursday, February 02, 2017 7:15 AM
To: ondary Indivic
Subject: RE: Cedars-Sinai Follow-Up Report of Non-compliance

Thank you for this report. Dr. Gopee will send a response soon.

Axel Wolff, M.S., D.V.M.
Director, Division of Compliance Oversight
OLAW

From: ondary Indivi [mailto ndary Indiv @cshs.org]
Sent: Wednesday, February 01, 2017 3:35 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: robert.maydwell@nih.gov; dary Ind @aaalac.org; Melmed, Shlomo, M.D. <Melmed@csmc.edu>; Magoffin, Denis, Ph.D. <Denis.Magoffin@cshs.org>; ndary Indiv <ndary Indiv @cshs.org>
Subject: Cedars-Sinai Follow-Up Report of Non-compliance

Dear Dr. Wolff,

Please find attached a letter from Dr. Shlomo Melmed reporting a non-compliance incident in research conducted at Cedars-Sinai Medical Center. Feel free to contact us with any questions or concerns.

Best,

Secondary Individual
Manager, IACUC Operations & Education
CSMC Office of Research Compliance & Quality Improvement
6500 Wilshire Blvd. Room #
Los Angeles, CA 90048
Phone Number | Phone Number
CEDARS-SINAI
LEADING THE QUEST FOR HEALTH

Follow-up report of noncompliance regarding National Cancer Institute Grants R01 CA188743 and R01 CA206220 (CSMC IACUC Study Title: New Nanoconjugates: for Human Glial Tumors and Metastatic Brain Tumors; CSMC IACUC #5289; Animal Species: Mice)

A3714-H

Office of Laboratory Animal Welfare

OLAW

Initial Report of Noncompliance

By: Neera Gopee

Date: 12-23-16 Time: 1:21 pm

Name of Person reporting: Secondary Individual
Telephone #: Phone Number
Fax #:
Email:

Name of Institution: Cedars Sinai Medical Center
Assurance number: D16-00420 (A3714-01)

Did incident involve PHS funded activity? Yes
Funding component: NIH | NCI
Was funding component contacted (if necessary): _____

What happened?
PI performed unauthorized procedure using dexmedine in 8 nude mice where 1 mouse died and the remaining mice experienced prolonged recovery

Species involved: mice
Personnel involved: PI
Dates and times:
Animal deaths: 1

Projected plan and schedule for correction/prevention (if known): _____

Projected submission to OLAW of final report from Institutional Official:

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Case #_____