



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: <http://grants.nih.gov/grants/olaw/olaw.htm>

FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 402-7065

January 6, 2020

Re: Animal Welfare Assurance
A3001-01 [OLAW Case R]

John A. Zaia, M.D.
Deputy Director for Clinical Research
City of Hope National Medical Center/Beckman Research Institute
1500 East Duarte Road
Duarte, CA 91010-3000

Dear Dr. Zaia,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your December 12, 2019 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at City of Hope- Beckman Research Institute. According to the information provided, OLAW understands that mice were subjected to an unapproved tail snip activity which led to the deaths of six mice and the euthanasia of two.

The corrective actions consisted of counseling the laboratory member responsible and the Principal Investigator (PI) that the activity had not been approved by the Institutional Animal Care and Use Committee (IACUC). The Principal Investigator was directed to amend the protocol to add the procedure and include endpoint criteria and monitoring. The PI was counseled on responsibility for overseeing all protocol activities and documentation. The PI and staff were retrained, the PI provided a training plan which requires assessment of staff proficiency, the PI must provide documentation of staff training and that staff has a copy of the protocol, cage cards will note which animals require increased observation, and a body scoring scale will be used. The PI was informed about the Veterinary Verification and Consultation process and the laboratory was placed under enhanced post-approval monitoring. The PI was counseled by the Institutional Official and IACUC on the corrective action and preventive plan. The IACUC will enhance oversight of the animal program to ensure that only approved procedures are performed. The NIH funding component was notified about the matter and the grant was not charged for any unauthorized animal activities.

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 the matter and find no cause for further action by this Office.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Contact



A3001-R
1500 East Duarte Road
Duarte, CA 91010-3000
Phone 626-256-4673
www.cityofhope.org

December 12, 2019

Division of Compliance Oversight
Office of Laboratory Animal Welfare
OLAW Division of Assurance
National Institutes of Health
Suite 360 MSC 7982
6705 Rockledge Dr.
Bethesda, MD 20817

To Whom It May Concern,

The City of Hope National Medical Center – Beckman Research Institute ("City of Hope"), in accordance with Assurance A3001-01 and PHS Policy IV.F.3, provides this report of noncompliance regarding a 'tail snip procedure' performed on mice, an activity not reviewed and approved by the City of Hope IACUC in a Principal Investigator's (PI) animal use protocol entitled "*Modulating the Immune System for Cancer Treatment*" (the "Protocol"). The study and procedure performed on these animals involved federal funds from NIH Grant R01CA185301.

Incident Description:

On September 7, 2019, the IACUC Executive Committee received information from the Center for Comparative Medicine (CCM) indicating the following concerns related to this Protocol:

- On September 6, 2019, CCM staff found a total of 6 mice dead. In addition, there were mice in each cage in varying in degree of paralysis, paleness, lethargy/moribund. There was an excess amount of blood staining in the cages and all mice from all four cages had a tail snip. The staff reviewed with the lab member these observations and confirmed the procedure performed. The staff informed the lab the tail snip procedure was not covered in their IACUC protocol.
- On September 8, 2019, the CCM found the remaining 2 mice were observed to be moribund and were also euthanized.

Corrective Response by IACUC/CCM:

To immediately address the concerns, the following actions were taken:

- On September 25, 2019, the IACUC Executive Committee discussed with the PI and lab members the incident, reviewed the Protocol and monitoring procedures.
 - o The PI was advised to submit a protocol amendment to add the tail snip procedure with clear delineation of the endpoint criteria and monitoring for the mouse model involved in this incident and a corrective and preventive action plan (CAPA). The amendment was submitted by the PI for the November 5, 2019 IACUC meeting and it is currently in review for approval consideration.
 - o The PI was reminded that only IACUC-approved procedures could be performed and that the 'tail snip procedure' was not approved.

On November 5, 2019, the IACUC Full Committee reviewed the case, determined that this incident constituted serious noncompliance and voted to report the incident to OLAW. The IACUC also

required additional items on the initial proposed CAPA with increase oversight, training, and monitoring. A summary of the outcome from this meeting was communicated to the PI in writing on November 11, 2019.

Corrective Action and Preventive Plan (CAPA):

1. PI's Oversight

- The PI was reminded of the expectation to be familiar with the approved IACUC protocol and must review all IACUC submissions prior to signoff. In a written plan, the PI was asked to list how the following will be documented: experiment presentations, PI approval, lab meeting minutes, etc. The PI was informed that an unannounced audit of experimental procedures can occur for the duration of the current approval period (up to 1 year). The PI provided a written response agreeing to this plan on November 20, 2019.

2. Mandatory Training

- All personnel listed on the Protocol, including the PI, were required to repeat mandatory training with the LRP Sr. Compliance Research Training Specialist. This training covered Protocol adherence; the responsibility for all individuals listed on the Protocol to review the Protocol; proper monitoring, care, and documentation. The retraining was completed as of November 11, 2019.
- The PI was required and has provided an outline of how personnel will be trained in the future, to include amendment reviews and protocol adherence, proficiency in performing specific skills, conducting survival surgery, post-operative care.
- In addition, the PI will be required to provide documentation of training that all lab staff members listed on the protocol have been provided with a hard copy of the protocol and have received retraining on the usage of the online protocol submission (known as iRIS).

3. Monitoring

- The PI was required as part of their CAPA that the daily monitoring will be documented on the appropriate yellow Animal Care Program "Investigator to Monitor" cards to identify cages containing animals that need increase observations. A body scoring scale was asked to be developed specific to the mouse model in this study to better assess the health of the experimental mice. The PI has agreed and implemented the required monitoring in consult with the veterinary staff. To ensure compliance, there will be an increase Post Approval Monitoring (PAM) visits to observe procedures and monitoring practices.

4. Additional Clarification

- The Committee emphasized to the PI how the IACUC Policy on Veterinary Verification and Consultation process works to facilitate animal welfare and research and compliance.

In addition to the CAPA noted above, the PI was requested and has met with the IO and the IACUC EC to ensure an effective CAPA is in place that addresses both short-term and long-term concerns.

For the relevant federal funding source, all expenses charged to the NIH grant related to the unapproved procedure were transferred to a non-sponsored source and the NIH funding component was notified of the situation. As a next step, the IACUC will work with CCM to better ensure and monitor that only approved procedures as described on the protocol are performed.

Please be assured that City of Hope takes this matter very seriously and remains committed to full compliance with the federal and state regulations and requirements.

We believe this letter fulfills our reporting obligations; however, please contact me at (b) (6) if you have any questions or require additional information.

Sincerely,

(b) (6)

John A. Zaia, MD
Institutional Official

cc: Nadia Carlesso, M.D., Chair, Institutional Animal Care and Use Committee
Richard W. Ermel, D.V.M., M.P.V.M., Ph.D., DACLAM, Attending Veterinarian
Alyse DiStefano, Director, Laboratory Research Protections
Amanda Hammond, Senior Director, Research Protections
(b) (6)
Anne Wigham, Director, Compliance – Research and Conflict of Interest
(b) (6)
Jaclyn Lucas, Director, Office of Sponsored Research

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, December 18, 2019 6:55 AM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Report of Noncompliance

Thank you for this report, (b) (6) We will send a response soon.

Axel Wolff, M.S., D.V.M.
Deputy Director, OLAW

From: (b) (6)
Sent: Tuesday, December 17, 2019 5:31 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: John Zaia <JZaia@coh.org>; Nadia Carlesso <ncarlesso@coh.org>; Richard Ermel <RErmel@coh.org>; Amanda Hammond <ahammond@coh.org>; (b) (6) Jaclyn Lucas <jalucas@coh.org>; Alyse DiStefano <adistefano@coh.org>; (b) (6)
Subject: Report of Noncompliance

To Whom It May Concern,

Attached please find a report of noncompliance for your review.

Please let me know if you have any questions.

Thank you,

(b) (6)

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