



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 22, 2019

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

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 January 9, 2019 letter regarding noncompliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals at the City of Hope National Medical Center – Beckman Research Institute. According to the information supplied, OLAW understands that a laboratory was found to be involved in multiple protocol noncompliances, institutional policy noncompliances, and providing inadequate postoperative care. The letter indicated that the associated animal activity involved funding from grant R01CA155769, and the following information related to the matter was described.

- On November 6, 2018, several mice that previously underwent intracranial surgery were reported to the laboratory to be in poor condition with the recommendation that these animals be euthanized. The animals were not euthanized, and four mice were found dead later that day. The following day, additional postoperative mice were found in poor condition and reported with the recommendation that the lab euthanize 13 mice.
- On November 9, 2018, the lab was notified that only one day of postoperative monitoring was documented for 30 postoperative animals. These animals should have had documentation for a minimum of seven postoperative days according to institutional policy.
- On November 12, 2018, additional surgeries were performed, and postoperative monitoring was not documented. The laboratory was notified of inadequate postoperative care that included lack of immediate postoperative administration of analgesics per protocol. Animals received analgesics later that day and all animals determined to be lethargic and near moribund were euthanized.
- It was also determined that a postdoctoral fellow performed intracranial surgical trauma procedures on 20 mice. Although intracranial surgery was in the IACUC-approved protocol, intracranial surgical trauma was not. Additionally, the postdoc was not approved to perform surgery on the protocol and had not completed the required in-person Rodent Survival Surgery training. It was stated that all of these mice were euthanized on November 14, 2018.

Corrective actions included the following.

- On November 13, 2018, the Center for Comparative Medicine (CCM) met with the Laboratory Manager to review the protocol and postoperative procedures. The CCM advised the manager that only approved procedures could be performed when it was discovered that the intracranial surgical trauma procedure was not in the IACUC-approved protocol. The following day, the CCM met with the postdoc to review postoperative procedures and reiterate that only approved procedures could be performed, and the intracranial surgical trauma procedure was not approved.

- After review by the IACUC Executive Committee, the principal investigator (PI) was issued a memo describing the concerns and the Executive Committee met with the PI on November 28, 2018.
- On December 4, 2018, the IACUC Full Committee reviewed the incident and voted to suspend all surgeries on the associated protocol.
- A protocol amendment to add the intracranial surgical trauma procedure and add the postdoc as a surgeon on the protocol was submitted by the PI on November 16, 2018 and was approved by the IACUC on January 8, 2019.
- All personnel including the PI underwent retraining regarding protocol adherence, administration of analgesics, and postoperative procedures and documentation.

Pending corrective actions that were described in the letter included the following.

- Prior to resuming surgeries, the postdoctoral fellow is required to complete in-person Rodent Survival Surgery training.
- The laboratory must complete a self-audit of all of their IACUC protocols to identify discrepancies between the described procedures and what is being done. Practices not approved in the protocol are to be discontinued and may not resume unless an amendment is submitted and subsequent IACUC approval is granted.
- Once the self-audit is complete, a Post Approval Monitoring visit will occur for observations of surgeries, postsurgical monitoring practices, and further protocol review. Unannounced audits of experimental procedures will occur for the remainder of the current approval period (up to one year).
- The PI will submit an outline of how new personnel will be trained as well as a plan to address the IACUC's concern regarding PI involvement and oversight.
- The IACUC will work with the CCM to improve compliance and monitoring to ensure that only properly trained individuals who are listed on an approved protocol perform surgery.

The letter indicated that 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. OLAW concurs with this action, and the Chief Grants Management Officer is copied on this letter.

Based on review of the information provided, OLAW is satisfied that appropriate measures have been taken to address the reported noncompliances. We appreciate being informed of these matters and find no cause for further action by this Office.

Sincerely,

 (b) (6)

Jane Na, DVM
Veterinary Medical Officer
Office of Laboratory Animal Welfare

cc: IACUC Contact
NIH National Cancer Institute, Chief Grants Management Officer

January 9, 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 an ‘intracranial surgical trauma 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 “*Role of Receptor for Advanced Glycation End Product (RAGE) Pathway in Brain Tumor Macrophage Function*” (the “Protocol”). The procedures performed on these animals involved federal funds from NIH Grant R01CA155769.

Incident Description:

On November 12, 2018, the IACUC Executive Committee received information from the City of Hope Center for Comparative Medicine (CCM) indicating the following concerns related to this Protocol:

- On November 6, CCM advised the laboratory to euthanize several mice that had previously undergone intracranial surgery and were in poor condition. The laboratory did not euthanize these animals and 4 mice were subsequently found dead on November 6, 2018.
- On November 7, 2018, the CCM found additional mice in poor postoperative condition, issued 11 health reports and advised the laboratory to euthanize 13 mice.
- On November 9, 2018, the CCM further notified the laboratory that 30 animals which had undergone intracranial surgery on October 26, 2018 had only one day of post-operative monitoring documented on the post-operative cage cards; this is a violation of City of Hope policy requiring daily documentation of post-operative monitoring of animals for 7 days post-surgery.
- On November 12, 2018, new intracranial surgery was performed and the laboratory did not label the cages with post-operative cards. The CCM notified the laboratory of inadequate post-operative care for these animals, as indicated by (a) failure to administer analgesics immediately following surgery, as required by Protocol, (b) poor condition of post-operative mice (lethargic, almost moribund), and (c) finding two mice inadvertently stuck together with surgical glue. Analgesics were administered to all mice later that same day after the laboratory was notified by CCM of these deficiencies.

A review of the Protocol revealed that while intracranial surgery was included in the IACUC approved protocol, some of the mice had undergone an ‘intracranial surgical trauma procedure’ which was not

described in the IACUC approved Protocol. Additionally, the postdoctoral fellow who performed the surgeries was not listed as approved to perform surgery and had not completed the required in-person Rodent Survival Surgery training.

Corrective Response by IACUC/CCM:

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

- All mice that had undergone intracranial surgery and were determined to be lethargic and almost moribund were euthanized by CCM on November 12, 2018.
- On November 13, 2018, CCM met with the Laboratory Manager to review the Protocol and post-operative procedures. It was during this discussion that it was determined that the 'intracranial surgical trauma procedure' was not described in the Protocol. CCM advised the Laboratory Manager that the unapproved procedure could no longer be conducted until it is approved by the IACUC. The Laboratory Manager was advised to work with the PI to submit a protocol amendment to add the intracranial surgical trauma procedure. The amendment was submitted by the PI on November 16, 2018 and was approved by the IACUC on January 8, 2019.
- On November 14, 2018, CCM met with the postdoctoral fellow who performed the surgeries to review post-operative procedures. CCM reiterated that only IACUC-approved procedures could be performed and that the 'intracranial surgical trauma procedure' was not approved.
- As of November 14, 2018, all 20 mice that had undergone the 'intracranial surgical trauma procedure' were euthanized.

On November 20, 2018, the IACUC Executive Committee met to discuss the incident. On November 26, 2018, the IACUC Executive Committee issued a memorandum to the PI describing the concerns. On November 28, 2018, the IACUC Executive Committee met with the PI and advised him that the incident would be reviewed at the next IACUC meeting on December 4, 2018.

On December 4, 2018, the IACUC Full Committee reviewed the case, determined that this incident constituted serious noncompliance and voted to suspend all surgeries under this Protocol, including those that were previously approved. Following receipt of additional information related to the procedures and timeline of events, the IACUC Full Committee met again on December 11, 2018 to vote on the final corrective action plan. A summary of the outcome from this meeting, the corrective action plan and the determination to report the incident to OLAW was communicated to the PI in writing on December 14, 2018.

Corrective Action Plan:

1. Mandatory Training
 - a. All personnel listed on the Protocol, including the PI, were required to repeat mandatory training with the Attending Veterinarian or designee. This training covered Protocol adherence; the responsibility for all individuals listed on the Protocol to review the Protocol; proper administration of analgesics; and post-operative monitoring, care, and documentation. Previously approved surgical procedures were not permitted to resume until all personnel listed on the Protocol had gone through this retraining. The retraining was completed as of December 21, 2018.
 - b. The postdoctoral fellow must complete in-person Rodent Survival Surgery training by end of January 2019. This individual may only resume surgeries after he has completed the Rodent Survival Surgery training, has been added to the Surgery section of the Protocol, and has undergone the mandatory retraining noted above.
2. Audit and Follow Up Monitoring

- a. The laboratory must perform a self-audit of all IACUC protocols by January 14, 2019, and any discrepancies that are identified must stop immediately, be reported to the IACUC and be rectified with an amendment.
 - b. Following the self-audit, a Post Approval Monitoring (PAM) visit will be scheduled to observe surgical practices and post-surgical monitoring practices and to further review all of the PI's approved experimental protocols.
 - c. Unannounced audits of experimental procedures will occur for the duration of the current approval period (up to 1 year).
3. Additional Documentation
- a. The PI must provide an outline of how new personnel will be trained in the future, to include conducting survival surgery, post-operative care, and protocol adherence, by January 14, 2019.
 - b. The laboratory must continue to use surgery cards to record post-operative monitoring and care.
 - c. The PI must provide a written plan describing how he will address the Committee's concern of PI involvement and oversight. This item must be completed by January 14, 2019.

In addition to the corrective action plan noted above, 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 individuals who are properly trained and are listed on an approved protocol are performing surgery.

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) ext. (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)

Jaclyn Lucas, Director, Office of Sponsored Research

Morse, Brent (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, January 14, 2019 8:12 AM
To: DiStefano, Alyse; OLAW Division of Compliance Oversight (NIH/OD)
Cc: Zaia, John; Carlesso, Nadia; Ermel, Richard; Hammond, Amanda; (b) (6)
(b) (6) Lucas, Jaclyn
Subject: RE: Report of Noncompliance

Follow Up Flag: Follow up
Flag Status: Flagged

Thank you for submitting this report We will send an official response soon.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: DiStefano, Alyse <adistefano@coh.org>
Sent: Friday, January 11, 2019 5:52 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Zaia, John <JZaia@coh.org>; Carlesso, Nadia <ncarlesso@coh.org>; Ermel, Richard <RErmel@coh.org>; Hammond, Amanda <ahammond@coh.org>; (b) (6) Lucas, Jaclyn <jalucas@coh.org>
Subject: Report of Noncompliance

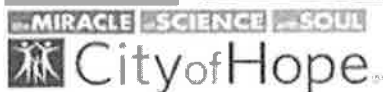
To Whom It May Concern,

Attached please find a report of noncompliance for your review.

Please let me know if you have any questions.

Thank you,

Alyse DiStefano
Director, Laboratory Research Protections
(b) (6) | adistefano@coh.org



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