



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) 480-3387

April 27, 2021

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

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 April 23, 2021 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the City of Hope National Medical Center-Beckman Research Institute. According to the information provided, OLAW understands that on January 19, 2021 your institution was notified of a protocol noncompliance. Mice that should have been checked daily were only checked once during the weekend of Saturday, January 16 and Sunday, January 17, 2021, resulting in pain and/or distress to the animals. On that weekend, eleven mice were found dead. It was also determined that one of the fellows was not listed on the protocol. However, this individual had completed all required IACUC trainings and was approved for animal activities under several of the PI's other protocols. This animal activity was PHS supported.

The corrective and preventive measures included a protocol amendment to ensure daily monitoring is clearly and consistently described. The body condition scoring system will be reviewed and updated and all of the PI's approved IACUC protocols were reviewed to ensure the personnel lists were updated and accurate. All personnel, including the PI, will undergo additional training and moving forward, daily monitoring will be documented on the appropriate Animal Care Program "Investigator to Monitor" cards. A post-approval monitoring (PAM) visit has been scheduled and must be completed before initiating any further mouse model studies.

All expenses related to the noncompliance issue that have been charged to the grant(s) will be transferred off those grants and instead charged to a non-sponsored source. Additionally, the NIH funding component will be notified of the situation.

OLAW appreciates the consideration of this matter by the City of Hope National Medical Center-Beckman Research Institute, which was consistent with the philosophy of institutional self-regulation. Based on the information provided, OLAW is satisfied that appropriate actions have been taken to investigate this incident, correct the noncompliance, and prevent recurrence. OLAW concurs that the incident warranted reporting. We appreciate being informed of this matter and find no cause for further action by this office.

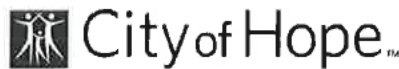
Sincerely,

Brent C. Morse -S

Digitally signed by Brent C.
Morse -S
Date: 2021.04.27 10:51:01 -04'00'

Brent C. Morse, DVM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC contact



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

April 23, 2021

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,

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 failure to monitor animals as described in the animal use protocol and unapproved personnel working under the animal use protocol entitled “Evaluation of CPG-siRNA for Targeting Human Leukemia Cells” (the “Protocol”). The project involved funds from NIH Grant P50CA107399 and 1R01-CA213131 for salary support for a postdoctoral fellow.

Incident Description:

The City of Hope Institutional Animal Care and Use Committee (IACUC) received an unanticipated problem report on January 19, 2021. The report indicated that an acute myeloid leukemia (AML) model was used in which NSG-SGM3 immunodeficient mice were engrafted with Cbf-Myh11 mouse leukemic cells and treated using CpG oligonucleotides or PBS alone. On Saturday, January 16 and Sunday, January 17, 2021, 11 mice were found dead from control and treated experimental groups. The Principal Investigator (PI) attributed the deaths to accelerated progression of AML in the immunodeficient mice. In the report, it was noted that the mice were observed every day on weekdays and only once during weekends, which is a deviation from the approved Protocol that indicates mice will be observed daily, including weekends. The IACUC reviewed this unanticipated problem report on February 9, 2021 and referred the follow up on this potential noncompliance issue to the IACUC Executive Committee (EC), which consists of the IACUC Chair, IACUC Vice Chair, Attending Veterinarian and Director, Laboratory Research Protections.

The IACUC EC sent a communication to the PI on February 25, 2021 informing the PI of the IACUC’s investigation and requesting a meeting to discuss. On March 9, 2021, the IACUC EC met with the PI and one of two post-doctoral fellows involved in the experiment. During this meeting, it was determined that one of the fellows was not listed on the Protocol; however, this individual had completed all required IACUC trainings and was approved for animal activities under several of the PI’s other protocols. It was also confirmed that the fellow did not monitor the animals each day over the weekend, as required per the Protocol. The PI took full responsibility for the incident and committed to developing a corrective and preventive action plan to address the two noncompliance issues – failure to monitor animals as described in the Protocol and unapproved personnel working on the Protocol.

On April 13, 2021, the IACUC Full Committee reviewed the case and voted to classify this as a serious noncompliance as it resulted in pain and/or distress to animals. The IACUC reviewed the PI's corrective action plan and requested further revisions, including documentation of monitoring and body condition scoring and completion of the post-approval monitoring before moving forward with additional AML models. The finalized plan is described below.

Corrective Action Plan:

- Review and Update of IACUC Protocols
 - The Protocol was amended to ensure daily monitoring after AML engraftment is clearly and consistently described. **Status:** The IACUC approved the amendment on March 19, 2021.
 - The body condition scoring system will be reviewed and updated to assist in assessing the health of the NSG mice, when to increase daily observations, and determine the endpoints. **Deadline:** April 30, 2021
 - All of the PI's approved IACUC protocols were reviewed to ensure the personnel lists were updated and accurate. **Status:** Completed March 10, 2021.
- Retraining of Laboratory Staff
 - All personnel, including the PI, will undergo additional training with the Senior Research Compliance and Training Specialist to review regulatory requirements for animal research, institutional policies and procedures, proper procedures for monitoring of animals and documentation of monitoring, and discuss best practices to ensure continued adherence to the approved protocol. **Deadline:** Retraining is scheduled for May 3, 2021.
- Monitoring of Animals
 - Moving forward, daily monitoring will be documented on the appropriate Animal Care Program "Investigator to Monitor" cards. The study team must use this card to identify cages containing animals that need more frequent observations. **Status:** The PI informed all laboratory personnel of this requirement and will ensure personnel are following the correct procedures. Ongoing post-approval monitoring will be performed by the Center for Comparative Medicine (CCM) staff and Senior Research Compliance and Training Specialist to ensure the laboratory is complying with this requirement.
- Post-Approval Monitoring
 - A post-approval monitoring visit (PAM) has been scheduled to ensure that procedures and monitoring are being performed according to the approved Protocol and institutional policies and procedures. **Deadline/status:** The IACUC has stipulated that this must be completed before initiating any further AML mouse model studies. The PAM will be scheduled after the retraining takes place on May 3, 2021.

All expenses related to the noncompliance issue that have been charged to the grant(s) noted above will be transferred off those grants and instead charged to a non-sponsored source. Additionally, the NIH funding component will be notified of the situation.

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: Markus Kalkum, Ph.D., Chair, IACUC
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

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, April 26, 2021 8:01 AM
To: Alyse DiStefano
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Report of Noncompliance

Thank you for this report, Ms. DiStefano. We will send a response soon.

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

From: Alyse DiStefano <adistefano@coh.org>
Sent: Friday, April 23, 2021 10:23 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: John Zaia <JZaia@coh.org>; Markus Kalkum <MKalkum@coh.org>; Richard Ermel <RErmel@coh.org>; Amanda Hammond <ahammond@coh.org>; (b) (6) Jaclyn Lucas <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

Alyse DiStefano

Director | Laboratory Research Protections
City of Hope | 1500 E Duarte Rd, Duarte, CA 91010
Tel: (b) (6) | Email: adistefano@coh.org

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