



DEPARTMENT OF HEALTH & HUMAN SERVICES

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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

July 6, 2022

Re: Animal Welfare Assurance
#A3272-01 [OLAW Case 2P]

Dr. Denis Wirtz
Vice Provost for Research
Johns Hopkins University
3400 N. Charles Street
Baltimore, MD 21218

Dear Dr. Wirtz,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your June 29, 2022 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Johns Hopkins University, following up on an initial telephone report on February 21, 2022. According to the information provided, OLAW understands that rats on an approved liver transplant study had been given alcohol for a period longer than stated in the protocol and had not been euthanized at the specified endpoint. Some animals were found to be in poor health, exhibiting weight loss and incisional herniation.

The immediate action taken upon discovery consisted of providing veterinary care to the rats. The corrective actions consisted of postponing additional surgeries, amending the protocol to clarify humane endpoint criteria and post-surgical monitoring, and clarifying the surgical procedures. To define the humane endpoints and allow for prompt termination, a body scoring system was developed. Upon resumption of the surgery there was direct oversight of the procedure by veterinary and Institutional Animal Care and Use Committee (IACUC) representatives and additional refinements were implemented.

Based on its assessment of this explanation, OLAW understands that measures have been implemented to correct and prevent recurrence of this problem. OLAW concurs with the actions taken by the IACUC to comply with the PHS Policy.

Sincerely,

(b) (6)

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

cc: IACUC Chair



June 29, 2022

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare
National Institutes of Health
Bethesda, Maryland 20892-6910

RE: Animal Welfare Assurance #A3272-01; Case 2P

Dear Dr. Wolff:

Please accept this letter as our final written report addressing Case#A3272-2P and the prompt report made to you by phone on February 21, 2022 by Dr. Brendan Canning, Chair of the Johns Hopkins University (JHU) Animal Care and Use Committee (ACUC). That prompt report detailed failure by the principal investigator to adhere to the approved protocol for use of rats in a liver transplant study funded by NIH Grant 5P50AA027054-05, "Multidisciplinary Approach to Study of Patients with Severe Alcoholic Hepatitis Undergoing Liver Transplantation—Project 4 Animal Transplant Models to Characterize Immune and Regenerative Effects of Alcohol." The ACUC investigated this matter as potential serious noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals (the "Policy") and determined that the investigator's failure to adhere to protocol required endpoints for study interventions and study endpoints constituted serious noncompliance.

In February of this year, JHU veterinary staff were notified that rats that had undergone liver transplants on the protocol associated with the above referenced grant were in poor health. This protocol evaluates the impact of chronic alcohol exposure on allograft rejection and immunosuppression after liver transplant, determining the effect of chronic and acute alcohol exposure on regeneration of small liver allografts, and developing a stem cell strategy to promote regeneration of small liver allografts following chronic and/ or binge alcohol feeding in rats. The approved protocol included plans for inducing liver failure in rats through provision of alcohol over a specified, five (5) week time frame, followed by liver transplant with a survival endpoint of thirty days (30) post-surgery. Clinical signs noted in post-surgical rats included weight loss and subcuticular incisional herniation. Veterinary staff took immediate steps to address the welfare of the rats.

Review by the veterinary staff and ACUC personnel of the rats' records revealed that the rats had been maintained for as long as sixty (60) days beyond ACUC approved endpoints after transplant (based on both clinical signs and total duration), and transplant recipient rats had received alcohol to induce liver toxicity for as long as eight (8) weeks. Published literature supports sustained alcohol treatment for eight weeks or longer as a scientifically appropriate and ethically sound intervention, but the ACUC approved protocol narrative was unambiguous in limiting the alcohol treatment to a 5 week duration, and setting a survival endpoint post-surgery at 30 days.

The ACUC Chair requested and the lab agreed to temporarily cancel all planned surgeries until JHU veterinarians and ACUC staff could coordinate observation of a surgery performed as described in the approved protocol narrative to inform corrective actions. The ACUC discussed the failure to adhere to the protocol at its meetings on February 17, 2022, March 17th, 2022, and April 15th, 2022, as well as the



necessary corrective actions. The ACUC determined that the failure to adhere to the protocol specified endpoints for the intervention and the study endpoint constituted serious noncompliance. Corrective actions requested by the ACUC included the submission of a protocol amendment to address required modifications to the experimental procedures, including more explicit descriptions of endpoints and post-surgical monitoring (and corrective surgeries), clearly defined criteria for monitoring potential harm to the animals that might require early termination of the study procedures (including both body weight assessments and body score indices), and a detailed description of surgical procedures. In addition, a detailed body scoring system was developed collaboratively by the lab and the attending veterinarians to ensure that animals were promptly removed from study when meeting protocol defined endpoints. After implementation of these additional corrective actions, a veterinarian and ACUC compliance staff observed a surgery and post-surgical hernia repair and made additional recommendations to the lab that were adopted.

The above corrective actions were reviewed at the ACUC meetings noted above and the ACUC accepted the corrective actions as adequate to address the identified noncompliance. The protocol amendment was also reviewed and approved prior to restarting experimentation. The IACUC considers this matter closed.

Please do not hesitate to contact me if you have additional questions.

Sincerely,

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Denis Wirtz, Ph.D.
Vice Provost for Research

cc: AAALAC International

Brendan J. Canning, Ph.D., Chair, Johns Hopkins University Animal Care and Use Committee

Eric Hutchinson, D.V.M., DACLAM, Attending Veterinarian and Assistant Vice Provost for Animal Research and Resources, Johns Hopkins University

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⏮ Reply all ⌵ 🗑 Delete 🚫 Junk 🚫 Block ⋮

RE: Report regarding OLAW case 2P

WA

Wolff, Axel (NIH/OD) [E]

Tue 7/5/2022 4:12 AM

To: Denis Wirtz <wirtz@jhu.edu>

Cc: OLAW Division of Compliance Oversight (NIH/OD)

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Thank you for this report, Dr. Wirtz. I will send a response soon.

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

From: Denis Wirtz <wirtz@jhu.edu>

Sent: Thursday, June 30, 2022 3:51 PM

To: Wolff, Axel (NIH/OD) [E] <wolffa@od.nih.gov>

Cc: Brendan Canning <bjc@jhmi.edu>; Eric Hutchinson <ehutchi8@jhmi.edu>;

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(b) (6)

Subject: [EXTERNAL] Report regarding OLAW case 2P

Dear Dr. Wolff,

Please find correspondence regarding Animal Welfare Assurance #A3272-01 (OLAW Case No. 2P).

Best regards,

Denis Wirtz

Denis Wirtz | wirtz@jhu.edu

Vice Provost for Research

TH Smoot Professor, Chemical and Biomolecular Engineering, Pathology, Oncology

Director Johns Hopkins Physical Sciences-Oncology Center (PS-OC)

Director Johns Hopkins Cellular Cancer Biology Imaging Research Center (CCBIR)

Johns Hopkins University and Johns Hopkins School of Medicine

3400 N. Charles St.

Baltimore, MD 21218

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<https://wirtzlab.jo>

hnshopkins.edu

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McCoy, Devora (NIH/OD) [E]

From: McCoy, Devora (NIH/OD) [E]
Sent: Monday, June 6, 2022 9:42 AM
To: bjc@jhmi.edu
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: Update on recent preliminary report

Good morning,

I'm reaching out to you about a recent preliminary report sent to us on 02/21/22 regarding people not being listed on a protocol used. I was wondering if you have an update or final report for us on this case?

Thanks,

Devora McCoy, BS, MBA
Program Analyst
Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
301-435-2390



Initial Report of Noncompliance

By: [REDACTED] (b) (6)

Date: 2/21/22

Time: 700 Voice Mail

Name of Person reporting: Brandon Carpin, I have chain

Telephone #: [REDACTED] (b) (6)

Fax #: [REDACTED] (b) (6)

Email: bsc

Name of Institution: Johns Hopkins U

Assurance number: A3272

Did incident involve PHS funded activity? Yes

Funding component: P50

Was funding component contacted (if necessary):

What happened?

Significant deviation from protocol - procedures not on protocol, people not listed on protocol

Species involved: Rat

Personnel involved:

Dates and times:

Animal deaths:

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

Projected submission to OLAW of final report from Institutional Official:

OFFICE USE ONLY

Case #