



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) 402-7065

March 17, 2021

Re: Animal Welfare Assurance  
#A3284-01 (OLAW Case 2I)

Dr. Jill C. Pipher  
Vice President for Research  
Brown University  
47 George St. - Box 1937  
Providence, Rhode Island 02912

Dear Dr. Pipher,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your March 16, 2021 letter responding to my March 8, 2021 request for additional information regarding an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Brown University. According to the information provided, OLAW understands the following:

- 1) To address significant footpad swelling in the mice, the amended protocol includes a pilot study to examine hock injections. If it becomes necessary to use footpad injections, only one foot will be used, no adjuvant will be mixed with the cell inoculum, and long acting analgesic agents will be given. The mice will be carefully monitored for swelling, pain, ambulating, and ability to access food and water.
- 2) Footpad injections will only be performed if the hock injection is unsuccessful.
- 3) Supportive care for the mice includes long acting analgesia, food on the cage floor, and diet gel.
- 4) The humane endpoints include a maximum tumor size, presence of pain/distress, and difficulty ambulating.
- 5) The amendment has been approved by the Institutional Animal Care and Use Committee (IACUC).
- 6) The IACUC and veterinary staff has counseled the investigator about potential animal welfare problems with this study. Using the hock injection is considered a refinement to minimize pain/distress. The mice will be closely monitored and humane endpoints will be enforced.

Based on its assessment of this additional information, OLAW has a better understanding of the actions being taken by the IACUC, veterinary staff, and investigator to ensure animal welfare. If not already proposed, the use of soft, deep bedding could also be considered. OLAW concurs with the actions taken by the institution to comply with the PHS Policy and will close this investigation, however, if any relevant issues arise (positive or negative), please inform us. Thank you for keeping OLAW apprised on this matter.

Sincerely,

(b) (6)

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

cc: IACUC Chair



**BROWN**

March 16, 2021

Brent Morse, DVM  
Director, Division of Compliance Oversight  
Office of Laboratory Animal Welfare  
National Institutes of Health  
Rockledge 1, Suite 360  
6705 Rockledge Drive  
Bethesda, MD 20892

RE: Noncompliance Report, Assurance D16-00183 (A3284-01)  
National Heart, Lung, and Blood Institute Award (HL146198, HL114501)

Dear Dr. Morse:

Please find Brown's responses below as it relates to the additional information requested by OLAW pertaining to the report of noncompliance sent on March 3, 2021:

1) If the amendment is approved, what actions will be taken to ensure that the mice do not sustain significant footpad swelling?

The amendment specifies that the lab will pilot the hock injection technique prior to utilizing footpad injection, as hock injections drain to the same lymph nodes and do not affect weight bearing structures. If the lab does utilize footpad injections, only one foot per animal can be injected with a maximum of 50 ul of cells. No adjuvants are included in the injected material. Buprenorphine SR must be provided for pain relief. The lab must carefully monitor animals (records on cage card) for signs of swelling, pain, and difficulty ambulating or reaching food and water.

2) Are footpad injections even allowed as part of an approved protocol?

Footpad injections are approved only in the event that the investigator can demonstrate that the hock injections have failed to achieve their scientific endpoints.

3) If a protocol is approved that allows footpad injections, what supportive care is in place?

Animals receive buprenorphine SR and may also receive food on the cage floor or diet gels if warranted.

4) Are humane endpoints established for such studies?

Yes- animals will be euthanized when the tumors reach a certain size (10 mm) or the animals demonstrate pain/distress or difficulty ambulating.

5) Was the amendment approved by the Institutional Animal Care and Use Committee?

This amendment was approved by the IACUC February 19, 2021.

6) Provide any additional information about the welfare of the mice under the proposed amendment.

The Brown University IACUC and the veterinary team is aware of the significant welfare concerns surrounding footpad injections and has taken great care to impress these upon the investigator. We expect that hock injections will eliminate the need for footpad injections altogether, which is also preferable to the investigator. Should footpad injections be required, animals will be monitored regularly and humane endpoints identified and enforced.

Brown University is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. If you have any questions or concerns regarding this report, please contact (b) (6)

Thank you for your consideration of this matter.

Sincerely,

(b) (6)

Jill Pipher, PhD  
Vice President for Research, Institutional Official  
Brown University, Box 1937

cc: Diane Hoffman-Kim, PhD, IACUC Chair  
Lara Helwig, DVM, Attending Veterinarian  
(b) (6)  
Keri Godin, Senior Director, Office of Research Integrity

## Wolff, Axel (NIH/OD) [E]

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**From:** Wolff, Axel (NIH/OD) [E]  
**Sent:** Wednesday, March 17, 2021 7:28 AM  
**To:** IACUC  
**Subject:** RE: OLAW Case A3284-2I

Thank you for this response, (b) (6) I will send a reply to the IO shortly.

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

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**From:** (b) (6) On Behalf Of IACUC  
**Sent:** Tuesday, March 16, 2021 3:31 PM  
**To:** Walker, Keri (NIH/OD) [E] <keri.walker@nih.gov>; Wolff, Axel (NIH/OD) [E] <wolffa@od.nih.gov>  
**Cc:** jill\_pipher@brown.edu; keri\_godin@brown.edu; Diane Hoffman-Kim <Diane\_Hoffman-Kim@brown.edu>; Lara Helwig <lara\_helwig@brown.edu>; (b) (6)  
**Subject:** Re: OLAW Case A3284-2I

Good afternoon,

Please find attached Brown's response to Dr. Wolff's request for additional information as it pertains to the March 3, 2021 report of noncompliance sent to OLAW. Please let me know if you have additional questions or need further clarification.

Sincere regards,

(b) (6)

### Helpful Links:

- Brown IACUC website: <http://www.brown.edu/research/RPO/IACUC>
- InfoEd: [infoed.brown.edu](http://infoed.brown.edu)

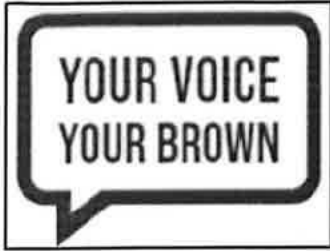
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On Mon, Mar 8, 2021 at 8:35 AM Walker, Keri (NIH/OD) [E] <[keri.walker@nih.gov](mailto:keri.walker@nih.gov)> wrote:

Dear Dr. Pipher,

Attached please find Dr. Wolff's *interim* response to OLAW Case A3284-21.

If you have any questions, feel free to contact us by phone or by e-mail.

Best Regards,

Keri

*Keri Walker*

*Program Analyst (Contractor)*

*Division of Compliance Oversight*

*Office of Laboratory Animal Welfare*

*National Institutes of Health*

*6700B Rockledge Dr., Suite 2500*

*Bethesda, MD 20892*

*301-435-2390*

*[keri.walker@nih.gov](mailto:keri.walker@nih.gov)*



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March 8, 2021

Re: Animal Welfare Assurance  
#A3284-01 (OLAW Case 2I)

Dr. Jill C. Pipher  
Vice President for Research  
Brown University  
47 George St. - Box 1937  
Providence, Rhode Island 02912

Dear Dr. Pipher,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your March 3, 2021 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Brown University. According to the information provided, OLAW understands that seven mice sustained rear foot pad swelling after being injected with a substance that had not yet been approved as a protocol amendment. This incident constituted repeat noncompliance for the individual responsible.

The corrective actions consisted of euthanizing the mice at the direction of the veterinarian. The responsible laboratory member's animal use privileges were suspended for 45 days, upon reinstatement the person will be placed on probation and enhanced oversight, and if additional noncompliance is identified the animal use privileges will be terminated.

Although the personnel issue appears to have been handled appropriately, OLAW has additional questions regarding the animal welfare implications as follows:

- 1) If the amendment is approved, what actions will be taken to ensure that the mice do not sustain significant footpad swelling?
- 2) Are footpad injections even allowed as part of an approved protocol?
- 3) If a protocol is approved that allows footpad injections, what supportive care is in place?
- 4) Are humane endpoints established for such studies?
- 5) Was the amendment approved by the Institutional Animal Care and Use Committee?
- 6) Provide any additional information about the welfare of the mice under the proposed amendment.

Please provide the requested information by **March 29, 2021**. Feel free to contact me should you have any questions.

Sincerely,

(b) (6)

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

cc: IACUC Chair





BROWN

March 3, 2021

Brent Morse, DVM  
Director, Division of Compliance Oversight  
Office of Laboratory Animal Welfare  
National Institutes of Health  
Rockledge 1, Suite 360  
6705 Rockledge Drive  
Bethesda, MD 20892

RE: Noncompliance Report, Assurance D16-00183 (A3284-01)  
National Heart, Lung, and Blood Institute Award (HL146198, HL114501)

Dear Dr. Morse:

The Brown University IACUC, through the Institutional Official (Jill C. Pipher, PhD), is writing to provide OLAW with a final report of the following noncompliance with the *PHS Policy on Humane Care and Use of Laboratory Animals* ("PHS Policy"):

On January 28, 2021, an animal care technician identified seven mice with significant footpad swelling in their hind feet. The mice were euthanized under the direction of a veterinarian due to the animal welfare concerns that existed. The responsible PI confirmed that the lesions were due to administration of a substance that was proposed in an amendment currently under review by the IACUC and not yet approved. Conducting procedures without IACUC approval leading to animal welfare concerns is now a repeated issue for this individual within the lab.

The IACUC discussed this issue of repeated noncompliance at its convened meeting on February 5, 2021. The following corrective actions were required effective 2/8/2021:

- The responsible lab member was suspended from all animal work for 45 days.
- Following this, the lab member will undergo a 45-day period of probation and monitoring. During this time, the lab member must keep a log of all animal work performed and what protocol the work falls under which must also be signed off by the PI.
- The next incident of noncompliance may result in permanent suspension from animal work.

Brown University is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. If you have any questions or concerns regarding this report, please contact (b) (6)

(b) (6)

Thank you for your consideration of this matter.

Sincerely,

(b) (6)

Jill Pipher, PhD  
Vice President for Research, Institutional Official  
Brown University, Box 1937

cc: Diane Hoffman-Kim, PhD, IACUC Chair  
Lara Helwig, DVM, Attending Veterinarian  
(b) (6)  
Keri Godin, Senior Director, Office of Research Integrity



## Wolff, Axel (NIH/OD) [E]

**From:** (b) (6) on behalf of IACUC <iacuc@brown.edu>  
**Sent:** Monday, March 1, 2021 10:36 AM  
**To:** OLAW Division of Compliance Oversight (NIH/OD)  
**Cc:** Jill Pipher; Keri Godin; Lara Helwig; Diane Hoffman-Kim; (b) (6)  
**Subject:** Event Report - Assurance A328401  
**Attachments:** NCReportOLAW - Final.pdf

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

Dear Dr. Morse,

Please see the attached reportable event that was discussed by the IACUC during its convened meeting February 5, 2021. Please let me know if you have any questions.

Sincerely,



### Helpful Links:

- Brown IACUC website: <http://www.brown.edu/research/RPO/IACUC>
- InfoEd: [infoed.brown.edu](http://infoed.brown.edu)

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