



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

July 8, 2019

Re: Animal Welfare Assurance
A3865-01 [OLAW Case U]

Dr. Joseph Incandela
Vice Chancellor for Research
University of California-Santa Barbara
(b) (4) Cheadle Hall
Santa Barbara, CA 93106-2050

Dear Dr. Incandela,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your June 20, 2019 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the University of California- Santa Barbara, following up on an initial telephone report on May 3, 2019 and an interim report on June 4, 2019 . According to the information provided, OLAW understands that 80 mice on an Alzheimer disease study were not euthanized at the timepoint described in the protocol, but rather one month later. Although the mice were not as active as they had been previously, they were not noted to be in pain or distress.

The corrective actions consisted of the Institutional Animal Care and Use Committee (IACUC) requiring certification by all Principal Investigators (PI) and staff that they have read the protocol and any amendments and understand the approved procedures. The PI involved stated that no additional animal work will be conducted on this protocol.

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

UC SANTA BARBARA

Institutional Animal Care and Use Committee

Santa Barbara CA 93106-5062

Tel: (805) 893-5855

Fax: (805) 893-2005

Email: iacuc@lifesci.ucsb.edu

<https://www.research.ucsb.edu/compliance/animal-subjects/>

June 20, 2019

Animal Welfare Assurance A3865-01 (D16-00497)

Dr. Axel V. Wolff, Director

Division of Compliance Oversight

Office of Laboratory Animal Welfare

National Institutes of Health

Rockledge One, Suite 360

6705 Rockledge Drive

Bethesda, MD 20892-7982

Dear Dr. Wolff,

In accordance with our Assurance and PHS Policy IV.F.3, I am writing to report an incident of protocol non-compliance involving the care and use of animals at the University of California, Santa Barbara. Below is the full investigation report into the incident preliminarily reported to you via a phone call from our IACUC Chair on May 3, 2019. The UCSB IACUC is convinced that appropriate remediations were enacted to prevent recurrence of the incidents described below.

Summary of Investigation:

On April 3, 2019, the IACUC Office received a forwarded message from the PI regarding his/her mice in the vivarium. The ARC Manager had emailed the PI to notify her/him that the mice on her/his protocol were now one month past the experimental endpoint identified in their IACUC protocol. While the ARC staff had

been hired by the PI to administer an experimental compound to the mice, the experimental treatment schedule was set by the PI and the ARC staff was responsible only for administering the experimental compound at bi-weekly (twice per week) intervals. The experimental compound was prepared and delivered by the lab to the ARC before each treatment (i.e., bi-weekly). The PI notified the IACUC Office that they would be euthanizing all of the mice in their colony within twelve days. The IACUC Chair subsequently asked to meet with the PI to regarding the change in the experimental endpoint for the mice.

The mice being used on the protocol were a transgenic strain, rTg4510, which is a commonly used model for studying the formation of neurofibrillary tangles associated with Alzheimer's disease and related neurodegenerative tauopathies such as frontotemporal dementia. These mice exhibit experimentally useful neurological phenotypes (impaired spatial learning and memory) and a potentially distressful phenotype in later stages (>6.5 months of age) in the form of progressive motor function abnormalities (amyotrophy and motor disturbance). From the protocol: "pathological lesions (mature tangles) are observed beginning at 2.5 months of age, and memory dysfunction is observed at 4.5 months". The endpoint outlined in the protocol states that an experimental compound (Cinnamaldehyde) will be tested for its ability to "alleviate/attenuate both tau tangles and behavioral pathology" at 6-6.5 months of age, "since this is the time at which memory dysfunction has been reported for this mouse model". The mice were to be euthanized for tissue collection at 6.5 months of age.

The IACUC Chair appointed a sub-Committee, comprised of himself and the Attending Veterinarian (AV), to investigate this potential incident of protocol non-compliance. On April 15, 2019, the IACUC Coordinator, Chair and AV met with the PI and another faculty member who had been enlisted to perform the euthanasia and tissue collection procedures. The PI confirmed at the meeting that all of the mice in this experiment (approximately 80 animals) had been euthanized. When asked why these mice were not euthanized according to the experimental endpoint described in the protocol, the PI admitted that it was due to (his own) human error. One of the collaborating investigators was not yet ready to carry out their studies as

previously planned, and consequently it was necessary to hold on to the animals longer than expected. Amidst this procedural adjustment, the PI admitted that he inadvertently overlooked the date of euthanization (March 7, 2019) stated in the most recent modification to the animal protocol. The PI confirmed that s/he was not planning on using any more animals under this protocol, unless requested by journal article reviewers.

After meeting with the PI, the Coordinator, Chair and AV met with the ARC Manager. S/he confirmed that the ARC had been administering the experimental compound to the mice according to the treatment plan set by the PI. While the Manager and the AV confirmed that no mice had been exhibiting symptoms of the potentially distressful phenotype, the Manager did mention that the mice were not looking as bright and active as they had been in previous months.

During the April 19, 2019 convened IACUC meeting, the IACUC Chair summarized the situation for the Committee and led a discussion of whether or not this incident was reportable to OLAW. This project is funded by an NIH grant (5R21AT008997). Following a discussion, the Committee voted that this incident should be reported to OLAW according to the Guidance of Prompt Reporting outlined in OLAW NOT-OD-05-034. A preliminary report via phone call was made to OLAW's Division of Compliance Oversight by the IACUC Chair on May 3, 2019.

During the May 17, 2019 convened IACUC meeting, the IACUC Chair summarized the discussion with OLAW's Division of Compliance Oversight, noting that they had specifically asked about remediation to prevent similar incidents in the future. The IACUC will require a signed statement from the PI and all personnel listed on the training roster attesting that they have read the protocol and will read all subsequent modifications. If the PI submits another IACUC protocol application in the future, s/he and all personnel on that protocol will be required to sign a similar attestation. The IACUC Chair also stated that he is planning on creating an assurance statement, based on the protocol assurance statement that PI's are already required to sign, that must be signed by all researchers working with animals to affirm that each of them has read and understands the procedures in the

protocol and all applicable modifications. The final version of this investigation report will be sent to OLAW and AAALAC.

This protocol is funded by an NIH grant (5R21AT008997-02). The UCSB Sponsored Projects Office (SPO) will work with the PI and NIH to ascertain if any grant money was used during this incident of protocol non-compliance.

If you have any additional questions or comments, please feel free to contact us. Thank you for your time.

Sincerely,

(b) (6)



Prof. Joseph Incandela

Institutional Official

Vice Chancellor for Research

(b) (4) Cheadle Hall

University of California, Santa Barbara

Santa Barbara, CA 93106-2050

incandela@research.ucsb.edu

Cc: Dr. Stuart Feinstein, IACUC Chair
Dr. Manuel Garcia, Campus Veterinarian
IACUC Office

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, July 5, 2019 7:01 AM
To: IACUC Office
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: FW: Incident Report for A3865-01

Thanks for sending it again. I will send the response shortly.
Axel Wolff

-----Original Message-----

From: IACUC Office <iacuc@lifesci.ucsb.edu>
Sent: Wednesday, July 3, 2019 6:48 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: Re: FW: Incident Report for A3865-01

Hi Axel,

I actually did resubmit that report to OLAW with our IO's signature on June 24th. I've attached the .pdf to this email. Please let me know if you have any other questions.

Thanks,

(b) (6)

On 7/2/2019 10:45 AM, OLAW Division of Compliance Oversight (NIH/OD) wrote:

> Hello (b) (6) in reviewing this case I noted that a previous case you had submitted never came with the final signed copy from the IO. It was sent June 4 and involved 80 mice on an Alzheimer study which were not euthanized at the timepoint described in the protocol. Please have Dr. Incandela sign the report and forward to OLAW. Thanks.

> Axel Wolff

>

> -----Original Message-----

> From: OLAW Division of Compliance Oversight (NIH/OD)

> <olawdco@od.nih.gov>

> Sent: Tuesday, July 2, 2019 8:00 AM

> To: IACUC Office <iacuc@lifesci.ucsb.edu>

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

> <olawdco@od.nih.gov>

> Subject: RE: Incident Report for A3865-01

>

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

>

> Axel Wolff, M.S., D.V.M.

> Deputy Director, OLAW

>

> -----Original Message-----

> From: IACUC Office <iacuc@lifesci.ucsb.edu>

> Sent: Monday, July 1, 2019 7:35 PM

> To: OLAW Division of Compliance Oversight (NIH/OD)

> <olawdco@od.nih.gov>

> Cc: Joseph Incandela <incandela@research.ucsb.edu>; Stu Feinstein
> <stu.feinstein@lifesci.ucsb.edu>; Manny Garcia
> <manuel.garcia@ucsb.edu>; (b) (6)
> Subject: Incident Report for A3865-01

> To Whom It May Concern:

> Attached is a letter that details an incident of protocol noncompliance at the University of California, Santa Barbara (A3865-01).

> The UCSB IACUC has investigated and reviewed the incident. This report includes the summary of the incident, as well as any Committee corrective actions.

> Please let me know if there are any questions.

> Sincerely,

> (b) (6)

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> (b) (6)

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(b) (6)

UCSB IACUC INVESTIGATION CHECKLIST

Summary of Investigation:

On April 3, 2019, the IACUC Office received a forwarded message from the PI regarding his/her mice in the vivarium. The ARC Manager had emailed the PI to notify her/him that the mice on her/his protocol were now one month past the experimental endpoint identified in their IACUC protocol. While the ARC staff had been hired by the PI to administer an experimental compound to the mice, the experimental treatment schedule was set by the PI and the ARC staff was responsible only for administering the experimental compound at bi-weekly (twice per week) intervals. The experimental compound was prepared and delivered by the lab to the ARC before each treatment (i.e., bi-weekly). The PI notified the IACUC Office that they would be euthanizing all of the mice in their colony within twelve days. The IACUC Chair subsequently asked to meet with the PI to regarding the change in the experimental endpoint for the mice.

The mice being used on the protocol were a transgenic strain, rTg4510, which is a commonly used model for studying the formation of neurofibrillary tangles associated with Alzheimer's disease and related neurodegenerative tauopathies such as frontotemporal dementia. These mice exhibit experimentally useful neurological phenotypes (impaired spatial learning and memory) and a potentially distressful phenotype in later stages (>6.5 months of age) in the form of progressive motor function abnormalities (amyotrophy and motor disturbance). From the protocol: "pathological lesions (mature tangles) are observed beginning at 2.5 months of age, and memory dysfunction is observed at 4.5 months". The endpoint outlined in the protocol states that an experimental compound (Cinnamaldehyde) will be tested for its ability to "alleviate/attenuate both tau tangles and behavioral pathology" at 6-6.5 months of age, "since this is the time at which memory dysfunction has been reported for this mouse model". The mice were to be euthanized for tissue collection at 6.5 months of age.

The IACUC Chair appointed a sub-Committee, comprised of himself and the Attending Veterinarian (AV), to investigate this potential incident of protocol non-compliance. On April 15, 2019, the IACUC Coordinator, Chair and AV met with the PI and another faculty member who had been enlisted to perform the euthanasia and tissue collection procedures. The PI confirmed at the meeting that all of the mice in this experiment (approximately 80 animals) had been euthanized. When asked why these mice were not euthanized according to the experimental endpoint described in the protocol, the PI stated that s/he was not aware of the birthdates of the mice (i.e., s/he had not been tracking their ages). The PI explained that the mice needed to undergo behavioral testing prior to the tissue collection, however, the faculty member who was to perform the behavioral testing procedures for the PI had not started the testing early enough to complete it prior to the experimental endpoint. The PI confirmed that s/he was not planning on using any more animals under this protocol, unless requested by journal article reviewers.

After meeting with the PI, the Coordinator, Chair and AV met with the ARC Manager. S/he confirmed that the ARC had been administering the experimental compound to the mice according to the treatment plan set by the PI. While the Manager and the AV confirmed that no mice had been exhibiting symptoms of the potentially distressful phenotype, the Manager did mention that the mice were not looking as bright and active as they had been in previous months.

During the April 19, 2019 convened IACUC meeting, the IACUC Chair summarized the situation for the Committee and led a discussion of whether or not this incident was reportable to OLAW. This project is funded by an NIH grant (5R21AT008997). Following a discussion, the Committee voted that this incident should be reported to OLAW according to the Guidance of Prompt Reporting outlined in OLAW NOT-OD-05-034. A preliminary report via phone call was made to OLAW's Division of Compliance Oversight by the IACUC Chair on May 3, 2019.

During the May 17, 2019 convened IACUC meeting, the IACUC Chair summarized the discussion with OLAW's Division of Compliance Oversight, noting that they had specifically asked about remediation to prevent similar incidents in the future. The IACUC will require a signed statement from the PI and all personnel listed on the training roster attesting that they have read the protocol and will read all subsequent modifications. If the PI submits another IACUC protocol application in the future, s/he and all personnel on that protocol will be required to sign a similar attestation. The IACUC Chair also stated that he is planning on creating an assurance statement, based on the protocol assurance statement that PI's are already required to sign, that must be signed by all researchers working with animals to affirm that each of them has read and understands the procedures in the protocol and all applicable modifications. The final version of this investigation report will be sent to OLAW and AAALAC.

PROTOCOL (PI being investigated)

Principal Investigator: John Lew	Phone: X 5336
Co-PI: Benjamin Reese	Phone: X 2091
Complete IACUC #: 6-16-920	IACUC Title: Inhibition of tau aggregation in a mouse model of Alzheimer's Disease
Species/Strain: Tg4510 Mice	Current housing location:

EVALUATION BY IACUC

- ☐ No further investigation warranted – Date: _____
- ☒ Proceed with investigation
- ☒ Notify Institutional Official
- ☒ Sub-Committee Appointed: 1. Stu Feinstein
2. Manny Garcia
- ☒ Report of Investigation (by Sub-Committee to the IACUC) submitted
- ☒ Convened IACUC meeting review - Date: May 17, 2019

☒ Final IACUC action – Date: May 17, 2019

☒ Notifications required (list): IO, PI, Co-PI, AV, IACUC Chair, Director of Research Integrity, OLAW, AAALAC

☒ Notifications sent - Date: June 4, 2019

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Tuesday, July 2, 2019 1:45 PM
To: iacuc (iacuc@lifesci.ucsb.edu)
Subject: FW: Incident Report for A3865-01

Hello (b) (6) in reviewing this case I noted that a previous case you had submitted never came with the final signed copy from the IO. It was sent June 4 and involved 80 mice on an Alzheimer study which were not euthanized at the timepoint described in the protocol. Please have Dr. Incandela sign the report and forward to OLAW. Thanks.
Axel Wolff

-----Original Message-----

From: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Sent: Tuesday, July 2, 2019 8:00 AM
To: IACUC Office <iacuc@lifesci.ucsb.edu>
Cc: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: RE: Incident Report for A3865-01

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

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

-----Original Message-----

From: IACUC Office <iacuc@lifesci.ucsb.edu>
Sent: Monday, July 1, 2019 7:35 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Joseph Incandela <incandela@research.ucsb.edu>; Stu Feinstein <stu.feinstein@lifesci.ucsb.edu>; Manny Garcia <manuel.garcia@ucsb.edu>; (b) (6)
Subject: Incident Report for A3865-01

To Whom It May Concern:

Attached is a letter that details an incident of protocol noncompliance at the University of California, Santa Barbara (A3865-01).
The UCSB IACUC has investigated and reviewed the incident. This report includes the summary of the incident, as well as any Committee corrective actions.

Please let me know if there are any questions.

Sincerely,

(b) (6)

--
(b) (6)

Morse, Brent (NIH/OD) [E]

A3865-01
awaiting LOS sig.

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Wednesday, June 05, 2019 7:26 AM
To: IACUC Office; OLAW Division of Compliance Oversight (NIH/OD)
Cc: Joseph Incandela; Manny Garcia; Stu Feinstein; (b) (6)
Subject: RE: Incident Report for A3865-01

Thank you for providing this report. Please have the Institutional Official, as the legal representative, sign the report or provide a cover letter, or otherwise acknowledge agreement with the IACUC's findings and corrective and preventive measures. Thank you again.

Sincerely, Brent Morse

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

Please note that this message and any of its attachments are intended for the named recipient(s) only and may contain confidential, protected or privileged information that should not be distributed to unauthorized individuals. If you have received this message in error, please contact the sender.

-----Original Message-----

From: IACUC Office [mailto:iacuc@lifesci.ucsb.edu]
Sent: Tuesday, June 04, 2019 6:55 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: Joseph Incandela <incandela@research.ucsb.edu>; Manny Garcia <manuel.garcia@ucsb.edu>; Stu Feinstein <stu.feinstein@lifesci.ucsb.edu>; (b) (6)
Subject: Incident Report for A3865-01

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Please let me know if there are any questions.

Sincerely,
(b) (6)

--
(b) (6)



Initial Report of Noncompliance

By: aw

Date: 5/3/19

Time: 1:45

Name of Person reporting: Sean Feinstein

Telephone #: (b)(6)

Fax #:

Email:

Name of Institution: U of Cal - Santa Barbara

Assurance number: A3865

Did incident involve PHS funded activity? Yes

Funding component: _____

Was funding component contacted (if necessary): _____

What happened?

80 Alzheimer Transgenic mice not euthanized at endpoint
Not showing signs of pain, distress. PI not experienced.

Species involved: Mice

Personnel involved:

Dates and times:

Animal deaths:

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

Study is over, probably no more animal work will be done

Projected submission to OLAW of final report from Institutional Official:

OFFICE USE ONLY

Case # _____