



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 23, 2018

Re: Animal Welfare Assurance
#A3234-01 (OLAW Case F)

Dr. Joseph Frascella
Vice President of Research
Legacy Health System
1225 NE 2nd Avenue
Portland, Oregon 97232

Dear Dr. Frascella,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your July 10, 2018 letter reporting two instances of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at Legacy Research Institute, following up on an initial report on April 17, 2018. According to the information provided, OLAW understands the following about the incidents and the corresponding corrective actions:

- 1) Twenty two mice were euthanized for brain tissue harvest although the approved protocol did not include the strain used and did not describe euthanasia procedures specifically to collect tissue. The investigator responsible was unclear as to which procedures were approved and which mice were assigned to the protocol.

Corrective action: The Principal Investigator and staff were counseled and retrained. Procedures were developed to ensure that mice are bred only for authorized purposes and that information is correctly entered onto the cage cards. All tissue collection activities must be covered by a protocol.

- 2) An experimental agent was given to six mice via brain injection although this procedure was not described in the protocol and three mice died.

Corrective action: The remaining three mice were euthanized. The Principal Investigator counseled the researcher responsible on the need for Institutional Animal Care and Use Committee (IACUC) approval of all animal activities. The technicians were counseled to check that all procedures have IACUC approval.

Based on its assessment of this explanation, OLAW understands that measures have been implemented to correct and prevent recurrence of these problems. 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

(b) (6)

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tissue collection. Interviews with Dr. Boison and [REDACTED] revealed vastly different recollections regarding experimental planning and work assignments. Additional interviews with laboratory staff, as well as review of a number of emails, revealed three basic issues: 1) Confusion regarding brainstorming versus directions to perform IACUC approved procedures, 2) Inadequate communication with breeding colony manager regarding assignment of offspring, and 3) Failure of research staff to cross reference the IACUC protocol to determine whether procedures are approved or if an amendment needs to be submitted and approved before work can proceed. The IACUC focused on issues affecting animal use and welfare; focusing on processes, retraining, and communication aides. Drs. Boison and (b) (6) were referred to Human Resources for further guidance and coaching due to the degree of miscommunication and misunderstanding regarding animal use.

Based on these initial reports, the IACUC reviewed and made specific findings and determinations on May 23, 2018, among which was to require Dr. Boison and a number of his staff to take corrective actions to ensure that they comply with IACUC procedures and requirements.

On June 12, 2018, Dr. Boison responded to the IACUC's requirements, detailing corrections implemented by him and his staff.

On June 21, 2018, the IACUC reviewed and acknowledged and accepted the corrective actions submitted by Dr. Boison, but requested additional confirmation of specific corrective actions.

On June 25, 2018, Dr. Boison responded to the IACUC's requirements for confirmation of corrective actions.

On June 26, 2018, the Attending Veterinarian attended the Boison Animal user group meeting to provide retraining regarding the IACUC approval process, the responsibility of the person performing the procedure to cross-reference the protocol and assure approval is in place, and the difference between utilizing remaining tissue from an animal euthanized for an approved project versus animals maintained for the sole purpose of tissue collection- the latter requiring specific IACUC approval.

Please see the attached documentation supporting these events. It is my hope that this letter and the accompanying documents provide an adequate explanation for these events and actions. However, please let me know if you need additional clarification or documentation or have questions regarding the resolution of these deviations. We look forward to discussing the issues in detail and providing more information or taking additional action as needed.

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BOILSON ADRIC CENTER

110-2017

Strain 05/81/61

Species Mouse Sex M

Vendor 1000/ 111

Age Wt 10/ 30/2017

Animal ID 89868, 89869, 89870, 89871, 89872

12954

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assigned to the cancer protocol. The intended Adk-tg and wild-type mouse use was to explore whether there are any developmental / age-related changes in the histopathology of different organs. Again, (b) (6) was not able to explain why those mice were on the cancer protocol. The intended use of all of the non-compliant mice was to do pilot studies using extracted tissues from the animals. The animals were not subjected to experiments. My overall conclusion is that (b) (6) was not aware that *sacrifice for tissue extraction* is an activity that requires adequate IACUC approval. He was under the assumption that as long as we have an active IACUC protocol, it is ok to sacrifice animals covered under that protocol for tissue extractions. A follow-up meeting for mouse breeding is scheduled for April 30.

Describe actions taken to prevent this type of event in the future:

Animal breeding is coordinated by our technician (b) (6). She breeds and distributes animals to our Postdocs and Research Associates. Mouse breeding was coordinated using excel sheets on our public folder, assigning animal use and need to specific investigators. Since April 10 we have implemented a rodent order form to be used by investigators to request mouse breeding by (b) (6). Investigators need to indicate the mouse line, sex, age, number of animals, date of need (this was part of the original excel-based system), but also purpose of experiment and IACUC protocol. This form needs to be signed off by Dr. Boison before (b) (6) is authorized to initiate the breeding of experimental animals. This procedure safeguards that (b) (6) breeds animals only for authorized uses. A follow-up discussion that includes all mouse users is scheduled for April 30.



LEGACY RESEARCH INSTITUTE
INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

ADVERSE EVENTS, UNEXPECTED OUTCOMES, PROTOCOL
DEVIATION FORM

Submit completed forms to:

(b) (6)

IACUC Chair:

Brad Fortune, PhD

| ph:

| bfortune@deverseye.org

Attending Veterinarian:

Jennifer Wilk, DVM, DACLAM

| ph:

| jenwilk@lhs.org

Date of form completion: 4/19/2018

Protocol #: N/A

PI:

(b) (6)

Protocol Title: N/A

Person completing form if not PI: Dr. Boison

Date of AE/UO/PD: 4/16/2018 Date Identified: 4/16/2018

Event: Protocol Deviation

Is the possibility of this event listed in the current protocol? ☐ Yes ☐ No ☒ N/A

Nature of Event – please describe what happened:

During our weekly Neurobiology staff meeting our Research Associates and Postdocs routinely present new research data, which are discussed by the team. Because (b) (6) was absent for a conference, his technician (b) (6) took over and presented data from one of (b) (6)'s projects. The data presentation caught the immediate attention of the Neurobiology group because (i) nobody was aware of this experiment (never presented before), and (ii) because it became evident that this experiment was not approved in our epilepsy IACUC protocol.

The experiment was performed as part of a new (b) (4) Grant on Sudden Unexpected Death in Epilepsy (SUDEP), which (b) (6) as the PI of this grant received from the (b) (4) (FY19 grant).

Six adult male C57Bl/6 mice received intrahippocampal injection of kainic acid (approved in epilepsy protocol) to generate a model of temporal lobe epilepsy. Six weeks later, the now epileptic animals received a single injection of the adenosine kinase inhibitor 5-ITU (3.2 mg/kg, i.p.; as approved in epilepsy protocol) followed 30 minutes later by an additional injection of kainic acid (25 mg/kg i.p.). This second application of kainic acid with the goal to trigger SUDEP is not approved in the epilepsy protocol. Three animals died within 4 to 12 hours after the second application of kainic acid (presumably from SUDEP), whereas three animals survived.

Describe the initial actions taken to manage the situation:

Dr. Boison investigated the situation and the three remaining mice have been euthanized.

Describe actions taken to prevent this type of event in the future:

Dr. Boison met with [REDACTED] on 4/19 to discuss the situation and to instruct him to get formal approval from the IACUC for his intended SUDEP studies. Dr. Boison will also bring up IACUC compliance at the next staff meeting on 4/23 and remind technicians to help maintaining IACUC compliance by cross checking whether any experiments they have been asked to do by their supervisors (Research Associates or Postdocs) are approved by the IACUC.

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5. Usage of collected tissues

The brain and liver tissues from those 37 naïve mice (Adk-tg and CamKII-Adk-L mouse lines) were collected on different dates (see attachment C). The cortex and hippocampi collected from Adk-tg mice and wild-type controls were used for Western blot study (NNMT, DNMT, SOD, and ADK) to evaluate their potential relationship between ADK-L. The tissues collected from CamKII-Adk-L mice were stored in -80C WITHOUT conducting any experiments.

** CamKII-Adk-L mice tissues were NOT used for any experiment, while Adk-tg mice brain tissues were used for Western blot study.*

Attachment list:

- A.** Email communications regarding mice request
- B.** Email communications regarding Dr. Boison's decisions of the use of CamKII-Adk-L mice
- C.** List of used (sacrificed) mice and detailed info.
- D-G.** Email communications regarding official assigned mice list for this experiment.

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Attachment C

Strain	ID	Born	Sac'd	Genotype	Tissue Collected	sex
CAMKIIa-Adk(long)	#B2074	1/25/2018	2/28/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2075	1/25/2018	2/28/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2076	1/25/2018	2/28/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2077	1/25/2018	2/28/2018	CAMKIIa-ADKL (+/-)	LV, CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#82078	1/25/2018	2/28/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2079	1/25/2018	2/28/2018	CAMKIIa-ADKL (+/-)	LV, CX, CB, HP, ST, OL	m
Adk-tg	#B2003	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	F
Adk-tg	#B2004	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	F
Adk-tg	#B2005	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	m
Adk-tg	#B2006	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	m
Adk-tg	#B2007	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	m
Adk-tg	#B2008	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	m
Adk-tg	#B2009	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	m
Adk-tg	#B2010	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	m
Adk-tg	#B2011	1/7/2018	2/2/2018	Tg (+)cre(-) Adk(-/-)	LV, CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2028	1/5/2018	2/2/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2029	1/2/2018	2/2/2018	CAMKIIa-ADKL (+/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2030	1/2/2018	2/2/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2031	1/2/2018	2/2/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2035	1/7/2018	2/2/2018	CAMKIIa-ADKL (-/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2036	1/7/2018	2/2/2018	CAMKIIa-ADKL (+/-)	LV, CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2194	3/8/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2195	3/8/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2196	3/8/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2197	3/8/2018	4/9/2018	CAMKIIa-ADKL (+/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2198	3/8/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2199	3/8/2018	4/9/2018	CAMKIIa-ADKL (+/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#82200	3/8/2018	4/9/2018	CAMKIIa-ADKL (+/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2201	3/8/2018	4/9/2018	CAMKIIa-ADKL (+/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2140	2/17/2018	4/9/2018	CAMKIIa-ADKL (+/-)	CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2141	2/17/2018	4/9/2018	CAMKIIa-ADKL (+/-)	CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2142	2/17/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2143	2/17/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	f
CAMKIIa-Adk(long)	#B2144	2/17/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#82145	2/17/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#82146	2/17/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	m
CAMKIIa-Adk(long)	#B2147	2/17/2018	4/9/2018	CAMKIIa-ADKL (-/-)	CX, CB, HP, ST, OL	m

Attachment D

(b) (6)

From: [REDACTED]
Sent: Sunday, January 28, 2018 21:32
To: [REDACTED] (b) (6)
Subject: adk tg and camkila adk long

Hi (b) (6)

I just weaned 9 adk-tg mice and 6 camkila adk-long for you. They are 3 weeks old.
I put them in your rack, you can find their information via "Green rack for investigators."

FYI, Camkila/adk-long (-/-) is the same as wild-type.

Let me know if you have any questions.

Thank you

Adk-tg	#B2003 F	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1	(b) (6)	110-- 2017
Adk-tg	#B2004 F	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1		110-- 2017
Adk-tg	#B2005 m	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1		110-- 2017
Adk-tg	#B2006 m	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD8		110-- 2017
Adk-tg	#B2007 m	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1		110-- 2017
Adk-tg	#B2008 m	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1		110-- 2017
Adk-tg	#B2009 m	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1		110-- 2017
Adk-tg	#B2010 m	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1		110-- 2017
Adk-tg	#B2011 m	1/7/2018	Tg (+)cre(-) Adk(-/-) ATD1		110-- 2017
CAMKIIa-Adk(long)	#B2028 f	1/5/2018	CAMKIIa-ADKL (-/-) ADKL9(2)		110-- 2017
CAMKIIa-Adk(long)	#B2029 f	1/2/2018	CAMKIIa-ADKL (+/-) ADKL2(2)		110-- 2017
CAMKIIa-Adk(long)	#B2030 f	1/2/2018	CAMKIIa-ADKL (-/-) ADKL2(2)		110-- 2017
CAMKIIa-Adk(long)	#B2031 f	1/2/2018	CAMKIIa-ADKL (-/-) ADKL2(2)		110-- 2017
CAMKIIa-Adk(long)	#B2035 f	1/7/2018	CAMKIIa-ADKL (-/-) ADKL2		110-- 2017

CAMKIIa-
Adk (long)

#B2086 ff

1/7/2018

CAMKIIa-ADKL
(+/+)

ADKL2



11/10/2017

Attachment E

(b) (6)

From: (b) (6)
Sent: Sunday, February 18, 2018 21:27
To: (b) (6)
Cc:
Subject: camklla-adk long

Hi (b) (6)

I just weaned 6 more Camklla-Adk (Long). They are 3 weeks old. You can find them in (b) (6) rack and in "green rack for investigator" WS.

Thank you
(b) (6)

CAMKIIa-Adk(long)	#B2074	f	1/25/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2075	f	1/25/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2076	f	1/25/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2077	m	1/25/2018CAMKIIa-ADKL (+/-)
CAMKIIa-Adk(long)	#B2078	m	1/25/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2079	m	1/25/2018CAMKIIa-ADKL (+/-)

Attachment F

Haiying Shen

From: (b) (6)
Sent: Monday, March 12, 2018 19:45
To: (b) (6)
Subject: camklla adk-long

Hi (b) (6)

They are the most recent Camklla Adk(Long) mice that I just weaned. They are 3 weeks old now.

CAMKIIa-Adk(long)	#B2140 f	DOB: 2/17/2018	CAMKIIa-ADKL (+/-)
CAMKIIa-Adk(long)	#B2141 f	2/17/2018	CAMKIIa-ADKL (+/-)
CAMKIIa-Adk(long)	#B2142 f	2/17/2018	CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2143 f	2/17/2018	CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2144 m	2/17/2018	CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2145 m	2/17/2018	CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2146 m	2/17/2018	CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2147 m	2/17/2018	CAMKIIa-ADKL (-/-)

- (b) (6)

Attachment G

(b) (6)

From: [REDACTED]
Sent: Monday, April 02, 2018 13:29
To: [REDACTED] (b) (6)
Subject: CamkIIa-adk long

Hi [REDACTED] (b) (6)

I just weaned 8 F+M CamkIIa-Adk long and they are 3 weeks old.
They are in your colony.
Let me know if you have any questions.
Thank you
-

CAMKIIa-Adk(long)	#B2194	f	DOB:3/8/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2195	f	3/8/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2196	m	3/8/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2197	m	3/8/2018CAMKIIa-ADKL (+/-)
CAMKIIa-Adk(long)	#B2198	m	3/8/2018CAMKIIa-ADKL (-/-)
CAMKIIa-Adk(long)	#B2199	m	3/8/2018CAMKIIa-ADKL (+/-)
CAMKIIa-Adk(long)	#B2200	m	3/8/2018CAMKIIa-ADKL (+/-)
CAMKIIa-Adk(long)	#B2201	m	3/8/2018CAMKIIa-ADKL (+/-)



Legacy Research Institute
1225 N.E. Second Ave.
Portland, OR 97232
503.413.2491 phone
503.413.4942 fax

May 31, 2018

Detlev Boison, Ph.D.
Chair, Neurobiology Research
Legacy Research Institute
1225 NE 2nd Ave.
Portland, OR 97232

Dear Dr. Boison:

Re: **DEVIATIONS REPORTS: Adenosine Kinase and Cancer, 110-2018, dated 4-10-18 and 4-11-18;** (b) (6)
(b) (6) **dated 4-16-18**

At the meeting of May 23, 2018, Legacy IACUC reviewed the following deviations reports submitted by you on April 19, 2018 as well as follow-up information you submitted via email on April 27, 2018:

- DEVIATION REPORT: 5-10-18: **Adenosine Kinase and Cancer, 110-2017**; Submitted by: D. Boison
- DEVIATION REPORT: 5-11-18: **Adenosine Kinase and Cancer, 110-2017**; Submitted by: D. Boison
- DEVIATION REPORT: 5-16-18: (b) (6) Submitted by: D. Boison, PhD

The IACUC also reviewed a separate deviation report submitted by (b) (6) dated 5-11-18 offering additional information about the deviations you submitted:

- DEVIATION REPORT: 5-11-18: "Memo regarding use of Adk-tg and CamKII-Adk-L(Tg) mice"; Submitted by (b) (6)

The IACUC acknowledged the information submitted in these reports and determined the following:

- Experiments carried out by (b) (6) ostensibly for support of your protocol **Adenosine Kinase and Cancer, 110-2017** were conducted in your lab, but were not approved by the IACUC.
- Because of the different accounts of how the experiments conducted by (b) (6) were developed and discussed by you and by members of your staff, the IACUC could not determine whether or not these experiments had been conducted with your approval and under your direction.
- The data from these experiments conducted by (b) (6) should not be destroyed, used, published or relied upon for further projects. All documentation and data regarding these experiments should be preserved and placed into secure storage until further notice.
- The IACUC determined that a total of N=34 mice (N=29 three-week old ADK-L transgenic and N=5 wild-type mice) were used (N=22 ADK-L transgenics) and intended to be used (N=12, including 5 wild-type) for the unapproved experiments by (b) (6). These mice were housed in cages that referenced **Adenosine Kinase and Cancer, 110-2017**, but also referenced a project entitled "Aging Study", a project or sub-study that has not been approved by the IACUC for the cancer protocol. Cage cards for this project were generated and attached to housing for mice to be used for this unapproved project. (b) (6)

(b) (6) euthanized 22 of these mice and intended to euthanize the remaining 12 mice for post mortem tissues studies that had not been approved by the IACUC. As a result of your intervention, the latter 12 mice still housed in these cages were not used in any experiment.

- The IACUC found that the display of cage cards on housing for the unapproved "Aging Study" was not clearly explained or resolved by you or (b) (6) nor was there clarity among members of your lab for how mice are to be transferred from your IACUC-approved breeding protocol to any other IACUC-approved protocol. The IACUC recognizes that you are in the process of establishing a clear and more robust system for managing this process and ensuring compliance among all members of the lab.
- The IACUC found that both you and (b) (6) believed that animals from the breeding protocol could be sacrificed for tissue studies not related to specific protocols approved by the IACUC.
- The IACUC found that mentorship, management and overall supervision of staff in your lab is deficient and inadequate with regard to the conduct of research overseen by the IACUC. The IACUC notes that additional concerns (separate from these deviations) regarding personnel conducting animal research in your lab demonstrate unequivocally that a substantial investment in training of senior investigators, as well as junior lab members (post docs) is mandated.
- The deviation reports submitted to the IACUC, as well as the findings and determinations made by the IACUC, and the corrective actions you submit will be reported to the Office of Laboratory Animal Welfare (OLAW) as soon as all the information is received pertaining to these deviations.

Based on these findings and determinations, the IACUC requires that you address the following concerns and provide a detailed corrective action plan for each concern. As you are ultimately responsible for compliance with IACUC requirements, the IACUC requires that the corrective action plan should include a detailed timeline for completion of all corrective actions requested, and that your corrective actions should be submitted to the IACUC within 25 days of the date of this letter.

1. The IACUC is concerned that you and many of your staff need additional training in compliance with IACUC oversight and would benefit greatly from further formal training. Therefore, the following staff in your office should undergo training in IACUC review, procedures and compliance:

- Detlev Boison, PhD

- (b) (6)
-
-
-

Your corrective actions for this re-training requirement should include specific training for each study staff appropriate to their position, role, and experience in your lab. Documentation of attendance at appropriate training is required for all staff. The IACUC strongly recommends upcoming local training sponsored by IACUC 101™ Series entitled IACUC 101 and IACUC 301 with OSU, OHSU, Portland VA, and UO on June 13-14, 2018 in Portland, Oregon; <https://s08.123signup.com/event/details/hzdqz>.

Please note that these course offerings occur prior to the end of the 25-day window for the IACUC receiving your detailed corrective action plan (cited above).

2. The IACUC is concerned that proposed projects and plans for research are miscommunicated to and/or misinterpreted by relevant staff. Therefore, meetings in your lab where new projects and future studies are discussed, planned or approved by you should be documented to include the following details: whether the projects are formally approved by you or not, whether amendments for an approved IACUC protocol need to be submitted to the IACUC and who is responsible for those submissions, whether new

protocols need to be designed and submitted to the IACUC, or whether the proposed projects fall under existing approved protocols or are outside the oversight of the IACUC.

3. The IACUC is concerned that many standard procedures regarding animal welfare in your lab are not clearly understood and/or not being followed. Therefore, schedule and provide additional training to your staff regarding the following, which you have briefly outlined as standard procedures or new corrective actions in your deviation report dated 4-11-18:
 - Animal Breeding and Transfer procedures;
 - Organ extraction proposals and approval by the IACUC;
 - Labeling of cage cards procedures;
 - The procedure to ensure that there is 1:1 correspondence between a protocol and activity. If no such procedure currently exists, one should be developed for your lab and staff training should be done to ensure such procedures are followed.
4. Provide a current census of animals, including those animals in the breeding colony and those approved for experimental activities;
5. Please respond to the requirements of this letter within 25 days of the date of this letter.

The Legacy IACUC is authorized by USDA license (92-R-0002) and is governed by an assurance with Office of Laboratory Animal Welfare (A3234-01) as well as Legacy Policy (100.16). The Legacy animal care program also maintains full AAALAC accreditation (Unit #000992).

If have questions, please contact

(b) (6)

(b) (6)@lhs.org.

Sincerely,

(b) (6)

Cc:

Brad Fortune, Chair

Joe Frascella, LRI VP of Research

Joe Cioffi, LRI Senior Director of Research



Detlev Boison, PhD

Director of Basic and Translational Research, Legacy Research Institute
Chair and Director, Robert Stone Dow Neurobiology Laboratories
Co-Director, Wayne D. Kuni & Joan E. Kuni Laboratory of Cancer Research
Adjunct Professor, Dept. of Neurology, Oregon Health and Science University
Adjunct Professor, Dept. of Veterinary Medicine, Washington State University
Legacy Research Institute
1225 NE 2nd Avenue
Portland, OR 97232

June 12, 2018

(b) (6)

(b) (6)

(b) (6) Fax

dboison@downeurobiology.org

RE: **DEVIATION REPORTS: Adenosine Kinase and Cancer, 110-2018, dated 4-10-18 and 4-11-18;** (b) (6) dated 4-16-18

Dear (b) (6)

Dear members of the Legacy IACUC:

In response to your letter from May 31, 2018 please find below a response and detailed action plan for each concern:

1. To obtain additional training in compliance with IACUC oversight Detlev Boison, PhD, (b) (6) (b) (6) have registered for and will attend the IACUC 101TM Series entitled IACUC 101 and IACUC 301 (organized by OSU, OHSU, Portland VA, and UO) on **June 13-14, 2018** in Portland, Oregon. After successful completion of the training, documentation will be submitted to the Legacy IACUC.
2. To avoid miscommunication and misinterpretation of research projects and plans the following measures have been taken:
 - (A) Beginning in **April 2018** we implemented a new internal rodent order form, which now is routinely used to request experimental animals from our breeding colony. The rodent request form details purpose of rodent order, planned experiment or procedure, IACUC protocol number, and details regarding the requested animals (number, sex, age). This form needs to be signed by Dr Boison. Our animal colony technician (b) (6) is authorized to release animals only, when animal use has been approved by Dr Boison.
 - (B) Beginning **June 11, 2018** all formal project discussions are handled in different project specific focus group meetings or in designated ad hoc meetings, if needed. Those are group discussions involving all investigators associated with a given project. Those discussions will be documented in written minutes, which will detail whether experiments have been approved by Dr Boison, whether experiments are covered under current IACUC protocols, or whether amendments are needed. In the latter case, it will be determined who is going to submit an amendment.
 - (C) We already implemented monthly animal breeding meetings to discuss logistics surrounding animal use and breeding needs. From **June 11, 2018** onwards this meeting has been expanded to a designated "animal use meeting" with mandatory attendance for all animal users (Research Associates, Postdoc, Technicians). This meeting will be scheduled every two weeks. During each meeting, everyone is expected to give a full account of all planned animal use in the upcoming two weeks and to provide evidence that all procedures are approved.
 - (D) At the general all-staff 8:30 lab meeting on **June 11, 2018** Dr Boison instructed the team to update the project board and to include more details. The project board, which is visible to all, should include a summary of the current status of ALL ongoing research projects in the entire lab. New items to be included on the board are current IACUC approval status for each experiment involving animals.

3. To provide additional training to my staff, during the animal use meeting on June 11, 2018 Dr Boison has provided training and discussed procedures regarding the following:

- **Animal breeding and transfer procedures:**
Implementation of a new form to be signed by Dr Boison, will guarantee that animals are only transferred from breeding to experimental use, if proper information (purpose of experiment, animal numbers, IACUC approval) is provided.
- **Organ extraction proposals and approval by the IACUC:**
Dr Boison informed the entire team that having animals and using them for organ extraction, requires adequate IACUC approval.
- **Labelling of cage card procedures:**
The following has been implemented: The responsible person for correct content on cage cards is the investigator who requested the animals. This investigator is responsible for proper cage card content and is required to check cage cards for accuracy, once cage cards have been printed and attached to the cage.
- **Development of a procedure to ensure 1:1 correspondence between a protocol and activity:**
The following has been implemented: All animal use information including experimental data are to be deposited in a publicly accessible IACUC folder (in project specific subfolders); this allows for transparency of procedures performed.

4. The June 4, 2018 census of our animals is:

110--2017	3
111--2017	28
114--2017	31
115--2017 (breeding cages)	52
115--2017	27
116--2017	13

We currently do not have any rats in our animal colony.

I sincerely hope to have addressed all concerns in a satisfactory manner. Please feel free to reach out to me in case there are any remaining questions or concerns.

Sincerely,

(b) (6)

Detlev Boison

Certificate of Attendance

June 14, 2018 - Portland, OR

Scenarios



Oregon State

**IACUC
101TM Series**



National Institutes of Health
Office of Laboratory Animal Welfare



**Detlev Boison
Legacy Research Institute**

A handwritten signature in black ink, appearing to read "Mary Lou James".

**Mary Lou James, BA, LATg, CPIA
Executive Director, IACUC 101TM Series**

Course meets the requirements for 6.0 hours of continuing education credit in jurisdictions which recognize AAWSB RACE approval; however participants should be aware that some boards have limitations on the number of hours accepted in certain categories and/or restrictions on certain methods of delivery of continuing education.

State(s) of Licensure: _____

License #(s): _____

Subject Matter Category: Legal
IACUC 101TM Series, St. Louis, MO

Program No. 556-28631

Delivery: Seminar/Lecture
RACE Provider #356

Certificate of Attendance

JUNE 13, 2018 - Portland, OR

The Basics



Oregon State

IACUC 101TM Series



National Institutes of Health
Office of Laboratory Animal Welfare



Detlev Boison

Legacy Research Institute

Mary Lou James, BA, LATG, CPIA
Executive Director, IACUC 101TM Series

Course meets the requirements for 6.5 hours of continuing education credit in jurisdictions which recognize AAASB RACE approval; however participants should be aware that some boards have limitations on the number of hours accepted in certain categories and/or restrictions on certain methods of delivery of continuing education.

State(s) of Licensure: _____
State(s) of Licensure: _____

Subject Matter Category: Legal
Subject Matter Category: Legal
IACUC 101TM Series, St. Louis, MO

Program No 55628835

License # (s):

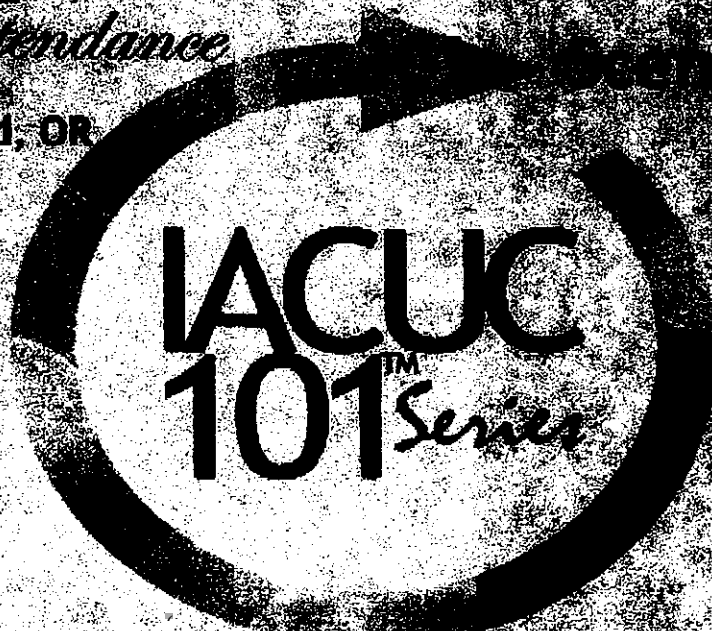
Delivery: Seminar/Lecture
RACE Provider #556

Certificate of Attendance

June 14, 2018 • Portland, OR



Oregon State



(b) (6)

Legacy Research Institute

Mary Lou James, BA, LATg, CPIA

Executive Director, IACUC 101™ Series

Course meets the requirements for 6.0 hours of continuing education credit in jurisdictions which recognize AAVSB RACE approval; however participants should be aware that some boards have limitations on the number of hours accepted in certain categories and/or restrictions on certain methods of delivery of continuing education.

Date(s) of Attendance: _____

Subject Matter Category: Legal
IACUC 101 Series, St. Louis, MO

Program No. 556-28631

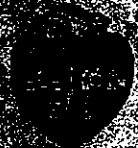
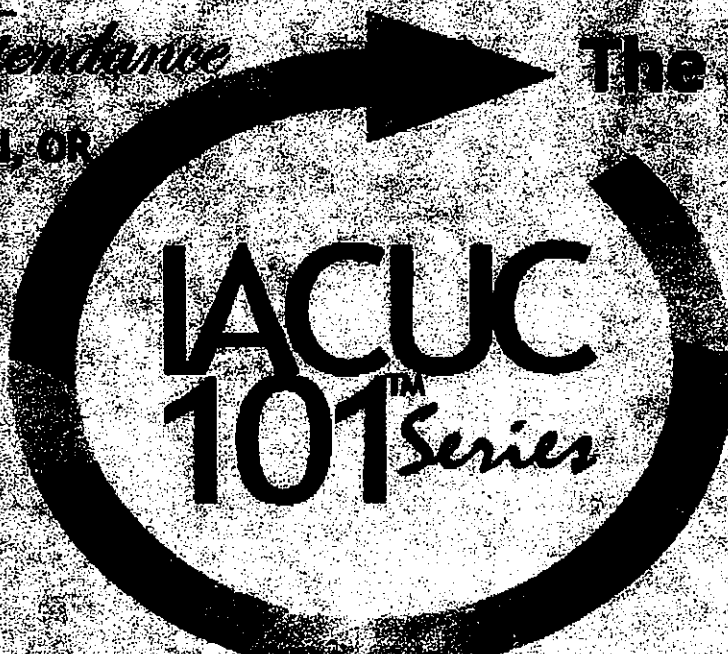
License # (s): _____

Delivery: Seminar/Lecture
RACE Provider #235

Certificate of Attendance

The Basics

June 13, 2018, Portland, OR



(b) (6)

Legacy Research Institute

Mary Lou James, BA, LATg, CPIA
Executive Director, IACUC101™ Series

Course meets the requirements for 6.5 hours of continuing education credit in jurisdictions which recognize AAVSB RACE approval. However, participants should be aware that some boards have limitations on the number of hours accepted in certain categories and/or restrictions on certain methods of delivery of continuing education.

Signature of Licensee: _____

License #(s): _____

Signature of Licensee: _____
IACUC101™ Series, St. Louis, MO

Program No. 556-25875

Delivery: Seminar/Lecture
RACE Provider #556

Certificate of Attendance

June 13, 2018 - Portland, OR

The Basics



Oregon State

IACUC
101TM Series



National Institutes of Health
Office of Laboratory Animal Welfare



(b) (6)

Legacy Research Institute

A handwritten signature in black ink, appearing to read "M. L. James".

Mary Lou James, BA, LATg, CPIA

Executive Director, IACUC101TM Series

Course meets the requirements for 6.5 hours of continuing education credit in jurisdictions which recognize AAVSB RACE approval; however participants should be aware that some boards have limitations on the number of hours accepted in certain categories and/or restrictions on certain methods of delivery of continuing education.

State(s) of Licensure: _____

License #(s): _____

Subject Matter Category: Legal
IACUC 101TM Series, St. Louis, MO

Program No. 556-25875

Delivery: Seminar/Lecture
RACE Provider #556

Certificate of Attendance

June 14, 2018 - Portland, OR

Scenarios



Oregon State

IACUC 101TM Series



National Institutes of Health
Office of Laboratory Animal Welfare



(b) (6)

Legacy Research Institute

Mary Lou James, BA, LATg, CPIA

Executive Director, IACUC 101TM Series

Course meets the requirements for 6.0 hours of continuing education credit in jurisdictions which recognize AAASB RACE approval; however participants should be aware that some boards have limitations on the number of hours accepted in certain categories and/or restrictions on certain methods of delivery of continuing education.

State(s) of Licensure: _____

License #(s): _____

Subject Matter Category: Legal
IACUC 101TM Series, St. Louis, MO

Program No. 55628631

Delivery: Seminar/Lecture
RACE Provider #526

Attendance

Scenarios

Portland, OR

IACUC
101TM Series



National Institutes of Health
National Institutes of Health
Office of Laboratory Animal Welfare



(b) (6)

University Research Institute

University Research Institute

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License #s:

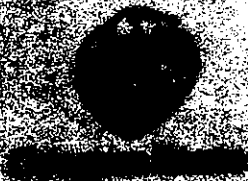
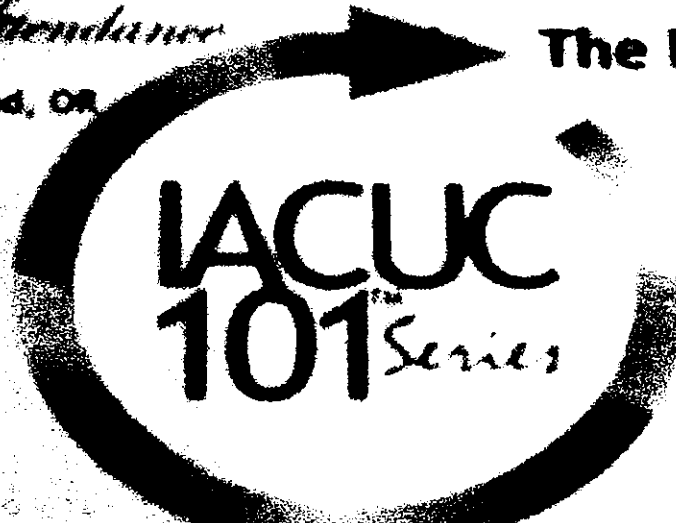
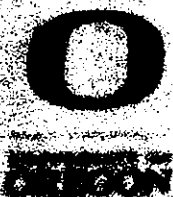
Deputy Seminar/Lecture

PAGE Broader #556

Certificate of Attendance

June 13, 2018 - Portland, OR

The Basics



(b)(6)

Legacy Research Institute

[Signature]

Barry Lee Jones, BA, LMS, CPA

Executive Director, IACUC 101 Series

This certificate is awarded to the following individual(s) for attending the IACUC 101 Series training session on the number of hours of training completed. The number of hours of training completed is recorded on the certificate.

Signature:

Delivery Method: Online
File Name: [illegible]



Legacy Research Institute
1225 NE Second Ave.
Portland, OR 97232
503.441.3240 / 1.800.472.2232
503.441.3442 fax

June 21, 2018

Denley Boison, Ph.D.
Chair, Neurobiology Research
Legacy Research Institute
1225 NE 2nd Ave.
Portland, OR 97232

Dear Dr. Boison:

Re: **DEVIATIONS REPORTS: Adenosine Kinase and Cancer, 110-2018, dated 4-10-18 and 4-11-18;**
(b) (6) **dated 4-16-18; RESPONSE LETTER 6-12-18**

At the meeting of June 21, 2018, Legacy IACUC reviewed your letter dated June 12, 2018 to the IACUC's previous request for information and corrective actions for the above deviations reports. The IACUC also reviewed the IACUC training records from yourself and others who attended the Portland IACUC training on June 13-14, 2018. The IACUC has received the training documents from all staff you required to attend the training.

The IACUC acknowledged and accepted the corrective actions with additional clarifications required:

- Dr. Jennifer Wilk, DVM, should be consulted on how best to ensure that IACUC approval of "organ extraction" procedures or protocols are implemented, as some current protocols may require specific amendments to specifically include organ extraction. Alternatively, some organ extraction may be appropriate under the current breeding protocol. Please confirm that you will consult with Dr. Wilk to ensure that all organ extraction procedures are submitted for IACUC approval, and that all staff understand the procedures for this activity.
- Regarding your plan outline in your letter detailing the recording of minutes of meetings where projects are discussed among staff, the IACUC requires that those minutes be made available upon request to the IACUC and to the LRI VP of Research, Dr. Joe Frascella. Please confirm.

The Legacy IACUC is authorized by USDA license (92-R-0002) and is governed by an assurance with Office of Laboratory Animal Welfare (A3234-01) as well as Legacy Policy (100.16). The Legacy animal care program also maintains full AAALAC accreditation (Unit #000992).

If have questions, please contact

(b) (6) at

(b) (6)

(b) (6) @lms.org.

Sincerely,

(b) (6)

Cc:

Brad Fortune, Chair

Joe Frascella, PhD, VP of Research

Joe Cioffi, PhD, Direct of Research



ROBERT STONE DOW NEUROBIOLOGY LABORATORIES

Detlev Boison, PhD

Director of Basic and Translational Research, Legacy Research Institute
Chair and Director, Robert Stone Dow Neurobiology Laboratories
Co-Director, Wayne D. Kuni & Joan E. Kuni Laboratory of Cancer Research
Adjunct Professor, Dept. of Neurology, Oregon Health and Science University
Adjunct Professor, Dept. of Veterinary Medicine, Washington State University
Legacy Research Institute
1225 NE 2nd Avenue
Portland, OR 97232

June 25, 2018

(b) (6)
Legacy Research Institute

(b) (6)
(b) (6) Fax
dboison@downeurobiology.org

RE: **DEVIATION REPORTS: Adenosine Kinase and Cancer, 110-2018, dated 4-10-18 and 4-11-18;** (b) (6) dated 4-16-18

Dear (b) (6)

Dear members of the Legacy IACUC:

In response to your letter from June 21, 2018 I am pleased to provide the following clarifications:

1. I have invited Dr. Jennifer Wilk to attend our bi-weekly 'Animal Use Meeting' to discuss IACUC compliance and to engage my team in interactions with our Attending Veterinarian. I will take this opportunity to consult with Dr. Wilk on compliance issues regarding "organ extraction" procedures and protocols and we will have a direct communication about those issues and the required regulations with my research team.
2. I confirm that minutes from our project meetings and animal use meetings will be made available upon request to the IACUC and to the LRI VP of Research, Dr. Joe Frascella.

Sincerely,

(b) (6)

Detlev Boison

From: Wolff, Axel (NIH/OD) [E]
Sent: Wednesday, April 18, 2018 7:06 AM
To: (b) (6)
Subject: RE: Legacy Research Institute, Portland, Oregon, reportable events

Thank you for this preliminary report, (b) (6) I will start a new case file and look forward to receiving the final report from the IO after the IACUC has completed its investigation.

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

From: (b) (6)@LHS.ORG]
Sent: Tuesday, April 17, 2018 5:39 PM
To: Wolff, Axel (NIH/OD) [E] <wolffa@od.nih.gov>
Cc: Fortune, Brad :LRI Research <bfortune@deverseye.org>; Wilk, Jennifer L :LRI Dir Comparative Medicine <JENWILK@lhs.org>; Frascella, Joe :LRI VP Research <JFRASCEL@LHS.ORG>; Cioffi, Joe :LRI Sr Dir Research Administration <JOCIOFFI@LHS.ORG>
Subject: Legacy Research Institute, Portland, Oregon, reportable events

Dear Dr. Wolfe,

I am the regulatory compliance specialist and IACUC Administrator for our institution. Dr. Brad Fortune is the IACUC Chair and Dr. Jennifer Wilk is the Attending Vet at Legacy Research Institute (LRI). Dr. Joe Frascella is the Institutional Official for LRI, and Dr. Joseph Cioffi is the Senior Director of Research.

I am contacting you to advise that we have two events that we believe should be reported to OLAW. We are in the earliest phase of gathering the information and will have more information submitted to us by the relevant investigator at the end of this week.

In the first instance a minor procedure (injection of an experimental agent) was performed. The procedure was listed in the grant application, but had not been added to the approved IACUC protocol.

In the second instance, a group of mice were transferred from a breeding protocol to an experimental protocol, but the strain of mice are not listed on the experimental protocol. These animals were euthanized for tissue collection; investigation is underway to determine whether any other procedures occurred premortem.

We will be providing more detailed information to your office as soon as it becomes available.

Thank you,

(b) (6)

(b) (6)