DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive - MSC 7982
Bethesda, Maryland 20892-7982
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive
Bethesda, Maryland 20817
Telephone (301) 496-7163
Facsimile (301) 402-2803

February 10, 2008

Re: Animal Welfare Assurance
A3196-01 [OLAW Case 3T]

Dr. Roberto Peccei
Vice Chancellor for Research
University of California, Los Angeles
405 Hilgard Avenue
Los Angeles, CA 90024-1405

Dear Dr. Peccei,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your January 31, 2008 letter reporting the suspension of an animal activity at the University of California- Los Angeles, following up on an initial email report on August 17, 2007. According to the information provided, OLAW understands that the veterinarian initially suspended the activity after which the Institutional Animal Care and Use Committee/Animal Research Committee (IACUC/ARC) voted to suspend the research protocol involving rabbit surgery. The reasons for the suspension consisted of numerous violations including work being conducted with animals by two individuals who were not listed on the protocol, improper carrying of the rabbits, an unattended rabbit in a cage with an open door, problems with administration of medications, difficulty of rabbits in accessing food due to Elizabethan collars, and staff not weighing the rabbits as required by the protocol. In addition, the rabbits were not being appropriately monitored post-operatively, there was an insufficient acclimation period prior to surgery, and the protocol did not specify humane endpoints when rabbits became paralyzed. Four rabbits were still on study following the suspension and the Principal Investigator was directed to conduct a terminal procedure. The PI failed to euthanize the rabbits in a timely fashion as directed.

The IACUC directed the veterinary staff to euthanize the rabbits and the protocol remained suspended. The PI had submitted a list of proposed corrective actions consisting of the development of a laboratory folder with checklists and relevant policies, counseling of staff, ongoing laboratory meetings to address animal issues, and assurance that the PI will work with the Division of Laboratory Animal Medicine. Although this plan was acceptable to the IACUC, the failure of the PI to euthanize the rabbits created doubt about his ability to comply with the regulations. Prior to allowing animal activities to resume the IACUC has required the investigative staff to undergo retraining, to work under direct veterinary oversight, and to submit ongoing post-surgery status reports to the IACUC. Continuation of approval of the research will be dependent on the IACUC's assessment of the reports. The suspension was lifted by the IACUC and the protocol, which had meanwhile expired, is currently under review. Continued approval of the protocol will be contingent upon compliance with the regulations.

Based on the information provided, OLAW is satisfied that appropriate actions have been taken to investigate, correct, and prevent recurrence of the noncompliance. OLAW understands that the protocol involved was not PHS-supported, but concurs that the incidents were serious and supports the actions taken by the IACUC. The establishment and application of policies and practices that are consistent with the provisions of the PHS Policy on Humane Care and Use of Laboratory Animals at UCLA are commendable and avoid the perception of a double standard.

Thank you for keeping OLAW apprised on this matter.

Sincerely,

Axel Wolff, M.S., D.V.M.
Director,
Division of Compliance Oversight

cc: William McBride, Ph.D., IACUC Chair
Kathy Wadsworth, Associate Director-Animal Subjects Research
Robert Gibbens, D.V.M., Western Regional Director, AC-APHIS-USDA

UCLA
UNIVERSITY OF CALIFORNIA,
LOS ANGELES

ROBERTO PECCEI
Vice Chancellor for Research

Box 951405
Los Angeles, CA 90095-1405
phone: 310-825-7943
fax: 310-206-6030
rpeccei@conet.ucla.edu

January 31, 2008

Axel V. Wolff, M.S., D.V.M.
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982

RE: Final Report of Incident of Noncompliance
Animal Welfare Assurance A3196-01

Dear Dr. Wolff:

I am writing to provide you with a final report regarding a suspension of activities, which was initially reported to you by Assistant Director Andrew Perkins on August 17, 2007, in accordance with PHS Policy IV.C.8[1]. As noted in the previous report, the protocol is not federally funded. As the protocol involves a USDA-covered species, Mr. Perkins also notified the USDA on August 17, 2007.

As noted in the initial report, the Chancellor's Animal Research Committee (ARC) met August 13, 2007 to review the actions that lead the veterinarian to suspend the animal activities July 31, 2007. In light of the concerns delineated in the initial report to OLAW, the ARC voted to suspend the protocol pending review and acceptance of a corrective action plan to address each of the ARC's concerns. At that time, the ARC noted that the investigator had four rabbits under study that would reach the experimental endpoint within the next several weeks. Since the inability to perform a follow-up analysis of these rabbits would required the use of additional animals at a later time, the investigator was advised that the ARC would consider authorizing the follow-up terminal procedures on the four animals provided that 1) certified and approved personnel were available to conduct the procedures, 2) failure to euthanize the animals at the specified

[1] PHS Policy IV.C.8, *"If the IACUC suspends an activity involving animals, the Institutional Official in consultation with the IACUC shall review the reasons for suspension, take appropriate corrective action, and report that action with a full explanation to OLAW"*

time point would not permit the collection of usable data from the animals, and 3) that the investigator could adequately justify these actions. Alternatively, in lieu of terminal surgery, the ARC authorized the Division of Laboratory Animal Medicine (DLAM) veterinary staff to carry out euthanasia of the animals for postmortem tissue analysis if this would not interfere with the research results.

On August 31, 2007, ARC Chair William McBride, Campus Veterinarian Marcelo Couto and Associate Director Kathy Wadsworth met with the PI to discuss the Committee's actions and to assist the PI in developing an effective corrective action plan. As recommended by Drs. McBride, Couto, and Ms. Wadsworth, the PI agreed to implement the following:

I. Development of a New Staff training folder to be provided to all new staff in his lab.
The folder will contain items likely to be helpful to new staff, including:

   1. A check list to be completed prior to the use of lab animals.

   2. A copy of ARC certification information:
   http://www.oprs.ucla.edu/animal/certification-info

   3. General ARC policies pertaining to his lab, as found on the ARC website. Some examples include:

      - The ARC Policy on Notification of Investigators with Sick or Injured Animals
      - The ARC Policy on Procedures Performed on USDA-Covered Species Involving the Use of General Anesthesia
      - The ARC Policy on Survival Surgery in USDA-Covered Species

II. He provided his assurance that he will contact Associate Director Wadsworth to arrange for an ARC/DLAM Educational lab meeting, to be attended by the PI and his lab staff, prior to scheduling the next animal procedure.

III. Additionally, the PI provided his assurance that he will continue to meet with his lab staff on a regular basis to discuss the protocol, husbandry issues, and the ongoing progress of the animal research.

IV. Lastly, the PI provided his assurance that he will work closely with DLAM on any future husbandry matters pertaining his animal research.

The above corrective action plan was found to be acceptable; however, the ARC expressed serious concern that the PI failed to comply with the Committee's determination regarding the remaining rabbits. Specifically, on September 19, 2007, the ARC was notified that none of the remaining rabbits had been euthanized as directed by the ARC. Upon finding the rabbits, a member of the DLAM veterinary staff contacted

the PI to inquire about why the animals had not been euthanized. He responded that he was *"planning on euthanizing all three in three weeks."* The Committee expressed concern that the proposed three-week delay *beyond* the three-week delay of the terminal surgeries that had already occurred, was scientifically and ethically unacceptable.

The PI was reminded that the Animal Welfare Act and PHS Policy require that investigators employ humane endpoints to minimize animal pain, distress, and suffering in laboratory animals. Failure to adhere to the approved endpoints established in the protocol constitutes a serious violation of PHS Policy IV.C. Additionally, failure to adhere to the determinations of the ARC constitutes a serious violation of UCLA's Animal Welfare Assurance with the NIH Office of Laboratory Animal Welfare (OLAW). Furthermore, implementation of any significant change to the protocol, such as extending the endpoint approved by the ARC, without prior approval, is a violation of PHS policy IV.C. The Committee therefore directed DLAM veterinary staff to euthanize the three remaining rabbits. The Committee also voted to continue the suspension of the protocol, pending the PI's response to the latest incident of noncompliance.

Though the ARC accepted the PI's aforementioned corrective action plan, and the animals were subsequently euthanized on October 5, 2007, the ARC remained concerned about the PI's ability to continue to comply with all federal, State and local policies and regulations governing the humane care and use of laboratory animals, once he receives approval to resume his study. As such, the Committee imposed the following monitoring plan for ensuring compliance:

1. An ARC/DLAM Educational Meeting will be held *prior* to resuming animal activities. Attending the meeting will be the PI, his lab staff, Associate Director Wadsworth and a member of the DLAM veterinary staff. The purpose of this meeting is to review ARC and DLAM policies and procedures, as well as address any questions or concern his laboratory staff may have.

2. DLAM veterinary oversight is required for all animal surgeries. As such, the PI was instructed to contact the DLAM veterinarian at least five (5) week days prior to each surgery to ensure the availability of a veterinarian at the time of the surgery. The PI was also reminded that surgical procedures with animals may <u>not</u> be conducted unless a member of the DLAM veterinary staff is present at the time of the surgery.

3. Following each animal surgery, the PI must submit a report to the ARC. The report must include:

    - A description of the surgery, including date and time the procedure began
    - The clinical status of the animal pre-surgery, during, and immediately post-surgery
    - The clinical status of the animal 48 hours post-surgery.

- A description of any untoward events, and their resolution.

The ARC further required that the report be submitted no later than five (5) days following the procedure.

4. The ARC will review all reports submitted for consideration of continued approval of this research protocol.

On November 28, 2007, the Committee voted to lift the suspension of this protocol, with the above provisos. Each of the investigator's reports will be reviewed by the convened Committee, at which time the ARC may evaluate the investigator's ability to comply with the ARC's requirements.

During the period of suspension, the previous approval period of the protocol expired, and the PI's continuation application is still undergoing ARC review as of the date of this letter. When approved, a codicil will be applied detailing the above monitoring requirements, and the proviso that continued approval is contingent upon fulfillment of the above, timely submission of the requested reports, and continued compliance with all pertinent regulations, policies and guidelines.

If you have any questions or concerns, please do not hesitate to contact me at (310) 825-7943.

Sincerely,

Roberto Peccei
Vice Chancellor for Research

cc: Dr. William H. McBride, Chair, ARC
Judith L. Brookshire, Director, OPRS
Kathy Wadsworth, Associate Director, Animal Subjects Research

Thank you for this preliminary report, Mr. Perkins. I'll open a new case file and look forward to receiving the final report from the IO.

Axel Wolff, M.S., D.V.M.
Director, Division of Compliance Oversight
OLAW

A3196-3T

From: Perkins, Andrew [mailto:APerkins@OPRS.UCLA.EDU]
Sent: Friday, August 17, 2007 3:26 PM
To: Wolff, Axel (NIH/OD) [E]
Cc: Brookshire, Judith
Subject: IACUC Suspension of Research Activities - Assurance #A3196-01

Dear Dr. Wolfe,

On behalf of the University of California, Los Angeles (UCLA, Assurance #A3196-01), I am writing to provide you with a preliminary report of an IACUC suspension of an approved research protocol. The approved protocol is not federally funded; however, since the suspension involves rabbits, this will also be reported to the USDA.

In particular, the Chancellor's Animal Research Committee (ARC) received a report on July 27, 2007 outlining several allegations of noncompliance involving four rabbits that had recently undergone surgery. The principal investigator was contacted on July 31, 2007 and asked to provide his comments on the following allegations:

1. Two individuals were observed handling laboratory animals prior to completion of all ARC training requirements and prior to their being listed on the approved protocol.

2. One of the individuals was observed holding a rabbit by the hindquarters and by the ears. All personnel are specifically informed during species-specific training for rabbits that holding or lifting these animals by the ears is prohibited.

3. An animal was left unattended in its cage with the door propped open.

4. The two individuals noted above appeared confused regarding the proper administration of post-operative medications.

5. The animals had not been acclimated to the Elizabethan collars that are typically applied to these animals following surgery; the animals were subsequently observed to have difficulty accessing food.

6. Finally, the two individuals appeared unaware that the animals must be weighed daily post-operatively, as specified in the approved protocol, and did not appear to understand how to use the scale.

Pursuant to these allegations, a Division of Laboratory Animal Medicine (DLAM) veterinarian ordered that all future surgeries be postponed pending ARC review of these concerns, in accordance with the *ARC Policy on Authority of the Attending Veterinarian* ("The attending veterinarian may immediately stop research activities under a protocol under a protocol for humane reasons or protocol deviations pending ARC review of an incident"). During a meeting held on August 13, 2007, the ARC reviewed the investigator's response dated August 7, 2007. The investigator provided his assurance that he would add the two above-noted individuals to his research protocol; however, the ARC remained concerned that several outstanding concerns regarding the training of these individuals as well as the oversight provided to his animals had not

been addressed, nor was an appropriate corrective plan provided. During this meeting, the ARC was advised of several additional concerns regarding this study:

1. Staff members did not appear to have been monitoring the investigator's animals during the post-operative period. The investigator was asked that the ARC expects that each principal investigator will ensure that personnel who are fully trained and qualified to assess animal health and well-being will monitor their animals on a daily basis, including weekends and holidays.

2. Animals were not provided a sufficient acclimation period prior to surgery, which may have contributed to several behavioral and health problems observed by the veterinarians following surgery. DLAM policy requires approval of a veterinarian for the use of animals within 7 days of arrival, and ARC policy requires that animals used in survival experiments must be provided a minimum of 48 hours, excluding the day of arrival, for acclimatization.

3. The approved protocol does not specify any humane endpoints concerning post-operative paralysis or paresis, which were involved in two rabbits. As this protocol is due for continuing review within the next two months, the ARC requested that the investigator revise his protocol to clearly identify specific criteria for premature euthanasia for animals that develop these conditions as a result of the surgeries.

In light of the above concerns, the ARC voted to suspend the protocol. The investigator was subsequently advised that no further experiments may be carried out until such time as the ARC has reviewed and accepted a detailed corrective action plan to address each of the ARC's concerns. The investigator was additionally asked to schedule a meeting with the Campus Veterinarian, ARC Chair, and Associate Director-Animal Subjects Research to review these concerns.

The ARC recognized that the investigator currently has four rabbits under study that will reach the experimental endpoint within the next several weeks, and that inability to perform a follow-up analysis of these rabbits may require the use of additional animals. Therefore, the investigator was advised that the ARC may consider authorizing the follow-up, terminal procedures on these four animals provided that 1) certified and approved personnel are available to conduct these procedures, 2) failure to euthanize these animals at the specified timepoint will not permit the collection of usable data from the animals, and 3) the investigator can adequately justify these actions. Alternatively, in lieu of terminal surgery, the ARC authorized the DLAM veterinary staff to carry out euthanasia of the animals for postmortem tissue analysis if this would not interfere with the research results.

A final report will be submitted by our Institutional Official, Vice Chancellor for Research Roberto Peccei, following successful resolution of these concerns.

Please feel free to contact me at (310) 206-7364 if you have any questions.

Sincerely,
Andy

Andrew D. Perkins
Assistant Director, Chancellor's Animal Research Committee
UCLA Office for Protection of Research Subjects
11000 Kinross Ave., Suite 102
Los Angeles, CA 90095-1694
tel (310) 206-7364, fax (310) 794-9565