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June 19, 2007

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Director, Division of Compliance Oversight  
Office of Laboratory Animal Welfare  
National Institutes of Health  
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**RE: Final Report of Suspension of Activities**  
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 Associate Director Kathy Wadsworth on March 5, 2007, in accordance with PHS Policy IV.C.8<sup>1</sup>. The incident was initially reported to the Chancellor's Animal Research Committee (ARC) on February 27, 2007 and involved multiple, serious violations of the ARC Policy on Maintaining Animals in Study Areas (attached). The protocol was not supported by federal funds, and did not involve USDA-covered species.

As Ms. Wadsworth informed you on March 5, 2007, a Specialist from UCLA's Office of Environment, Health and Safety (EH&S) inspected a study room in response to complaints from UCLA staff regarding an animal smell emanating from the room<sup>2</sup>. At that time, the EH&S Specialist noted that mice were housed in the room. When the Biosafety Officer questioned ARC staff about the room, it was noted that the room was

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<sup>1</sup> 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"

<sup>2</sup> The EH&S Specialist gained access to the room via UCLA custodial staff.

approved as a "Research Area" (i.e., an area where animals are held for < 12 hours), but was not approved as a housing location.

On the morning of February 27, 2007, Associate Director Kathy Wadsworth contacted the Principal Investigator responsible for the room, to obtain entry to the room to confirm the EH&S Specialist's findings, and to permit DLAM husbandry staff to inspect the animals' health status. The PI informed Ms. Wadsworth that he did not have the key, but that the room was used by a member of his research staff ("Dr. E") who did have the key.

At 2:00 p.m. of the same day, Ms. Wadsworth, DLAM Executive Director Marcelo Couto, ARC Assistant Director Andrew Perkins, and a DLAM health technician, met with "Dr. E" to inspect the room. Upon entering the room, the following violations of ARC Policy and the *Guide for the Care and Use of Laboratory Animals* were noted:

- Approximately 46 cages of mice were stacked on the lab bench, many stacked three-high, impairing ventilation of the lower cages. "Dr. E" indicated that he had "solved" the ventilation problem by lifting the filter tops to allow more air in. Unfortunately, this resulted in the upper cages appearing precarious and possibly impairing function of the sipper tubes used to provide water to the animals<sup>3</sup>.
- "Dr. E" indicated that the animals had been housed for 2-3 months in the room. Although he stated that the animals were monitored daily, there was no documentation to verify his claim<sup>4</sup>.
- The room had near-zero ventilation, which produced a very strong odor. Further, the airflow in this room was such that odors and allergens were blown into the common corridor.
- Cages were stored amongst unknown/unlabeled chemicals<sup>5</sup>.
- No standardized light cycle was in use<sup>6</sup>.
- There was no monitoring of temperature/humidity<sup>7</sup>.
- Many overcrowded cages, some of which were seriously overcrowded, were noted.
- Wire lids, filter tops, and other caging items were stored uncovered on the floor.
- The room was generally cluttered, dirty, and unsuitable for use as a housing area.

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<sup>3</sup> ARC Policy on Maintaining Animals in Study Areas: "... provisions must be made to ensure that harmful or unacceptable concentrations of toxic gases, odors, or particles" do not accumulate in an animal's primary enclosure."

<sup>4</sup> : "Daily observation of animals must be recorded in the study area log."

<sup>5</sup> : "Hazardous biological, chemical, or physical agents must not be stored or used where animals are housed."

<sup>6</sup> : "Light in animal holding rooms should provide for adequate vision and for neuroendocrine regulation of diurnal and circadian cycles...A time-controlled lighting system should be used to ensure a regular diurnal cycle, and timer performance should be checked periodically to ensure proper cycling."

<sup>7</sup> : "Temperature and humidity must be monitored and recorded on a daily basis to ensure that adequate levels of these environmental factors are maintained in the study area."

The inspection team was unable to obtain a definitive answer about whether the research staff had entered the vivarium barrier facility after working in this room. This was of significant concern due to issues of cross-contamination and infection within the animal vivarium. Additionally, "Dr. E" implied that All-Trans-Retinoic acid and Cadmium chloride were administered to mice in the unauthorized housing room. As such, it did not appear that appropriate precautions were taken by personnel involved in the care and use of the mice, including use of appropriate Personal Protective Equipment (PPE), and proper medical waste disposal for bedding and animal carcasses according to procedures established by EH&S. Moreover, the inspection team was not advised of the possible presence of carcinogens prior to entering the room. It was also unclear where "Dr. E" euthanized animals housed in the unauthorized housing room (the protocol indicates that euthanasia is to be conducted in a room which is off limits to animals that have been removed from the vivarium).

At the time of the inspection, "Dr. E" was advised of the following: 1) He was to identify animals that could be euthanized immediately; 2) All remaining animals were to be transferred to an appropriate animal room and all overcrowded cages separated no later than the next morning. DLAM staff confirmed that all animals were transferred to the animal room, and overcrowded cages separated that afternoon; 3) Existing experiments could be completed in the return room; however, per standard DLAM breeding policy, any new experiments must be carried out in the barrier facility and not in the return room.

In accordance with the ARC Policy on Authority of the Attending Veterinarian<sup>8</sup>, DLAM Executive Director Couto suspended all animal activities in the unauthorized room. Due to the serious nature of the incident, as the Institutional Official for UCLA, I suspended all activities conducted under the protocol until such time that the ARC was able to conduct a full review of the circumstances relating to the incident. While I understood the disruption the suspension placed on the ongoing research, I believed this was the most appropriate action based on the concerns raised by the inspection team. In my letter of suspension to the Principal Investigator, I documented the findings of the inspection team, which led to my decision to suspend the protocol. I also expressed to the PI my concern that he did not have access to the room, nor did anyone else, most notably the Campus Veterinarian, which is a violation of ARC Policy<sup>9</sup>.

In accordance with the ARC Policy on Investigating Allegations of Mistreatment or Other Noncompliance Issues<sup>10</sup>, the investigator was offered the

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<sup>8</sup> ARC Policy on Authority of the Attending Veterinarian, "the attending veterinarian may immediately stop research activities conducted under a protocol for humane reasons or protocol deviations pending ARC review of an incident."

<sup>9</sup> ARC Policy on the Authority of the Attending Veterinarian: "The attending veterinarian must have unrestricted access to all areas where animals are used or housed (including the vivarium, research laboratories, and research study areas)."

<sup>10</sup> "In every investigation, the person(s) against whom the complaint has been raised shall be given notice of the concern and provided an opportunity to address the allegations in writing."

opportunity to address this incident. This matter, and the Principal Investigator's comments regarding the incident, were reviewed at the convened meeting of the ARC on March 12, 2007.

In his response, the PI affirmed that the mice were housed in the unauthorized room:

*"It was done by a graduate student in an attempt to breed additional mice to hasten his experiments. The student was the only person with access to the room and knowledge of the extent of the conditions. Although the implication is that the conditions in the room were bad, it has determined by the reports from [“Dr. E”] that the breeding in the room was occurring at a much better rate than in the B-floor vivarium (number of litters maintained by females without cannibalization).”*

In response to the use of cadmium chloride, the PI stated:

*“It may be true that the room was not approved by the IBC [Institutional Biosafety Committee] for administration of cadmium chloride, although I do not know if this is true, but the room was clearly approved for mouse experiments with radiolabelled cadmium (Cd-109). A Radiation Safety Officer inspected the facility for this purpose a number of years ago. It is my recollection, that this authorization was also deemed acceptable by the Biosafety Officer at the time, but I am unsure of this. The only person that had access to the room was a graduate student, who is a physician, and has knowledge of the toxicity of cadmium. Non-research personnel were not given access to the room. The cages from the room were taken to the same facility that cages are taken to from the vivarium room.”*

In response to the perceived lack of oversight for the experiments conducted under the PI's approved protocol, he stated:

*“I am willing to take responsibility for the lack of oversight and I am assuming that you will direct punitive measures accordingly. I admit that my style of management allows students a tremendous amount of freedom. However, it is not unusual for me to not have a key to a small room where research is occurring. Students frequently maintain the only key (except for the persons responsible for maintenance of the facilities) for such small research facilities. The room in question is a darkroom facility. It may be that I actually have a key to the room, but in fact I have dozens and dozens of keys in my office, and I was unable to locate and I am still unable to locate a key to that room.”*

The Committee informed the PI that though they appreciated his willingness to take responsibility for the violations pertaining to this protocol, they continued to express serious concern regarding his reaction to the violations. Regarding his response to his justification for using the room for breeding purposes, the Committee expressed grave concern that these statements implied his support for the unapproved

housing, as well as his disregard for the policies and regulations pertaining to laboratory animal housing at UCLA. In the Committee's subsequent correspondence to the PI, they underscored that failure to adhere to applicable regulations is unacceptable regardless of the experimental outcome.

In response to the use of cadmium chloride in that room, the Committee reminded the PI that though the room was previously approved for use of *radiolabelled* cadmium (Cd-109), at the PI's request, the Radiation Safety Division surveyed the room on August 31, 2005 and removed Cd-109 from his radioactive material use authorization. The ARC was notified that the last shipment of Cd-109 was received by the PI on October 23, 2003, and the IBC had not inspected or approved the room for administration of cadmium chloride.

In response to the PI's comment regarding his "*style of management [which] allows students a tremendous amount of freedom.*" the Committee reminded the PI that the University, investigators and their research staff, and the ARC share a collective responsibility for the ethical conduct of research at UCLA. The Committee also reminded the PI that as Principal Investigator, he is responsible for upholding the federal, State and local policies and regulations governing the humane care and use of laboratory animals. The PI was also reminded that as Principal Investigator, he is accountable for ensuring that all personnel listed under his approved protocol(s) understand all procedures described therein and perform their duties in accordance with the aforementioned regulations and policies.

In order to understand the extent of the violations cited above, the ARC requested an audit of all of the PI's currently approved protocols. The audit took place on April 2 & 3, 2007, and involved a complete inspection of all animal facilities used to house his animals, and concluded with a meeting with the PI and his lab staff to determine their knowledge of the protocols and the applicable regulations and policies pertaining to his research. During the meeting, the PI and his staff demonstrated a thorough understanding of all aspects of the approved protocols, though it was clear that he and his staff required additional training in the use of biohazardous agents.

The Committee reviewed the results of the audit during the meeting held on April 9, 2007. They determined that additional actions were required prior to lifting the suspension of the study, including development of a corrective action plan to prevent future noncompliance. In order to assist the PI in developing an appropriate plan, the Committee requested that the following actions be included in the corrective action plan:

- a. To improve communication within his lab, the ARC requested that the PI initiate regular, weekly lab meetings with his staff to discuss study progress, as well as to discuss issues and questions pertaining to the research.

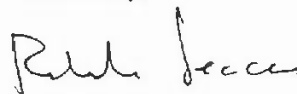
- b. Arrange a meeting between the PI, his staff, and the Biosafety Officer, to review the Agent Summary sheets for Cadmium Chloride and all-trans retinoic acid. During the meeting, the Biosafety Officer would also reviewed proper handing and storage of biohazardous agents, we well as proper disposal of any subsequent waste materials.
- c. Re-inspection and re-certification of the fume hood in the investigator's lab.
- d. Amend the protocol to include the investigator's lab as a research area, and indicate the use of the fume hood in that room.

The Committee also required that the PI and his research staff each undergo retraining in medical waste management, hazardous chemical waste procedures, and SPF barrier procedures, prior to lifting the suspension of the protocol. The PI was also required to undergo retraining in the applicable federal, State, and local laws and regulations pertaining to research involving vertebrate animals.

During the ARC meeting of April 25, 2007 the Committee reviewed the corrective action plan provided by the PI. As recommended, the PI and his staff completed most of the required retraining, and will conduct weekly lab meetings. The remaining actions to be completed included retraining in medical waste management, hazardous chemical waste procedures, and SPF barrier procedures, and re-inspection of the fume hood located in the PI's lab. As such, the Committee voted to lift the suspension of the study. The investigator was also notified that the suspension was lifted contingent upon his continued compliance with all federal, State and local policies and regulations governing the humane care and use of laboratory animals. The PI was also notified that the ARC will conduct periodic unannounced inspections of his laboratory and animal facilities, beyond the required semiannual inspections.

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

Encl: ARC Policy on Maintaining Animals in Study Areas

cc w/o encl: Linda Rosenstock, Dean, School of Public Health  
William H. McBride, Chair, ARC  
Judith L. Brookshire, Director, OPRS  
Kathy Wadsworth, Associate Director, Animal Subjects Research