Stop Animal Exploitation NOW!

Robert Hull, Senior Associate Vice President for Research, 11/1/19
Rensselaer Polytechnic Institute
110 8th St.
Troy, NY 12180
Via email: hullr2@rpi.edu

Associate Vice President Hull,

I am writing to you today to ask that you take administrative action to permanently revoke animal use privileges for multiple individuals connected to an animal experiment which Rensselaer Polytechnic Institute Administration has previously suspended. This situation is of the utmost importance because it impacts not only the project which was suspended but may potentially impact the integrity of the entire Rensselaer Polytechnic Institute research program.

An Rensselaer Polytechnic Institute report dated 5/16/19 states:

"This report summarizes the investigation and remediation of issues that led to the suspension of protocol number INT-001-17, 'The 3D whole body distribution of cancer probes using optical tomography imaging" in the laboratory of Professor Xavier Intes. This protocol employs mice. Based on concerns raised by the Attending Veterinarian (AV), Dr. Neda Bajalo, our Institutional Animal Care and Use Committee (IACUC) informed Dr. Intes of the suspension on April 1. . . .

The issues raised by the AV, and relayed to Dr. Intes on April 5 and in the preliminary report to OLAW on April 4 were in four areas:

Issue #1: Incomplete animal-related records (e.g., identification, medical, husbandry, and irregularities in maintenance of records).

Issue #2: Participation in animal procedures by personnel who have not been adequately trained.

Issue #3: Apparent conduct of animal related procedures inconsistent with approved protocols.

Issue #4: Apparent escorted entry to the animal facility of unauthorized personnel."

After discussing the overall concerns specific examples of issues are discussed in more detail:

"There were incidences of animal mis-identification and other errors in record keeping by Dr. Intes' group. . . . There were concerns raised to the IACUC committee that the students were altering records after the fact. . . . The AV brought to the attention of IACUC that students within Dr. Intes' group had placed their initials against procedures for which they were either not listed on the protocol and/or not adequately trained. Of particular concern was the administration of retro-orbital injections, a procedure requiring substantial training and skill.

. . . it was discovered during the investigations that two mice from a strain not identified in the protocol had been allowed into the BRC in Dec 2018 (those allowed under the protocol are Cl:NU(NCr)-Foxn1nu; SHO-HA-PrkdcscidHrhr; nude BALB/c; and the unapproved strain was NOD-SCID). The PI acknowledges that he overlooked the necessary protocol modification. Under subsequent anesthesia in the BRC performed by the AV, one of the mice died on 12/14/18 (the necropsy revealed no specific cause of death, but it was noticed that the mouse was underweight and dehydrated). . . . The second mouse was euthanized over two months later (03/01/19) by the AV as it had shown deteriorating health in the previous few days . . ."

So, in summary, untrained staff performed unapproved procedures, and also failed to keep adequate records -- apparently also including '***altering records after the fact'*** (falsifying records?), and allowed unapproved personal into the animal facility. Additionally, mice of an incorrect strain were used, and had to be euthanized after extensive suffering including being underweight and dehydrated. Significant issues are also raised as to whether these animals have been provided adequate food, fasting, etc.

This is extremely disturbing for many reasons. First, the way that these procedures are being performed, and the serious systemic errors connected to these procedures, indicate that little if anything of scientific value can come of such a botched project. Second, two animals have died unnecessarily. Third, the documentation errors include '***altering records after the fact'*** -- which could be taken as falsifying records, potentially to obscure wrongdoing. Fourth, this project has been funded by two grants which collectively expended approximately $1,000,000 over the course of two years, so taxpayer dollars are being wasted.

There are better things that can be done with these valuable federal resources. Therefore, I am calling upon your office to do three things to restore the credibility of the Rensselaer Polytechnic Institute research program:

1. Launch an immediate and independent investigation into every protocol in which the offending Principal Investigator (Dr. Intes) and any/all of the connected graduate students were involved.

2. Permanently revoke the animal use privileges of the graduate students, and the PI. Their total lack of concern for proper procedure should indefinitely disqualify them from participation in all animal related projects.

3. Publicly disclose the species and number of animals used in this project, along with the veterinary records for these animals, so that their condition and welfare can be assessed.

This incident has seriously damaged the integrity of the Rensselaer Polytechnic Institute research program. You must act decisively to restore the lost credibility.

I will await action from your office, and expect to receive a reply within five (5) business days.

Sincerely,

Michael A. Budkie, A.H.T.

Michael A. Budkie, A.H.T.,
Executive Director, SAEN

Attachment: Rensselaer Polytechnic Institute Report

A3538

Rensselaer Office of the Vice President for Research

Final Report on Investigation and Remediation of Issues Leading to Protocol Suspension in Laboratory of Professor Xavier Intes.

Robert Hull, PhD
Institutional Official, Rensselaer Polytechnic Institute
May 16, 2019

Institutional Assurance Number: D16-00327
Active grants listed on protocol: NIH NIBIB R01 EB019443-01A1 and NIH R01 CA 207725-01A1

1. **Background and Executive Summary of Findings**

This report summarizes the investigation and remediation of issues that led to the suspension of protocol number INT-001-17, "The 3D whole body distribution of cancer probes using optical tomography imaging" in the laboratory of Professor Xavier Intes. This protocol employs mice. Based on concerns raised by the Attending Veterinarian (AV), Dr. Neda Bajalo, our Institutional Animal Care and Use Committee (IACUC) informed Dr. Intes of the suspension on April 1. They then provided a specific list of concerns to him, relating to activities spanning the previous two months, on April 5. The Institutional Official (IO) informed OLAW of this suspension on April 4. Subsequently, three groups at Rensselaer, coordinated by the Institutional Official, have investigated different aspects of the issues leading to the protocol suspension. IACUC evaluated the specifics of the alleged violations, and made determinations relating to corrective measures in operation of the specific protocol. The management of our Center for Biotechnology and Interdisciplinary Studies (CBIS), in which the animal care facility is located as part of our BioResearch Core (BRC), investigated to determine which additional procedures within the BRC need to be modified. A committee led by the IO assessed broader issues of culture, communication and procedures relevant to the broader issues surrounding the suspension. Interviews were held with the AV, the IACUC chair, Dr. Intes, the Director of the CBIS Cores, and the students and postdoc (b) (6) [redacted] performing the research. This report incorporates the findings and summaries of the three investigating groups. Our intent is to provide a transparent, thorough and critical analysis of the issues identified, and to establish corrective mechanisms such that these issues cannot arise again in the future.

The issues raised by the AV, and relayed to Dr. Intes on April 5 and in the preliminary report to OLAW on April 4 were in four areas:

Issue #1: ***Incomplete animal-related records (e.g., identification, medical, husbandry; and irregularities in maintenance of records)*** In our investigation, we found there were incidences of record keeping errors by Dr. Intes' group. This was in part a result of confusion among the students in the group regrading the specific record procedures instructions. However, there was no evidence of any harm to animals resulting from these errors. Nor did we find any intent to falsify records. Further details and corrective actions are described in sections 2.1b and 2.1.c of this document.

Issue #2: ***Participation in animal procedures by personnel who have not been adequately trained.*** We concluded that the primary issue, again, was record-keeping. Students in Dr. Intes' lab were sometimes initialing against summaries they had written of the day's entire procedures, rather than identifying who explicitly had performed each procedure. In addition there was student confusion between receiving "certificates of successful training" from the AV, and their status for performing that procedure on the protocol. Further details and corrective actions are described in sections 2.2.b and 2.2.c of this document.

Issue #3: ***Apparent conduct of animal related procedures inconsistent with approved protocols.*** The AV had indicated concerns about the incomplete records of animal return to the BRC, and restoration of food after fasting. In our investigation, we found that procedure protocols were being followed, but, again, inaccurate record keeping was at fault. We concluded that the mice were returned to the BRC at the end of each day as required in the protocol, and that food had been restored within the fasting window. During the investigation we also found that two mice from a strain not listed in Dr. Inte's protocol were introduced into the BRC. Although there is some existing literature demonstrating that similar procedures had been applied safely to the same strain, one of the mice died under anesthesia. Further details and corrective actions are described in sections 2.3.b and 2.3.c of this document.

Issue #4: ***Apparent escorted entry to the animal facility of unauthorized personnel.*** We determined that the access status for the individual involved, a collaborating postdoc from Albany Medical Center, was unclear to the students in Dr. Intes' group, based on previous approved access, and communications from the AV. Further details and corrective actions are described in sections 2.4.b and 2.4.c of this document.

2. Detailed Findings and Corrective Actions

2.1 Issue 1: Maintenance of complete animal related records.

2.1.a Issues: A key factor in this protocol is that mice are repeatedly transferred to an imaging laboratory in a separate building on campus, as described in the protocol (this building is separated from the animal care facility by a 2-3 minute walk). The protocol provides for removal of mice to this separate building for periods up to 12 hours (not overnight). Through BRC procedures, the animals can be transferred from the BRC to this imaging laboratory between the hours of 7 am and 7 pm. The issues raised by the AV centered around insufficient record keeping in terms of when the mice were removed and returned to the BRC, details of when specific protocol procedures were performed, and inaccuracies in identification of some animals. These concerns were at the level that it was initially unclear in one instance as to whether the animals had correctly been returned to the BRC for four consecutive days (see section 2.3).

2.1.b Findings. We determined that:
(i) There were incidences of animal mis-identification and other errors in record keeping by Dr. Intes' group.

(ii) There was confusion among the students in the group as to what the specific record procedures instructions were, e.g. whether records should be kept per cage or per animal, and where specific details should be recorded. There are three separate record keeping systems within the BRC: individual cards associated with each cage; an erasable board in the quarantine area where Dr. Intes' mice are housed; and an electronic dropbox (in addition of course to the records in students' lab books). The AV informed us that clear training was provided as to which information should be provided in which system. The students informed us this was done orally, yet the instructions were still not sufficiently clear to them, even after requests for clarification.
(iii) There were concerns raised to the IACUC committee that the students were altering records after the fact. We determined that where this occurred it was a good faith attempt to provide the additional required information gleaned from directives from the AV, for example to separate records for each individual mouse from the record of a cage, or adding details due to Dropbox synchronization issues. We conclude that the group members did not falsify records in any fashion.

2.1.c. Corrective Mechanisms
(a) All users of the BRC facility are in the process of being retrained in the full set of procedures for facility use, comprising three major components: website-based training, classroom- and facility-based orientation sessions, and hands-on animal use training. The critical importance of complete and error-free record keeping will be continuously reinforced to all users of the BRC.
(b) All Standard Operating Procedures (SOPs) for the BRC are being reviewed and updated as relevant (see section 3). This process is complete for the SOPs relevant to the issues related to this report.
(c) To aid real time electronic capture of records of procedures through a cloud-based hub and timely assessment of animal movement in and out of cages, additional wireless systems and electronic notebooks for use within the BRC will be established by Oct 30, 2019.

2.2 *Issue 2: Participation in animal procedures by personnel who have not been adequately trained.*

2.2.a. Issues. The AV brought to the attention of IACUC that students within Dr. Inte's group had placed their initials against procedures for which they were either not listed on the protocol and/or not adequately trained. Of particular concern was the administration of retro-orbital injections, a procedure requiring substantial training and skill.

2.2.b Findings. We determined that:
(i) The fundamental problem was that students in Dr. Intes' lab were initialing against summaries they had written of the day's entire procedures, rather than identifying who explicitly had performed each procedure.
(ii) For the retro-orbital injections, it was confirmed that the only member of Dr. Intes' team who performed such procedures was the (b) (6) who is trained in this procedure, and listed in the protocol.
(iii) There was some confusion as to status following training by the AV. In some instances, students were provided "certificates of successful training", but the AV subsequently raised

concerns about whether they were adequately trained. Also there was student confusion as to whether completion of that training were sufficient to perform a procedure. Of course it is also necessary for the student to be listed for the specific procedure on an approved protocol or amendment.

2.2.c. Corrective Mechanisms

(a) The need to explicitly identify in the records which individuals performed each specific procedure will be re-emphasized in all training sessions and in relevant SOPs and other training materials.

(b) The need to be both adequately trained, as determined by the AV (see (c) below) and to be listed for that specific procedure on an active protocol, will be re-emphasized as requirements to perform a procedure in all training sessions and in relevant SOPs and other written procedures.

(c) A new form will be generated and implemented, by May 31 2019, that will record a request by a PI for training for each specific procedure for each specific student, citing the specific approval from the particular protocol for the exact student-procedure. The form will record the student or postdoc status (approved for procedure, further training needed, or reason why individual is not equipped to perform procedure) after each applicable training session. This will replace the current use of "certificates of successful training".

(d) The ubiquitous use of an electronic record keeping system such as Mentor (see section 3 below) will ensure that protocol and training status is readily available to students, postdocs, staff, PIs, AV, IACUC members and IO at any time.

2.3 Issue 3: Apparent conduct of animal related procedures inconsistent with approved protocols

2.3.a. Issues. The two concerns the AV noted in this respect were: 1. That it was unclear in one instance as to whether the animals had correctly been returned to the BRC for four consecutive days, and 2. That on one occasion, the start time for food deprivation was noted, but not the time when food was returned. The protocol allows for a maximum deprivation of 20 hours.

2.3.b Findings. We determined that protocols were being followed, but incomplete record keeping was at fault. In particular:

(i) The mice were returned to the BRC from the imaging laboratory at the end of each day as required in the protocol. Because of the high level of concern regarding this issue, we provide detailed specifics in this instance. Two record keeping issues were identified that led to the initial (albeit incorrect) impression of absence for four days. The first was that the daily cage count by BRC personnel typically occurs around 4 pm, whereas the BRC rules allow return of the animals up to 7 pm. The second was due to an error by the student returning the mice each day. Not having access to his cell phone in the facility, per BRC policy, he mis-remembered the date when writing on the erasable board on the first return and then incremented by one day from that incorrect date on subsequent returns. He informed us he did tell a BRC staff member of that error at the time. While this is an insufficient attention to record keeping, we are confident that the animals were indeed returned each day as required.

(ii) Food is provided back to the mice in the imaging laboratory, within the 20 hour fasting window. However, in the instance noted above, there was a record keeping oversight, highlighting the importance of the measures described in section 2.1.c.
(iii) In addition, it was discovered during the investigations that two mice from a strain not identified in the protocol had been allowed into the BRC in Dec 2018 (those allowed under the protocol are Crl:NU(NCr)-Foxn1nu; SHO-HA-PrkdcscidHrhr; nude BALB/c; and the unapproved strain was NOD-SCID). The PI acknowledges that he overlooked the necessary protocol modification. Under subsequent anesthesia in the BRC performed by the AV, one of the mice died on 12/14/18 (the necropsy revealed no specific cause of death, but it was noticed that the mouse was underweight and dehydrated). In our investigation, the PI provided us with existing literature that demonstrated that similar fasting / anesthesia procedures this mouse had experienced had been applied safely to the same strain, but not specifically with the xenografted tumors in these mice. The second mouse was euthanized over two months later (03/01/19) by the AV as it had shown deteriorating health in the previous few days; necropsy showed that it's death was likely due to fur found in the stomach-duodenum junction, preventing the passage of food.

2.3.c. Corrective Mechanisms
(a) The necessary corrective mechanisms for findings (i) and (ii) relate to full and accurate record keeping and are described in section 2.1.c.
(b) We are adamant that the issues in finding (iii) will not reoccur. To prevent any such reoccurrence, no mice will be accepted in to the BRC facility without explicit checks that the specific strain is approved in the specific protocol of the faculty group receiving the mice. This will require both a written guarantee and hard copy of the relevant section of the protocol to be provided by the relevant PI to the BRC prior to shipment of the first batch of a given mouse strain, and an electronic check by the AV (using the comprehensive electronic system to be implemented, per section 3.iii). Further, the provider of the mice will have to send all pertinent information one week prior intended shipment including: number of animals , strain, identification number if applicable, date of birth, sex and current health record. The relevant SOP(s) will be updated accordingly. We will also continuously reinforce to all BRC users that any change to procedures described in the protocol must be preceded by an approved protocol amendment.

2.4 Issue 4: Apparent escorted entry to the animal facility of unauthorized personnel.

2.4.a. Issues. The AV reported that on multiple occasions, the (b) (6) (b) (6) had been escorted by a member of Dr. Intes' group into the BRC. The AV believed that at the time, (b) (6) did not have authorized BRC access as she did not have formal visiting status to RPI.

2.4.b. Findings. We determined that:
The AV was incorrect in her assessment of this issue. (b) (6) who is approved personnel on the IACUC protocol, had previously lost her direct electronic access to BRC due to a "time out" mechanism for external personnel/visitors. Subsequently, there was an email from the AV to Dr. Intes' students stating that (b) (6) could access the BRC for approved protocol-related actions if accompanied by a group member or by the AV. Thus we

conclude that (b) (6) [redacted] access to BRC was not intentionally in violation of IACUC or BRC protocols.

2.4.c Corrective Measures

(i) (b) (6) [redacted] is an integral part of the experiments in the Intes group, and her role is appropriately described in the protocol. Per recommendation by our IACUC, she will continue to have access to Dr. Intes' imaging laboratory, on the condition of a 24 hour interval between contact with rodents in the BRC and those in her home facility, per standard BRC procedures. Given the details and needs of this specific protocol, the IACUC did not recommend reinstatement of her access to the BRC at this time.

(ii) More generally we will initiate additional procedures for ensuring that no unauthorized access to the BRC occurs. These procedures will include a monthly check on electronic key access to the BRC against the list of authorized personnel, and a "positive acknowledgment" mechanism at the point of entry, which will only allow access to authorized personnel if they respond positively to an electronic message stating that no unauthorized personnel are accompanying them.

3. Additional items observed during the investigation

(i) It was apparent during the investigations that there were issues in communication of concerns between the AV and the Intes team. As a result we have designed a new procedure for transmitting concerns about any procedure or action by any user within the BRC. A form has been developed where the AV describes to the PI the relevant concern, if prior discussions have not adequately resolve the issue. The PI / authorized senior personnel on the protocol has three working days to respond. The form goes in parallel to the IACUC chair and to the IO. If the response satisfies the AV that the issue is resolved and/or arose from a misunderstanding, the case is closed. Otherwise, if there are remaining concerns, the AV makes a full report to the IACUC which will proceed with an investigation.

(ii) While most of the communications between the AV, IACUC chair, BRC management and IO were found to be effective, the AV did identify the need for better access to the IO. As a result recurring biweekly meetings between AV and IO have been scheduled, starting immediately.

(iii) A comprehensive electronic tracking mechanism for all protocols, training status, and IACUC related business will be implemented. We have evaluated and are currently activating the Mentor system. This will be fully implemented and be the required method for tracking these activities by July 31, 2019.

(iv) To ensure continuing expertise, the IO, AV and IACUC chair will attend an external workshop on animal welfare procedures in the next six months, and at least once every two years thereafter.

(v) All staff within the BRC and CBIS will attend a communication workshop facilitated by our division of Human Resources.

(vi) The Office of Research will continue to ensure there are adequate funds and personnel support for all activities described in this document.

(vii). All SOPS within the BRC are being reviewed and will be updated as appropriate, based both specifically upon the actions identified in this document, and upon evolving best practices generally. This process will be completed by June 15th, 2019.

(viii) An additional concern that arose during the investigation was that it was discovered in late April that the anesthesia machine vaporizer in the Intes imaging laboratory had not been certified for several years, and the delivery of isoflourine was not within specification, causing an extended period for an animal to be anesthetized (note that this is a separate instrument to the one employed in section 2.3.b.iii). The apparatus was sent out for certification and maintenance immediately after learning of this issue. It was serviced, calibrated and certified to be within "Calibration Specifications" and to pass all functional test, on May 2, 2019, arriving back to RPI on May 8, 2019. We are confident that this issue did not lead to animal suffering due to the administration of several accompanying procedures: the depth of anesthesia was monitored by checking the paw pinching reflex before starting the experiment, and the animals' breathing rate was monitored during experiments and adverse events were never observed. Regular inspections of Dr. Intes' laboratory by IACUC will now include a check on equipment calibration records.

4. Status of Protocol Reinstatement

Our IACUC committee sent to the PI on 05/09/19 a document that detailed actions required for protocol reinstatement, and for continuing operations thereafter. These include a thorough update of the protocol confirming all procedures, personnel roles, and mouse strains to be employed; (re-)certification on specific CITI training modules (in addition to the in-house retraining procedures detailed above) for group members including the PI; record keeping retraining based on a new document describing specific guidelines for this specific protocol (as it is distinct from other protocol's our institution because it involves imaging procedures in a separate building); and advanced notice and detailed information of mice being sent from collaborators at the Albany Medical Center (we note also that additional controls on acceptance of mice from Albany Medical Center are being considered by our BRC management). The PI is highly motivated to have the protocol re-instated and we expect that all the necessary actions will be completed, and the protocol reinstated in the near future.

5. Summary

We conclude from our investigations that the issues associated with the suspension of the protocol arose primarily from a combination of inconsistencies, errors and lack of understanding in record keeping procedures, and from the lack of standardized communication mechanisms. In addition we have identified an isolated instance of two mice from an unapproved strain being allowed into the facility. We take these shortcomings extremely seriously, and have put extensive corrective measures in place to ensure they cannot reoccur, as detailed in this document. All personnel involved are dedicated to ensure that our procedures eliminate all possibility of animal pain and suffering, and we are confident that the combination of continuing rigorous application of our existing procedures, combined with the addiitonal procedures described in this document, will ensure that goal.

Respectfully,

(b) (6)

Robert Hull, PhD
Institutional Official and Senior Associate Vice President for Research
Rensselaer Polytechnic Institute