DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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Office of Laboratory Animal Welfare
Rockledge One, Suite 360
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October 26, 2012

Re: Animal Welfare Assurance
A4365-01 [OLAW Case 2C]

Tanja Popovic, M.D., Ph.D.
Chief Science Officer
Centers for Disease Control
1600 Clifton Road NE, MS D-14
Atlanta, GA 30333

Dear Dr. Popovic,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your October 24, 2012 letter providing the update requested in my September 24, 2012 letter to allow this Office to monitor the final actions taken in response to an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the Centers for Disease Control and Prevention (CDC). According to the information provided, OLAW understands the following:

1) The Principal Investigator involved in the noncompliance resigned from CDC and another qualified senior scientist now serves as Acting Team Lead.

2) A management assessment was conducted on the animal research activities performed by the Rabies Team. Identified deficiencies are being addressed by the Acting Team Lead. The quality of protocols submitted to the Institutional Animal Care and Use Committee (IACUC) by the Rabies Team has improved.

3) The Rabies Team is improving record keeping practices to include better data recording, documenting pathogens used, and accurate recording of clinical signs in animals. The record keeping standard operating procedures (SOP) will be implemented within 90 days.

4) The procedures for handling and storing biologics, tissues, reagents, and biohazards are being revised and will be implemented within 90 days.

5) A post-exposure plan for personnel at risk of exposure to non-rabies lyssaviruses was developed by the Office of Safety, Health, and Environment and submitted to the IACUC.

6) The previous noncompliance for the PI in question had resulted in the IACUC imposing a six month suspension of animal use privileges along with the required corrective actions. During this time the Rabies Team activities were monitored by the Post Approval Monitoring Liaison; protocol quality was improved; communication among the investigators, attending veterinarian, and the IACUC was enhanced; the IACUC imposed requirements were met; and the suspension was subsequently lifted. The noncompliance involving unapproved collaboration with another institution by the PI was discovered thereafter and led to the actions described in the prior letter to OLAW.

Based on its assessment of these explanations, OLAW now has a complete understanding of all of the corrective and preventive measures taken in response to the noncompliance. OLAW hereby closes this investigation but requests a brief update following the 90 day implementation period to confirm that the proposed SOPs have been implemented. Your thorough resolution of this matter is commendable and consistent with the PHS Policy philosophy of monitored self-identification and correction. Thank you for keeping OLAW apprised on this matter.

Sincerely,

Axel Wolff, MS, DVM

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

cc: Michael Arrowood, Ph.D., IACUC Chair
2nd [redacted] Chief, Animal Care and Use Program Office

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention

October 24, 2012

Axel Wolff, MS, DVM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive; MSC 7982
Bethesda, MD 20892

Dear Dr. Wolff:

I am writing in response to your letter of September 24, 2012 requesting additional information regarding OLAW Case 2C, A4365-01 (Centers for Disease Control and Prevention, Atlanta). The recommendations of the CDC-Atlanta IACUC are listed below, followed by the most recent information regarding actions taken.

Recommendation #1: Investigator be removed from all animal protocols and be ineligible to be either PI or associate on animal protocols at the CDC and should no longer have access to animal facilities. The IACUC recommends that this ban be permanent.

Status: The CDC-Atlanta IACUC voted on October 3, 2012 to institute a permanent ban on any involvement by the investigator with animal activities at CDC. A few days earlier (on September 27, 2012), however, the investigator resigned from CDC. A qualified, senior level scientist, who was not a member of the Rabies Team, is currently serving as Acting Team Lead.

Recommendation #2: The IACUC recommends that CDC leadership consider conducting a thorough program review of the investigator's management of the Rabies Team animal research activities.

Status: Senior management of the National Center for Emerging and Zoonotic Infectious Diseases directed the conduct of a management assessment as recommended, and has received a final report. Management deficiencies identified in the report are being addressed by the Acting Team Lead. Careful review by the Team Lead and Branch Chief (one level up) of proposed animal activities has already resulted in improved quality of submissions to the IACUC. The overall goals and direction of animal research by the Rabies Team will be evaluated by an external peer review panel October 29-30, 2012.

Recommendation #3: Record keeping SOPs need to be developed by the Rabies Team and reviewed by the IACUC that address the many deficiencies noted during the investigation. This includes better data recording on animal clinical record sheets as well as in laboratory records. In particular, the notation of inocula, especially of pathogens needs to be explicitly clear. Notation of clinical signs needs to be clear and thorough. The IACUC requests additional training to ensure the interpretation of clinical signs is accurate and consistent between and among Rabies Team staff and Animal Resources Branch staff.

Status: A thorough review of record keeping practices is underway with the Acting Team Lead. An implementation plan will begin following completion of the external peer review October 29-30, 2012. Full implementation of the plan is expected within 90 days.

Recommendation #4: Specimen management and handling concerns were raised during this investigation. The IACUC requests that procedures for collecting and storing tissues, biologics, and reagents by the Rabies Team be thoroughly updated. This also includes updates to specimen inventory systems. Consideration should be made to redistribute materials containing non-rabies lyssaviruses into restricted access freezers and to keep such materials away from other rabies "street" virus materials, tissues, and reference diagnostic specimens and reagents.

Status: A thorough review of specimen inventory and management is underway. The Acting Team Lead is directing the review with assistance from the CDC's Laboratory Science, Policy and Practice Program Office. Development of an implementation plan will begin following the external peer review October 29-30, 2012 and full implementation is expected within 90 days.

Recommendation #5: Safety concerns raised during the IACUC investigation documented inadequate protection from infection by rabies vaccines and anti-rabies immune globulin-based post-exposure prophylaxis in animals challenged with non-rabies lyssaviruses (in particular WCBV and LBV). The IACUC recommends that the Rabies Team work with the Office of Safety, Health and Environment and the CDC Occupational Health Clinic to establish a post-exposure treatment/prophylaxis strategy for personnel at risk of exposure to non-rabies lyssaviruses.

Status: Development of a post-exposure plan was coordinated by the Director of CDC's Office of Safety, Health and Environment and submitted to the IACUC on September 27, 2012.

You also requested an updated report on the status of previous corrective actions involving this investigator.

On April 22, 2011 the investigator received a notice of suspension from animal activities by the IACUC along with a list of requirements to be met in order for the IACUC to reconsider his suspension after a period of six months. The investigator complied with all the requirements (with the exception noted below), and there was a marked improvement in the quality of the animal use proposals submitted to the IACUC, as well as communication between the Rabies Team members and the Attending Veterinarian and IACUC. The Rabies Team was highly cooperative with the Animal Care and Use Program Office in enhancing oversight of animal procedures by the Post Approval Monitoring Liaison. The IACUC voted unanimously at the October 7, 2011 meeting to lift the sanctions imposed on the investigator. It was not until September 13, 2012 that the investigator notified the IACUC Chair that he had not fulfilled the requirement to notify the IACUC of any other collaboration with other institutions. It does not appear that any other members of the Rabies Team were aware of that collaboration.

Please let me know if you need any clarification or additional information regarding the actions and plans described above. I will be happy to provide future updates if needed.

Sincerely,

Tanja Popovic, MD, PhD, F (AAM), AM (AAFS)
Deputy Associate Director for Science
Institutional Official

DEPARTMENT OF HEALTH & HUMAN SERVICES

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September 24, 2012

Re: Animal Welfare Assurance
A4365-01 [OLAW Case 2C]

Tanja Popovic, M.D., Ph.D.
Chief Science Officer
Centers for Disease Control
1600 Clifton Road NE, MS D-14
Atlanta, GA 30333

Dear Dr. Popovic,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your September 19, 2012 letter reporting an instance of noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals at the Centers for Disease Control and Prevention (CDC), following up on an initial report on August 13, 2012. According to the information provided, OLAW understands that non-human primates were inoculated with viruses that were different from the ones described on the Institutional Animal Care and Use Committee (IACUC) approved protocol, that primates potentially progressed beyond the approved humane endpoints, that primates were repeatedly challenged with different viruses although this was not described in the protocol, and that animal care staff was not informed about potential health risks associated with handling these primates. These noncompliant incidents are in addition to previous ones (reported to OLAW in closed case A4365-1R) for this Principal Investigator (PI) which included not monitoring rabies infected skunks as described in the approved protocol and not disclosing animal study collaboration with a foreign site.

The corrective actions required by the IACUC in April 2011 for the prior noncompliance consisted of suspending the PI's animal research privileges, retraining the PI and staff on reporting noncompliance, disallowing publication of data that was acquired without IACUC approval, counseling the PI on disclosing all collaborative work proposed on protocols, having the IACUC review all proposed publications from this PI's research team, placing the PI's animal research privileges on probation, having an alternate PI assigned to the protocol in question with approval of the content by the primary PI, having proposals from this group presented to the IACUC in person by the PI, and placing the laboratory under enhanced IACUC oversight. Additional actions requested by the IACUC for the current noncompliance include permanent removal of the PI from the conduct of animal activities, reviewing the PI's overall program management, enhancing record keeping by this research group, enhancing specimen management and storage, and developing a post-exposure treatment regiment for individuals exposed to the non-rabies lyssaviruses.

Based on the information provided, OLAW understands that measures are being implemented to correct and prevent recurrence of these problems. In order for OLAW to monitor the ultimate outcome of this issue we will keep the current case open. Please provide OLAW with a summary of the requested action plan and schedule which is to be prepared by the Director of the Division of High Consequences Pathogens and Pathology and by the CDC Associate Director for Science. Also, describe the outcome of the additional action items proposed by the IACUC as well as the status of the prior required corrective actions.

Please provide these updates or an interim report by **November 1, 2012**. Thank you for keeping OLAW apprised on this matter.

Sincerely,

Axel Wolff, MS, DVM

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

cc: Michael Arrowood, Ph.D., IACUC Chair
2hdrs [redacted] Chief, Animal Care and Use Program Office

Wolff, Axel (NIH/OD) [E]

From: Wolff, Axel (NIH/OD) [E]
Sent: Wednesday, September 19, 2012 11:30 AM
To: Popovic, Tanja (CDC/OD/OADS)
Subject: RE: Final report from CDC

Thank you Dr. Popovic. I'm glad this was successfully resolved. I will go over these documents carefully and send you a response soon.
Axel Wolff

From: Popovic, Tanja (CDC/OD/OADS)
Sent: Wednesday, September 19, 2012 11:19 AM
To: Wolff, Axel (NIH/OD) [E]
Cc: Popovic, Tanja (CDC/OD/OADS); 2ndry [redacted] CDC/OD/OADS)
Subject: Final report from CDC
Importance: High

Dear Dr. Wolff,

Here is the final report on the investigation of noncompliance I consulted with you 6 weeks ago (Report to IO Rabies Allegations 091712scanned.pdf) with supporting attachments. This was an extensive investigation as you will see from the report. I am also attaching a memo from me to the PI's supervisor 2nd [redacted] Scan of IO memo to 2nd [redacted] 18Sep2012.pdf), regarding the implementation of the IACUC's recommendations.

Thank you very much for your guidance in this matter.

Tanja

Tanja Popovic, MD, PhD, F(AAM), AM(AAFS)
Deputy Associate Director for Science
Centers for Disease Control and Prevention
Phone: telepho [redacted]
Fax:
Email: TPopovic@cdc.gov

From: Wolff, Axel (NIH/OD) [E]
Sent: Tuesday, August 14, 2012 7:42 AM
To: Popovic, Tanja (CDC/OD/OADS)
Subject: RE: Brief update

Thank you for this preliminary report, Dr. Popovic. I will start a new case file. If the IACUC investigation finds no evidence of noncompliance OLAW will negate this file. If noncompliance is substantiated, please notify me and indicate what, if any, preventive measures will be taken.

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

U.S. DEPARTMENT OF H. .TH AND HUMAN SERVICES Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

September 17, 2012

Tanja Popovic, MD, PhD, F(AAM), AM(AAFS)
Deputy Associate Director for Science
Centers for Disease Control and Prevention
Phone: [redacted]
Fax:
Email: TPopovic@cdc.gov

Dr. Popovic,

On Monday, August 13th, 2012 Dr. Tanja Popovic, the CDC Institutional Official (IO) charged the CDC IACUC to lead an investigation related to allegations of non-compliance with PHS Policy and CDC IACUC approved animal protocols by members of the CDC Poxvirus and Rabies Branch. In response, an IACUC subcommittee was formed to investigate the following allegations:

1. **Conducting an experiment(s) on non-human primates (NHP) without a CDC IACUC approved animal protocol; specifically, inoculating (challenging) NHP with lyssaviruses not authorized on the CDC IACUC approved animal protocols conducted in the rabies laboratory.**
2. **Failing to promptly apply necessary humane euthanasia at appropriate times upon NHP exhibiting clinical signs of infection (as specified by the euthanasia criteria in the CDC IACUC approved animal protocol).**
3. **Endangering health of staff who handle lyssavirus-challenged NHP by failing to inform staff that the current rabies vaccine may not provide protection (immunity) against the lyssaviruses used in the NHP studies.**

The IACUC subcommittee interviewed most of the Rabies Team laboratory staff to inquire about information relevant to the investigation. Documents including animal clinical records related to the CDC-approved animal protocols applicable to non-human primate (NHP) studies between 2005 and the present were examined. Documents detailing experimental studies, including spreadsheets, laboratory protocols, inventories, and draft manuscripts were collected and examined. Freezers belonging to the Rabies Team were secured on 8/10/2012, prior to the onset of the IACUC investigation, and selected NHP samples (tissues, blood, etc...) were removed to a secure freezer using chain of custody procedures. The IACUC subcommittee requested and facilitated the transfer of additional samples on 8/27/12.

Upon review of the documents and information obtained during the staff interviews, the IACUC reports these essential findings:

1. **NHP studies were conducted by the Rabies Team that were not authorized in the applicable CDC IACUC-approved protocols (#1310, #1482).**
2. **Insufficient evidence is available to support the allegation that Rabies Team staff allowed NHP to progress through clinical signs that exceeded the euthanasia criteria specified in the applicable CDC IACUC-approved protocols.**
3. **Experiments using NHP did include the use of non-rabies lyssaviruses for which the conventional rabies vaccine and post-exposure prophylaxis is apparently inadequate and this information was not explicitly communicated to Rabies Team staff and CDC Animal Resources Branch (ARB) staff.**

Supporting information:

Allegation #1:

Upon review of the applicable IACUC-approved protocols, the following was noted: [redacted] was the Principal Investigator (PI) for all protocols involving NHP between 2005 and 2010 (protocol 2131 was amended in September of 2011 to replace [redacted] as PI with [redacted] Protocols 1310 and 1482 both indicated that experimental studies would utilize "rabies" viruses as described in the following excerpts (see also attached copies):

Protocol 1310 (approved 8/13/2003, approval period: 8/13/2003 through 8/12/2006):

"51. Question: Please give the main infectious agent(s) in this study:

Answer: 1) Lyssaviruses (i.e., rabies virus street isolates)"

Protocol 1482: (approved 10/24/2006, approval period: 10/24/2006 through 10/24/2009)

"Please give the main infectious agent(s) in this study:.....2.42

Lyssaviruses (i.e., rabies virus street isolates)"

Note, in the above excerpts, the phrase "i.e., rabies virus street isolates" should be read "that is, rabies virus street isolates" and as such, restricts the use of lyssaviruses for which "rabies virus street isolates" applies. To the IACUC, this limits the studies to the use of rabies viruses typically used to validate the effectiveness of vaccines and post-exposure prophylaxis (PEP) products.

Information provided independently by [redacted] and [redacted] indicated that NHP covered by protocol 1310 were challenged with non-rabies lyssaviruses, specifically West Caucasian Bat Virus (WCBV) and Lagos Bat Virus (LBV) in July of 2006. [redacted] was PI on this protocol and performed all NHP inoculations (viruses and other biologics). A draft manuscript (provided by [redacted] describing these experiments clearly documents the use of NHP that had previously been vaccinated, survived challenge with rabies "street" virus (canine origin) and were subsequently challenged with WCBV and LBV. Given the phylogenetic and antigenic differences, and the incomplete or lack of vaccine cross-protection, the IACUC considers neither of these non-rabies lyssaviruses to be "rabies virus street isolates" and thus are not covered by the approved protocol. Furthermore, the experimental design described in the protocol does not explicitly include the challenge of surviving animals (i.e. animals that have been vaccinated and challenged with rabies virus and survived) with non-rabies lyssavirus isolates. [redacted] was not an associate on protocol 1310 and did not participate directly in the animal study. His involvement was limited to supplying virus isolate samples to [redacted] for use in the animal challenges and conducting necropsies (after animals died or were humanely euthanized). [redacted] was not familiar with the content of protocol 1310 and, therefore, was unaware that the virus challenge study was not explicitly authorized. During the interview with the IACUC subcommittee, [redacted] considered the virus challenge study to be encompassed by the language in the protocol, but the IACUC disagrees.

Additional information provided by [redacted] and [redacted] indicated NHP covered by protocol 1482 were challenged with a "fresh" LBV isolate in January of 2008. [redacted] was PI on this protocol and performed all NHP inoculations (viruses and other biologics) while [redacted] was included as an associate and was responsible, in part, for NHP sedation, blood sample collection, euthanasia, and necropsy. Despite being an associate on this protocol, [redacted] was not familiar enough with the protocol to know whether the LBV challenge was authorized by the language of the protocol. In this instance, NHP were originally challenged with rabies "street" virus and rescued by subsequent vaccination (compared to an apparent control NHP which succumbed). The surviving NHP were challenged with LBV and did not develop clinical signs or have detectable LBV upon

euthanasia and necropsy at approximately 5 weeks post challenge. As with the 2006 study (under protocol #1310), the LBV challenge study in 2008 (under protocol #1248) was not explicitly authorized, nor the additional experimental use of NHP that survived vaccine efficacy and rabies challenge studies. While [redacted] considered the virus challenge study to be encompassed by the language in the protocol, the IACUC disagrees.

The IACUC would like to emphasize that this report does not address the scientific merit of studies addressing the pathogenicity and virulence of non-rabies lyssaviruses (this judgment is usually made by the Branch and Division before protocols are submitted to the IACUC), rather we are considering whether the NHP studies were authorized by the IACUC, and whether there are safety-related concerns for the studies.

Based on interviews and limited experimental documentation, other NHP studies conducted between 2005 and 2010 appear to have used rabies "street" viruses and most of the studies appear to be consistent with the scope of work in the IACUC-approved protocols (#1310, #1482, #1829, and #2131). However, in some instances animals were repeatedly challenged with rabies viruses even though this is not explicitly described in the protocols. The IACUC considers these repeat challenge studies to be additional examples of protocol non-compliance.

Allegation #2:

The IACUC subcommittee reviewed available animal clinical records (obtained from CDC ARB files), laboratory documents (where available from the staff in the Poxvirus and Rabies Branch), and information obtained during oral interviews with the Poxvirus and Rabies Branch staff. Evidence is insufficient from these sources to verifiably support or refute the allegation. Nevertheless, staff responses during the interviews consistently indicated NHP were promptly euthanized upon demonstrable signs of rabies infection. During the period between 2005 and 2010, at least 2 NHP were reported to have been found dead in cages following challenge with infectious rabies viruses. This is consistent with the timeframe of onset of clinical signs and the progression to death and consistent with the anticipated clinical outcomes described in the IACUC-approved protocols. This span of time can be short, i.e. is it recognized that animals may progress to death within 6 to 12 hours after clinical signs become apparent. Despite routine and enhanced behavioral monitoring of NHP following virus challenge, animals may have presented signs and succumbed to infection between observational periods and thus escaped protocol-mandated euthanasia.

Allegation #3:

NHP studies conducted under the direction of [redacted] in 2006 and 2008 employed non-rabies lyssaviruses, specifically West Caucasian Bat Virus (WCBV) and Lagos Bat Virus (LBV). Conventional rabies viruses (typically canine rabies) are considered Biosafety Level 2 pathogens in-part because efficacious vaccines and post-exposure prophylaxis (PEP) options are provided to research and husbandry staff that work with these viruses and with infected animals. Staff in the Poxvirus and Rabies Branch, as well as ARB staff/contractors, are required to be vaccinated and to maintain adequate titers in order to work with these viruses or with infected animals. However, a 2005 publication (see attached) from the CDC Rabies Team documented inadequate protection from infection by rabies vaccination and PEP in animals (hamsters and ferrets) challenged with non-rabies lyssaviruses, especially WCBV and LBV:

> **Hanlon, C. A., I. V. Kuzmin, J. D. Blanton, W. C. Weldon, J. S. Manangan, and C. E. Rupprecht. 2005. Efficacy of rabies biologics against new lyssaviruses from Eurasia. Virus Research 111:44-54.**

Interviews with Rabies Team staff and with ARB staff familiar with the studies conducted in 2006 and 2008 reinforce the conclusion that communication from [redacted] did not adequately describe the biosafety differences between conventional rabies viruses used routinely in animal studies versus the

non-rabies lyssaviruses (WCBV and LBV) used in some NHP studies. Staff were surprised to witness NHP succumb to challenge by these viruses given the NHP had survived conventional rabies virus challenge. ARB and some Rabies staff were reportedly unaware of the identity of the viruses used in these studies and were unaware of the heightened biosafety concerns associated with these studies. During the interview conducted by the IACUC subcommittee, dismissed the issue of communicating these details by suggesting the staff would not understand the significance of describing the viruses as WCBV or LBV, since the staff would have "understood" these were merely "rabies" studies and would have performed their duties at BSL2 and ABSL2 levels, expected for studies involving rabies viruses. The IACUC finds this sort of disregard for the safety of the Rabies and ARB staff disturbing because exposure to non-rabies lyssaviruses could lead to an untreatable and fatal laboratory-acquired infection. At a minimum, animal protocol PIs are required to inform the protocol associates of the details of the animal studies and to communicate the safety-related issues associated with the pathogens used in animal studies. This communication appears to have been shared incompletely with the staff. Had the staff been informed that the WCBV and LBV challenges in NHP might have biosafety risks exceeding those of rabies "street" viruses, additional biosafety measures may have been required. Furthermore, the IACUC was likewise unaware of plans to use these viruses at the time of the original protocol reviews. Again, had the IACUC been aware or become aware via application for protocol amendment, additional safety review considerations (e.g. risk assessment) may have been requested from the Rabies Team and the Office of Health and Safety (now Office of Safety, Health, and Environment). While the primary laboratory transmission risk associated with rabies viruses is animal bites and puncture wounds (e.g. needle sticks during inoculations or blood collection), there are rare, but documented cases of rabies transmission via mucous membrane exposure or aerosol exposure. The latter is a potential concern especially during necropsies. Rabies staff were present when performed necropsies of WCBV and LBV challenged NHP and only conventional safety procedures were apparently used (typical of necropsies of NHP challenged with rabies "street" viruses). Whether additional containment or safety measures should have been used is a moot point since the events have already occurred. In contrast, recent IACUC approval of Rabies Protocol 2312 on 4/27/2012 states that samples where phylogroup II lyssaviruses (including LBV) may be present, as a precautionary measure, will be worked with in an ABSL-3 setting. It should be noted that WCBV is even more divergent than LBV and is not considered a member of either phylogroup I or II, based on phylogenetic and antigenic differences.

Recommendations:

The Rabies Team has significantly improved the content and quality of animal protocols submitted to the CDC IACUC over the past year. This has coincided with an IACUC imposed requirement, due to unrelated IACUC non-compliance findings, that be restricted from serving as PI on the protocols. Additional emphasis on improved communication with the IACUC has been documented. The implementation of "introductory" Post Approval Monitoring (PAM) meetings and PAM meetings by the Animal Care and Use Program Office (ACUPO) has further improved communication between research staff responsible for animal protocols, ARB, and the IACUC. While the allegations in this investigation are primarily focused on events that occurred in 2006 and 2008, has a documented history of non-compliance with IACUC protocols: see attached memo dated 4/22/2011, and related issue of protocol non-compliance revealed 9/13/2012). The IACUC recommends the following actions be considered in light of the results of this investigation and the pattern of non-compliance with IACUC-approved protocols and IACUC policies:

1. **be removed from all animal protocols and be ineligible to be either PI or associate on animals protocols at the CDC and should no longer have access to animal facilities. The IACUC recommends this ban be permanent.**
2. **The IACUC recommends that CDC leadership consider conducting a thorough program review of management of the Rabies Team animal research.**

3. **Record keeping SOPs need to be developed by the Rabies Team and reviewed by the IACUC that address the many deficiencies noted during this investigation. This includes better data recording on animal clinical record sheets as well as in laboratory records. In particular, the notation of inocula, especially of pathogens needs to be explicitly clear. Notation of clinical signs needs to be clear and thorough. The IACUC requests additional training to ensure the interpretation of clinical signs is accurate and consistent between and among Rabies staff and ARB staff. There is an example SOP for recordkeeping available from ARB that may serve as a template or starting place for the Rabies Team.**
4. **Specimen management and handling concerns were raised during this investigation. The IACUC requests that procedures for collecting and storing tissues, biologics, and reagents by the Rabies Team be thoroughly updated. This also includes updates to specimen inventory systems. Consideration should be made to redistribute materials containing non-rabies lyssaviruses into restricted access freezers and to keep such materials away from other rabies "street" virus materials, tissues, and reference diagnostic specimens and reagents.**
5. **Safety concerns raised during the IACUC investigation documented inadequate protection from infection by rabies vaccines and anti-rabies immune globulin-based post-exposure prophylaxis in animals challenged with non-rabies lyssaviruses (in particular WCBV and LBV). The IACUC recommends that the Rabies Team work with OSHE and the CDC Occupational Health Clinic to establish a post-exposure treatment/prophylaxis strategy for personnel at risk of exposure to non-rabies lyssaviruses.**

Finally, the IACUC has determined that the samples collected from the Poxvirus and Rabies Branch freezers and secured for potential analysis and identification of lyssaviruses are not needed to support the IACUC's investigation. As such, the IACUC releases any hold on these samples. The original request to secure the samples and the Rabies Team freezers may yet apply and the IACUC defers to this authority to make any further decisions about releasing the samples and/or freezers from custody and returning these to the Poxvirus and Rabies Branch.

Respectfully,

Michael Arrowood, Ph.D.
IACUC Chair
Research Microbiologist
CDC/NCEZID/DFWED/WDPB
Building 23, Ro[redacted]
1600 Clifton Rd., MS D66
Atlanta, GA 30329-4018
telephon[redacted] (phone)
(fax)

From: Popovic, Tanja (CDC/OD/OADS)
Sent: Monday, August 13, 2012 4:17 PM
To: Wolff, Axel (NIH/OD) [E]
Cc: Popovic, Tanja (CDC/OD/OADS)
Subject: Brief update

Dear Dr. Wolff,

Here is a brief update on the recent developments we discussed over the phone a few days ago. As you know, over the past few days some allegations of serious concern have been brought to my attention. I understand the allegations to be:

- Conducting an experiment on non-human primates (NHP) without an IACUC approved protocol; specifically, inoculating (challenging) NHP with a lyssavirus other than those authorized on other IACUC-approved protocols conducted in the rabies laboratory
- Allowing animals to proceed in disease course beyond humane criteria for euthanasia
- Endangering health of staff who handles the NHP by not making them aware of potential health risks due to the lack of immune protections associated with exposure to a lyssavirus, other than those for which the current rabies vaccine provides protection

In response to these allegations of possible noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals, and in my role as the Institutional Official for Animal Care and Use (IO), I immediately started taking action. I engaged the Atlanta IACUC Chair and Alternate Chair and charged them to lead an investigation to substantiate these allegations and clarify if there is evidence to support them. I formally made that charge to the entire Atlanta IACUC at their meeting today Monday, August 13, 2012 at 12:30 pm. With the full support of the Atlanta IACUC Chair and Alternate Chair, on Friday, August 9, 2012, I also provided additional recommendations for the following actions to be taken:

- In order to expeditiously conduct this investigation, specimens from animals will be needed for an independent review. Even though this specific experiment is alleged to have taken place 2 years ago, there is reason to believe that the specimens of NHP that might have been used in this experiment continue to exist within the rabies laboratory. Therefore, it is of utmost importance to ascertain their whereabouts, secure them in the appropriate manner, and conduct necessary testing for timely resolution of these allegations. Obviously, it is essential to ensure clear chain of custody for the specimens throughout the process.
- Because in this specific instance, the allegation is that the Rabies Team Lead aided in the conduct of this experiment, it is the IO recommendation that the process of acquiring these specimens in an expeditious and safe manner be overseen by the next levels of the supervisory chain (Branch Chief and the Division Director).

I will keep you apprised as the investigation progresses. Thank you for your support and guidance.

Tanja

Respectfully,

Tanja Popovic, MD, PhD, F(AAM), AM(AAFS)
Deputy Associate Director for Science
Phone: [redacted]
Fax:
Email: TPopovic@cdc.gov

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Memorandum

Date 22 April 2011

From Animal Care and Use Program Office (ACUPO) on behalf of the Institutional Animal Care and Use Committee (IACUC), CDC-Atlanta

Subject Non-compliance with PHS Policy and approved animal use protocol 2206RUPSKUL

To [redacted], Rabies Research Team, Poxvirus and Rabies Branch

The IACUC referred to below is the Institutional Animal Care and Use Committee of the Centers for Disease Control and Prevention (CDC), Atlanta.

Shortly after an animal delivery was made to the CDC-Lawrenceville campus and as a result of a conversation between the CDC Atlanta Post Approval Monitor and the driver of the delivery truck, the acting Chief of the Animal Care and Use Program Office (ACUPO) received notification of a potential protocol non-compliance on December 01, 2010. The IACUC Chair was immediately notified. After several email exchanges with the Principal Investigator, [redacted] the IACUC Chair confirmed on December 13, 2010 that a protocol noncompliance had occurred.

Additionally, on January 17, 2011, a second non-compliance incident was reported to the ACUPO Chief by the Attending Veterinarian, Lawrenceville campus, involving an apparent failure to monitor infected animals in accordance with the approved protocol. The ACUPO Chief immediately notified the IACUC Chairperson, who confirmed the non-compliance with the Attending Veterinarian.

The non-compliance involved (1) non-disclosure of collaboration with [redacted] whereby animals are housed, vaccinated, and bled prior to transport to CDC Atlanta for challenge with rabies virus and (2) failure to monitor rabies infected animals as stipulated in the approved animal protocol (2206RUPSKUL).

A subcommittee of the IACUC was formed and consisted of the Chair, Michael Arrowood, and 4 additional members. An investigation of the non-compliance was conducted and results reported to the full IACUC during a teleconference held March 29, 2011.

These represent the fourth and fifth incidents of non-compliance involving this PI and reported to the IO and OLAW since 2007. The nature of the incidents, as well as the pattern of non-compliance, suggests to the IACUC that steps need to be taken to ensure improvement in communication, management, and coordination regarding animal based research by the Rabies Team within the Poxvirus and Rabies Branch. The recommendations of the CDC Atlanta IACUC, based on the above situation have been presented to the Poxvirus and Rabies Branch Chief, and ACUPO Chief, and are detailed below:

1. For a period of 6 months from the date of this notice, [redacted] shall not be directly involved in handling or working with research animals, nor shall he permitted to enter the animal facilities. During this period required additional training will include a review of "To Report or Not to Report," taken from the Office of Extramural Research web site [redacted] and the investigators listed on Protocol 2206 RUPSKUL (Protocol 2248, resubmitted) will review this material with the objective of gaining an understanding as to what types of protocol noncompliance must be reported. It includes guidance and clarification by the Office of Laboratory Animal Welfare (OLAW) in the box on pages 3-4. Confirmation that the investigators have read and understood the guidance presented in the scenario will be made by e-mail to the IACUC. After a period of 6 months and the documented completion of this training, the IACUC will re-evaluate this restriction.

2. Data collected under animal use protocol 2206RUPSKUL may not be available for submission for publication until the original protocol (renewal) is amended to document the collaboration with [redacted]. A renewal/revision of the affected protocol should fully document pre-existing and ongoing collaboration before submission to the IACUC. Consequently, any current draft publication or future publication will be disallowed for submission until all reference to work done **without** proper IACUC approval is removed.

3. [redacted] has been notified that all collaborative activities must be disclosed to the IACUC in a proposed animal use protocol or discussed with the Animal Care and Use Program Office or IACUC Chairperson prior to protocol submission to determine the proper course for appropriate IACUC review. If any other such collaborations have not been disclosed to date, [redacted] will be subject to further sanctions. See point 2 for eligibility of data for publication under any other such protocols.

4. All future manuscripts/abstracts in which animals have been used by the Rabies Team shall be cleared through the IACUC in addition to the other clearance channels (the IACUC does not have authority for retroactive approval and thus cannot approve publication of research that was not conducted under full IACUC approval). The IACUC is not requesting that existing publications affected by this circumstance be retracted at this time. However, it is expected that any related protocol non-compliance be addressed within the next 6 months otherwise, retraction of publications may become necessary.

5. If [redacted] is found to be involved in future incidents of non-compliance with PHS Policy, the Animal Welfare Act and Regulations, animal care and use standards as outlined in the Guide, any IACUC-approved animal use protocol, or fails to report inadvertent non-compliance, the result may be complete and indefinite suspension of his privilege to use animals in research at CDC.

6. The IACUC supports the change in Principal Investigator (PI) of this protocol renewal (2248) to a senior investigator involved in the study [redacted] Furthermore, for any protocol with ongoing animal work where [redacted] is the PI, an alternate PI must be assigned to oversee the study for the next 6 months provided the above training (point 1) is adequately documented. This change must be submitted as an amendment in Topaz and must be approved by the IACUC.

7. For any new or existing protocol, where a change in PI is warranted, [redacted], as Team Leader of the Rabies Team, must certify in writing (e-mail) that he has read and approved the content of the protocol submitted in Topaz.

8. The PI, along with [redacted], if he is not the PI, of any future animal use proposal originating from the Rabies Team will be required to present the proposal in person to the IACUC at a fully convened meeting. This is effective until a majority vote to terminate this condition is made by a quorum of the CDC Atlanta IACUC.

9. To facilitate post-approval monitoring (PAM) by the IACUC, the PI will provide the IACUC with a schedule of procedures for the skunk protocol (renewal upon approval, 2248) spanning the next 6 months to coincide with the enhanced period of oversight mentioned above.

The IACUC has unanimously agreed to the actions outlined above. [redacted] has the right to contest any of the finding[redacted]d stipulated requirements enumerated ab[redacted], by submission of a request to appear before the full CDC Atlanta IACUC at the next scheduled meeting.

In addition to the specific actions noted above, the IACUC discussed how the Committee can continue and enhance vigilant protocol and policy adherence among all CDC Atlanta investigators who use animals in their research. Every Center that has investigators using animals has representative members on the IACUC, and the recommendation for each member to discuss IACUC issues at respective Branch or Division meetings was restated.

Michael Arrowood, Chair
CDC Atlanta
Institutional Animal Care and Use Committee

cc: [redacted], Attending Veterinarian, CDC-Atlanta, L
[redacted] Chief (acting) Animal Care and Use Program Office
[redacted] Chief, Poxvirus and Rabies Branch, CDC-Atlanta
[redacted], Director, Division of High Consequence Pathogens and Pathology, CDC-Atlanta
[redacted] Associate Director of Laboratory Science, NCZEID, CDC-Atlanta
Tanja Popovic, Deputy Director, Office of Associate Director for Science, CDC-Atlanta

Arrowood, Michael J. (CDC/OID/NCEZID)

From: Arrowood, Michael J. (CDC/OID/NCEZID)
Sent: Wednesday, February 16, 2011 4:43 PM
To: [redacted] (CDC/OID/NCEZID)
Subject: RE: Protocol update

[redacted]

Here is a follow-up to my earlier email. During the last IACUC monthly meeting questions related to protocol compliance were raised during the review of the resubmitted skunk protocol (2206): primarily regarding the updated section describing the collaboration between your research group and your colleagues in Canada. I noted during the discussion your earlier email indicating, in general, that your other protocols did not involve similar collaborations. Nevertheless, several committee members wanted specific input from you regarding your other protocols, including recently expired protocols and those soon to expire (see list below). The concern raised was that if any of these protocols involve(d) external collaborations equivalent or comparable to protocol 2206 and your Canadian colleagues the IACUC would need to get copies of the approvals for each of the studies from the external institution(s) (much like the document you sent previously for the last skunk protocol). Ultimately, the CDC IACUC must document that the animals used at CDC were covered by approvals from the CDC IACUC and/or the external institution(s). Data generated from the animals not covered by approved protocols should not be published, certainly not before documentation is updated to show required approvals were in place at the time of the studies.

Protocol Number	Protocol Short Title	Expiration Date
1364RUPRACL-A2	Efficacy of experimental oral rabies vaccines in raccoons	8/24/2007
1544RUPRACL-A3	Efficacy of experimental oral rabies vaccines in raccoons	7/31/2010
1394RUPSKUL-A3	Oral efficacy of experimental rabies vaccines in skunks	2/7/2008
1601RUPSKUL-A2	Oral efficacy of experimental rabies vaccines in skunks	2/6/2011
2206RUPSKUL-A2	Oral efficacy of experimental rabies vaccines in skunks	2/6/2011
1652RUPFOXL-A2	Efficacy of experimental rabies vaccines in gray foxes	6/16/2011
2213RUPFOXL-A2	Efficacy of experimental rabies vaccines in gray foxes	6/16/2011
1795RUPFOXL	Efficacy of experimental rabies vaccines in red foxes	12/3/2012
2137RUPFOXL	Efficacy of experimental rabies vaccines in red foxes	12/3/2012

As I mentioned in my previous email, a subcommittee was assembled to look more closely at protocol compliance issues and there may be additional requests for information from you by the committee. I know some of these questions may seem redundant, but I do appreciate your help in clarifying this matter.

Michael Arrowood
CDC IACUC Chair

From: (CDC/OID/NCEZID)
Sent: Thursday, February 10, 2011 1:00 PM
To: Arrowood, Michael J. (CDC/OID/NCEZID)
Subject: RE: Protocol update

Dr. Arrowood,

Which protocol compliance?

From: Arrowood, Michael J. (CDC/OID/NCEZID)
Sent: Wednesday, February 09, 2011 4:37 PM
To: (CDC/OID/NCEZID)
Subject: Protocol update

I wanted to provide some feedback to you regarding issues raised at the last IACUC meeting (Monday, February 7th). Dr. [redacted]'s vampire bat protocol (2124) of was on the agenda, but the subcommittee focusing on this protocol had not had a chance to meet after the interaction with [redacted] (January 24th) and upon receipt of the risk assessment documents from OSHE at the end of last week. The subcommittee is scheduled to meet on February 16th and will likely have additional suggestions for revising the protocol. I do not consider the process (timeline) unusual given the extensive review recently applied to another bat protocol. There are important issues that need to be fully considered before the protocol is approved, but I wanted to assure you that the review process was moving forward.

Also considered at the last IACUC meeting were issues related to the resubmission (renewal) of the skunk protocol (2248) which was returned for modification. One question was raised indicating [redacted] had not electronically signed the protocol before submission. It was further decided that a subcommittee should be assembled to address questions regarding protocol compliance. Indeed, the subcommittee may submit questions to you regarding your existing protocols, especially as they relate to animal monitoring and potential collaborations with outside organizations. It is possible the subcommittee may recommend restrictions or other actions regarding your protocols.

I do want to reiterate my earlier concern that if any of your other protocols (beyond the skunk protocol) involve collaborations with outside institutions that you update/amend the protocols appropriately and promptly.

I regret having to bring some of these items to your attention, but wanted you to be aware of the IACUC's concerns and actions. If you have any questions, let me know. I will certainly update you as events proceed.

Thank you,

Michael Arrowood

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention

January 18, 2013

Dr. Axel Wolff
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
Rockledge One, Suite 360
6705 Rockledge Drive, MSC 7982
Rockledge, MD 20892-7982

Dear Dr. Wolff:

In your letter of October 26, 2012 regarding A4365-01 OLAW Case 2C, you requested a brief update after 90 days confirming that proposed new SOPs had been implemented. The laboratory has implemented new SOPs for recordkeeping which will be fully operational once scanners and computers to help support data retrieval are received. New SOPs for handling and storing biologics, tissues, reagents, and biohazards have been defined and implemented. Full implementation will be achieved when inventory and space allocation is completed.

Please let me know if you need any additional information.

Sincerely,

Tanja Popovic, MD, PhD, F(AAM), AM(AAFS)
Deputy Associate Director for Science
Centers for Disease Control and Prevention

Memorandum

Date September 18, 2012

From Dr. Tanja Popovic, Deputy Associate Director for Science

Subject Atlanta IACUC Report on non-compliance with the PHS Policy on Humane Care and Use of Laboratory Animals

To [redacted]
Director, Division of High Consequence Pathogens and Pathology

Dear [redacted]

Please find attached the report of the Atlanta IACUC that led an investigation related to allegations of non-compliance with PHS Policy on Humane Care and Use of Laboratory Animals at the CDC Atlanta facility. The IACUC investigated 3 allegations, two of which were substantiated and for one there was insufficient evidence. The IACUC provided 5 recommendations in its report.

As the CDC Institutional Official (IO) I fully support the findings of the report and its recommendations as written.

I am kindly asking that within 30 days of the receipt of this letter and the report you provide me and the Atlanta IACUC Chair, Dr. Michael Arrowood, with an action plan that outlines specific steps (and the timeline) to be taken to implement the IACUC's recommendations. Furthermore, given the gravity of the findings and recommendations and their reflections on the overall scientific credibility of [redacted] actions, I have also consulted with [redacted] CDC's Associate Director for Science. We both urge you to give serious consideration to [redacted] ability to provide appropriate scientific leadership and oversight to the Rabies Team.

Please do not hesitate to contact me with any questions or concerns.

Respectfully,

Tanja Popovic, MD, PhD, F(AAM), AM(AAFS)
Deputy Associate Director for Science
Phone: [redacted]
Fax:
Email: TPopovic@cdc.gov

CC:
Dr. Michael Arrowood, Chair, Atlanta IACUC
[redacted] Associate Director for Science, CDC
Chief Operating Officer, CDC