DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: http://grants.nih.gov/grants/olaw/olaw.htm

FOR EXPRESS MAIL:
Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

December 20, 2021

Re: Animal Welfare Assurance
A3377-01 [OLAW Case 8T]

Dr. David P. Norton
Vice President for Research
University of Florida
(b) (4) Grinter Hall
Gainesville, FL 32611-5500

Dear Dr. Norton,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your December 16, 2021 letter reporting an adverse event involving mice at the University of Florida, following up on an initial report on November 12, 2021. According to the information provided, OLAW understands that two mice died and twelve required euthanasia following injection of a vaccine boost. The procedure had been performed in accordance with the approved protocol, the laboratory staff had been appropriately trained, injection materials had been prepared aseptically, dosages were correct, no materials had expired, and the adjuvant had been appropriately stored and handled.

The immediate action taken upon discovery consisted of notifying the veterinary staff which provided supportive care to affected mice. The corrective actions consisted of ordering a new bottle of adjuvant, using pharmaceutical grade sterile water for future dilutions, and amending the protocol to further clarify the immunization procedures.

Based on its assessment of this explanation, OLAW understands that although no specific cause could be identified for the adverse response to the injections, additional steps have been taken to reduce the likelihood of a recurrence. Unless notified to the contrary, OLAW assumes that subsequent conduct of the protocol procedures, with the additional proposed actions in place, have not resulted in problems. Please inform this Office promptly if adverse events continue on this study. Thank you for keeping OLAW apprised on this matter.

Sincerely,

(b) (6)

Axel Wolff, M.S., D.V.M.
Deputy Director
Office of Laboratory Animal Welfare

cc: IACUC Chair

Wolff, Axel (NIH/OD) [E]

A 3377

From: [redacted] (b) (6)
Sent: Monday, December 20, 2021 11:54 AM
To: OLAW Division of Compliance Oversight (NIH/OD)
Cc: Rao, Malla (NIH/NIAID) [E]; [redacted] (b) (6)
Subject: [EXTERNAL] OLAW letter - clarification
Attachments: 2021Nov01olaw.-.pdf

Importance: High

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Wolff,

I hope that this correspondence finds you and your loved ones well during these challenging times.

I was notified that the attached letter was sent to you by the University of Florida.

Unfortunately, the draft of the letter was not routed through me prior to its release to confirm content and grant assignment. With an opportunity to review the draft, I would have corrected the reference of the activities to R01AI132547, to avoid any confusion.

I have a single IACUC protocol #201909359, which includes all of the animal-related activities of funded awards for my program as well as activities covered by intramural discretionary funds. The extramural awards are listed below.

Foundation Awards:

- Lead optimization of an evolution-proof malaria transmission-blocking vaccine immunogen that is based on a mosquito protein target and effective against both *P.falciparum* and *P. vivax* (Global Health Innovative Technology Fund)
- Process Development and Clinical Manufacturing of an Immuno-focused, Mosquito-based Pan-malaria transmission-blocking vaccine: AnAPN1 v. 2.0. (Global Health Innovative Technology Fund)
- First in Human Trial of the Pan-Malaria Transmission-Blocking Vaccine AnAPN1 (Global Health Innovative Technology Fund)

NIH Awards:

- RDT-undetectable Malaria in the DR Congo: Epidemiology and Development of Alternatives (R01AI132547)
- A biodegradable nano-microparticle prime-boost vaccine strategy (R01AI114609, NCE ended on 03/31/2021)

RE: RDT-undetectable Malaria in the DR Congo: Epidemiology and Development of Alternatives (R01AI132547)

The previous IACUC chair of UF requested that I include the following text (below, blue) in my animal protocol to cover the Contract Research Organization's (CRO; GenScript) animal procedures for monoclonal antibody development for a parasite biomarker (PSSP17) that would be used to support the development of a saliva-based diagnostics for malaria, that would be implemented in the DRC once the test has been developed.

VERTEBRATE ANIMALS

Monoclonal antibodies (mAbs) against the two candidate biomark will be produced by GenScript (860 Centennial Ave.Piscataway, NJ 08854 USA). This Contract Research Organization was used in the original development of the PSSP17 LFIA, which was accomplished within only a 5-month time frame and as such, will facilitate the production of mAbs using their specific Germinal Center Associated Nuclear Protein (GANP) mouse model (provided in collaboration with TransGenic, Inc. Japan) to generate high-affinity mAbs during the grant tenure period

As you can see, the above activities linked to R01AI132547 do not match the content of the letter with respect to the letter's reference to an immunization study using nanoparticles and peptide antigens that was done at UF (as opposed to GenScript). The study described in the letter had nothing to do with the R01AI132547, but are tied to follow-up work that stemmed from discoveries made from the "R01AI114609: A biodegradable nano-microparticle prime-boost vaccine strategy". These follow up activities were supported in part by the Global Health Innovative Technology Fund malaria vaccine development awards listed above and intramural funds.

Please do not hesitate to reach out to me if you require additional clarifications.

Thank you for your time, and my sincerest apologies to you and (b) (6) for any confusion this error has caused.

Sincerely,

(b) (6)

A3377 - 8T

UF UNIVERSITY of FLORIDA

Office of the Vice President for Research

223 Grinter Hall
PO Box 115500
Gainesville, FL 32611-5500
352-392-1582
352-392-9605 Fax

December 16, 2021

Axel Wolff, DVM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
Rockledge 1, Suite 360
6705 Rockledge Drive
Bethesda, MD 20892

Dear Dr. Wolff:

The University of Florida, in accordance with Assurance D16-00244 and PHS Policy IV.F.3., provides this report of an adverse event regarding mice death following immunization. A preliminary report was sent to OLAW on November 12, 2021 by IACUC Chair Daniel R. Brown.

On September 29, 2021, 48 naïve mice were immunized with a nanoparticle- and CpG-conjugated peptide antigen via intradermal injection at the proximal tail (a route described as subcutaneously at lateral base of tail in the approved protocol). On October 27, 2021, 38 of the mice received a booster immunization of a squalene-based oil-in-water adjuvant plus either unconjugated peptide (as described in the approved protocol; Group A, n = 23 boosted) or the conjugated peptide (Group B, n = 15 boosted) via the same route. Within 20-30 minutes following the booster, the lab staff member noticed 2 dead mice and 12 others in distress/dying. The staff member immediately euthanized those 12 mice. Due to this development, the remaining initially immunized mice did not receive either booster. Once the remaining 24 boosted mice appeared stable, the staff member worked with Animal Care Services (ACS) veterinary staff to give those mice supportive care.

The self-report stated that all materials were prepared using aseptic technique in a biosafety cabinet to allow materials to come to room temperature 30 minutes before boosting (as previously done). The booster dose comprised of each antigen (either naked or conjugated peptide) reconstituted in autoclaved DI water, obtained from a Millipore system, as was done during the priming dose 28 days earlier, wherein no adverse reactions were observed. The bottle of adjuvant was received on September 12, 2021 and kept at 4°C, and was used only once, 3 weeks before for another immunization (no adverse reactions occurred in any of the 8 mice injected at that time).

The lab staff confirmed that none of the reagents were expired. All dilutions (and calculations) were checked and confirmed by lab staff that they had been done correctly. Personnel performing the immunization were trained by the Principal Investigator on the technique used for injection and immunization procedures.

The IACUC full committee voted on December 7, 2021 that this incident was an adverse event and was reportable through the IO to regulatory agencies. The following corrective actions have been implemented:

1. The lab has ordered a new bottle of adjuvant to use in the next set of immunizations.
2. Though there were no reported issues in the past regarding reconstituting the antigen, the lab will use pharmaceutical grade sterile water to reconstitute the naked or conjugated peptide, and related antigens for future injections.
3. A modification has been submitted to clarify the discrepancies between the approved protocol and details of this incident regarding the immunization procedure (substances administered, route of delivery, volume delivered, time point, anesthesia) identified during this investigation.

This study is funded by the following grant:

- National Institutes of Health: R01AI132547- *RDT-undetectable Malaria in the DR Congo*

The NIH funding components have been notified of the adverse event.

The University of Florida is committed to protecting the welfare of animals used in research and appreciates the guidance and assistance provided by OLAW in this regard. Should you have any questions regarding this report, please contact Daniel R. Brown, Ph.D., IACUC Chair.

Thank you for your consideration of this matter.

Sincerely,

(b) (6)

David Norton, Ph.D.
Vice President for Research
Institutional Official

(b) (6)

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, December 20, 2021 7:24 AM
To: Research - IACUC
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: [EXTERNAL] Reportable Adverse event (2021Nov01) [ref:_00D412ElGo._5001K14gYWD:ref]

Thank you for this report, (b) (6) We will send a response soon.

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

From: Research - IACUC <iacuc-crm@research.ufl.edu>
Sent: Friday, December 17, 2021 4:05 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: drbrown@ufl.edu; mmahoney@ufl.edu; Rao, Malla (NIH/NIAID) [E] <mrao@niaid.nih.gov>; Joseph, Jessica (NIH/NIAID) [C] <jessica.joseph@nih.gov>
Subject: [EXTERNAL] Reportable Adverse event (2021Nov01) [ref:_00D412ElGo._5001K14gYWD:ref]

To All Concerned,

I am sending the attached report of an adverse event from the University of Florida (D16-00244). A preliminary report was sent on November 12, 2021 via email by Dr. Daniel R. Brown.

The protocol involved is funded by the NIH and the applicable program official and grants management specialist are cc'd on this email.

Please acknowledge receipt and let me know if you have any questions.

Best,

(b) (6)

A3377-8T

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Monday, November 15, 2021 7:01 AM
To: Brown,Daniel R
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: Potential IACUC Non-Compliance

Thank you for this preliminary report, Dr. Brown. We will start a new case file.

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

From: Brown,Daniel R <drbrown@ufl.edu>
Sent: Friday, November 12, 2021 10:39 AM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Cc: (b) (6)
Subject: Potential IACUC Non-Compliance
Importance: High

To All Concerned,

This is preliminary report of a situation involving unanticipated acute mortality of mice at the University of Florida (Assurance #D16-00244). Briefly, it was self-reported to the IACUC that at least 14 mice died or had to be euthanized due to pain and distress evident within minutes after injection of a vaccine boost. The IACUC-approved vaccine development study involved (UF protocol #201909359) is funded by the NIH.

On 08 November 2021, IACUC staff and I initiated an investigation. A final report to our IACUC is expected within 30 days.

Please contact me with any questions or concerns.

UF UNIVERSITY of FLORIDA

Daniel R. Brown, PhD
Chairman, UF Institutional Animal Care and Use Committee
Associate Professor of Infectious Diseases & Immunology
College of Veterinary Medicine
University of Florida
Gainesville FL 32611-0880 USA
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drbrown@ufl.edu