



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

April 6, 2022

Re: Animal Welfare Assurance
A3306-01 [OLAW Case 3H]

Dr. Terence Flotte
Dean, Provost and Executive Deputy Chancellor
University of Massachusetts Medical School
55 Lake Avenue North
Worcester, MA 01655

Dear Dr. Flotte,

The Office of Laboratory Animal Welfare (OLAW) acknowledges receipt of your March 18, 2022 letter reporting an adverse event at the University of Massachusetts Chan Medical School. This letter had not been preceded by a preliminary report to OLAW.

According to the information provided, this Office understands that the University of Massachusetts Chan Medical School Animal Care and Use Committee (ACUC) determined that an adverse event occurred with respect to: unexpected mortality in mice undergoing protocol approved procedures. The final report states on November 1, 2021, eight mice received facial vein injections of recombinant AAV expressing FOXG1, as gene therapy for FOXG1 syndrome. The injections were uneventful, but no animals survived beyond 16 days post-injection. It is understood that no observable health concerns occurred prior to death. Per the report, the laboratory and researcher have extensive experience successfully performing these injections and preparing solutions of this nature. In response to the incident, the investigator optimized the gene therapy by utilizing weaker or neuron-specific promoters to drive FOXG1 expression. The IACUC reviewed the matter and corrective actions at the convened meeting on December 13, 2021. The committee agreed with the corrective actions and required the investigator to report back on the outcome of the animals following use of the alternate promoter. On January 24, 2022, it was reported that the facial vein injections were well-tolerated with 3 alternate promoters. The IACUC was satisfied with the outcome and has required no additional corrective actions.

It is noted that NIH funds were not used to support these research activities. Based on its assessment of this explanation, OLAW understands that the University of Massachusetts Chan Medical School has implemented appropriate measures to correct and prevent recurrences of these problems.

We appreciate being informed of these matters and find no cause for further action by this Office.

Sincerely,

Jacquelyn
T. Tubbs -S

Digitally signed by Jacquelyn T.
Tubbs -S
Date: 2022.04.06 07:41:36 -04'00'

Jacquelyn Tubbs, DVM, DACLAM
Senior Animal Welfare Program Specialist
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Contact



Institutional Animal Care and Use Committee (IACUC)
Office of Research
University of Massachusetts Chan Medical School
55 Lake Avenue North
Worcester, MA 01655-0002

3/18/2022

Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health
6700B Rockledge Drive, Suite 2500
Bethesda, MD 20892

Dear members of the Division of Compliance Oversight,

The University of Massachusetts Chan Medical School, in accordance with Assurance #D16-00196 (A3306-01) provides this report of unanticipated mortality for your consideration, associated with IACUC protocol PROTO202000182.

On November 1, 2021, 8 mice received facial vein injections of recombinant AAV expressing FOXG1, as gene therapy for FOXG1 syndrome. The injections were uneventful, however, no animal survived past 16 days of receiving the injection. There were no observable health concerns preceding mortality.

The laboratory and researcher involved had extensive experience successfully performing facial vein injections of gene therapies, including AAV expressing FOXG1, and preparing solutions of this nature. The proposed cause was an overexpression and/or off-target expression of FOXG1. To prevent this in the future, the PI optimized the gene therapy strategy by use of weaker or neuron-specific promoters to drive FOXG1 expression.

The outcome and preventative measures were evaluated during a convened meeting of the IACUC on December 13th, 2021. The IACUC agreed with the proposed cause and corrective actions and required the PI to report back on the outcome of the animals after use of an alternate promoter. The PI reported on January 24, 2022 that facial vein injections were well-tolerated with 3 alternate promoters. The IACUC was satisfied with this outcome and required no additional corrective actions.

NIH funds were not used to support the research activities described in this report.

Thank you for your consideration and guidance on these matters. Please contact me with questions or concerns.

Sincerely,

(b) (6)

Terence Flotte, M.D.
Institutional Official
Dean, Provost and Executive Deputy Chancellor
University of Massachusetts Chan Medical School

Wolff, Axel (NIH/OD) [E]

From: OLAW Division of Compliance Oversight (NIH/OD)
Sent: Friday, March 25, 2022 8:22 AM
To: (b) (6)
Cc: OLAW Division of Compliance Oversight (NIH/OD)
Subject: RE: OLAW Reports University of Massachusetts Chan Medical School D16-00196 (A3306-01)

Thank you for these reports. We will send responses soon.

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

From: (b) (6)
Sent: Wednesday, March 23, 2022 2:15 PM
To: OLAW Division of Compliance Oversight (NIH/OD) <olawdco@od.nih.gov>
Subject: [EXTERNAL] OLAW Reports University of Massachusetts Chan Medical School D16-00196 (A3306-01)

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Dear OLAW Division of Compliance Oversight,

On behalf of the University of Massachusetts Chan Medical School Institutional Official, Dean Flotte, I am submitting two reports for your consideration.

1. ReportOLAW_D16-000196 (A3306-01)_PROTO202000182
2. ReportOLAW_D16-000196 (A3306-01)_PROTO202100035

Please contact me with questions or concerns. We appreciate your guidance on these matters.

Thank you,

(b) (6)

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