June 11, 2024

Interim Staff Report on Investigation into Risky MPXV Experiment at the National Institute of Allergy and Infectious Diseases

ENERGY & COMMERCE
CHAIR RODGERS

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Executive Summary

Since October 2022, the Committee on Energy and Commerce's Republican Members (E&C or the Committee) have been investigating a research project on MPXV, a virus that causes mpox (formerly known as "monkeypox"), planned and/or conducted at the National Institute of Allergy and Infectious Diseases (NIAID). Under Rule X clause 1(f) of the U.S. House of Representatives, E&C is the committee with jurisdiction over public health agencies, including NIAID's parent agency, the National Institutes of Health (NIH), and federal biomedical research. The Committee has a long history of conducting oversight of federally funded virology research, including investigating accidents at high-containment laboratories, and examining federal policies related to biosecurity, biosafety, and potentially risky experiments.[1]

A September 15, 2022, *Science* magazine article on MPXV included an interview with Dr. Bernard Moss, a preeminent pox virologist who has worked for decades at NIAID and is a NIH Distinguished Investigator.[2] In the interview, Dr. Moss noted he and his colleagues had

[1] This includes investigating the circumstances around the Food and Drug Administration's (FDA) discovery of unregistered and improperly stored smallpox vials in a cold storage room the agency then used at the NIH in 2014 in violation of international agreements limiting retention of smallpox in the United States to the Centers for Disease Control and Prevention (CDC) and in Russia at the State Research Center of Virology and Biotechnology, also known as the Vector Institute. *See Concerns over Federal Select Agent Program Oversight of Dangerous Pathogens: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 115th Cong. (Nov. 2, 2017); *Bioresearch Labs and Inactivation of Dangerous Pathogens: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 114th Cong. (Sept. 27, 2016), CHRG-114hhrg23012.pdf (govinfo.gov); *How Secure are U.S. Bioresearch Labs? Preventing the Next Safety Lapse: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 114th Cong. (Apr. 20, 2016), CHRG-114hhrg20712.pdf (govinfo.gov); *Outbreaks, Attacks, and Accidents: Combatting Biological Threats: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 114th Cong. (Feb. 12, 2016), CHRG-114hhrg25164.pdf (govinfo.gov); *Review of CDC Anthrax Lab Incident: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 113th Cong. (July 16, 2014), CHRG-113hhrg92323.pdf (govinfo.gov).https://www.govinfo.gov/content/pkg/CHRG-115hhrg28141/html/CHRG-115hhrg28141.htm; *Bioresearch Labs and Inactivation of Dangerous Pathogens: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 114th Cong. (Sept. 27, 2016), CHRG-114hhrg23012.pdf (govinfo.gov); *How Secure are U.S. Bioresearch Labs? Preventing the Next Safety Lapse: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 114th Cong. (Apr. 20, 2016), CHRG-114hhrg20712.pdf (govinfo.gov); *Outbreaks, Attacks, and Accidents: Combatting Biological Threats: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 114th Cong. (Feb. 12, 2016), CHRG-114hhrg25164.pdf (govinfo.gov); *Review of CDC Anthrax Lab Incident: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 113th Cong. (July 16, 2014), CHRG-113hhrg92323.pdf (govinfo.gov).

[2] Kai Kupferschmidt, *Moving Target: The Global Monkeypox Outbreak is the Virus an Unprecedented Opportunity to Adapt to Humans. Will it Change for the Worse?* SCIENCE (Sept. 16, 2022), https://www.science.org/content/article/will-monkeypox-virus-become-more-dangerous.

swapped dozens of genes from the much more transmissible, but less deadly, clade II MPXV into the more deadly clade I MPXV. The article stated that the Moss team was "planning to try the opposite, endowing clade II virus with genes from its deadlier relative."[3] The proposal to transfer genes from the deadlier clade I into the more transmissible clade II alarmed some scientists who believed a more potent version of the mpox outbreak strain could spark an epidemic that would be substantially more lethal.[4]

In oversight requests to the NIH, E&C sought information to better understand the potential risks and benefits of the experiment Dr. Moss had described in the *Science* magazine interview, in particular the proposal to transfer genes from clade I into clade II. As described by Dr. Moss, the experiment appeared to qualify as gain-of-function research of concern (GOFROC) because it planned to enhance the transmissibility and pathogenicity of clade II MPXV by inserting genes from clade I MPXV. [5] Moreover, it also appeared to implicate federal policies or practices regarding dual-use research of concern (DURC) by utilizing gene transferring techniques that, if misapplied, pose a significant threat to public health and human safety. [6]

Over a period of 18 months, the Department of Health and Human Services (HHS), the NIH, and NIAID repeatedly obstructed and misled the Committee about whether the transfer of genes from clade I into clade II experiments described by Dr. Moss in the *Science* article had been approved or conducted. Initially, HHS and the NIH refused to answer any questions about the research. HHS also refused to provide most of the requested documents to the Committee unless they had already been made public. Eventually, some requested documents were made accessible, but only if Committee staff went to HHS offices to review these documents *in camera*. To the extent HHS and the NIH provided briefings, documents, or document viewings, it was almost always to avoid either a transcribed interview or a subpoena.

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[3] *Id*.
[4] Jocelyn Kaiser, *Making Trouble*, SCIENCE (Oct. 19, 2022), https://www.science.org/content/article/u-s-weighs-crackdown-experiments-could-make-viruses-more-dangerous.
[5] TODD KUIKEN, CONG. RESEARCH SERV., IF12021, GLOBAL PANDEMICS: GAIN-OF-FUNCTION RESEARCH OF CONCERN, (2022), https://crsreports.congress.gov/product/pdf/IF/IF12021.
[6] U.S. Health & Human Serv., Public Health Emergency, Science Safety Security, Dual Use Research of Concern (last updated June 3, 2021), https://www.phe.gov/s3/dualuse/Pages/default.aspx.

In multiple letters and other communications, HHS and the NIH repeatedly told the Committee the most dangerous MPXV experiments[7] had not been "formally proposed" or "planned," had never been approved or conducted, and were not currently under consideration. The NIH also issued public statements making the same assertion and even forced *Science* magazine to issue a clarification for one article on the experiment.[8]

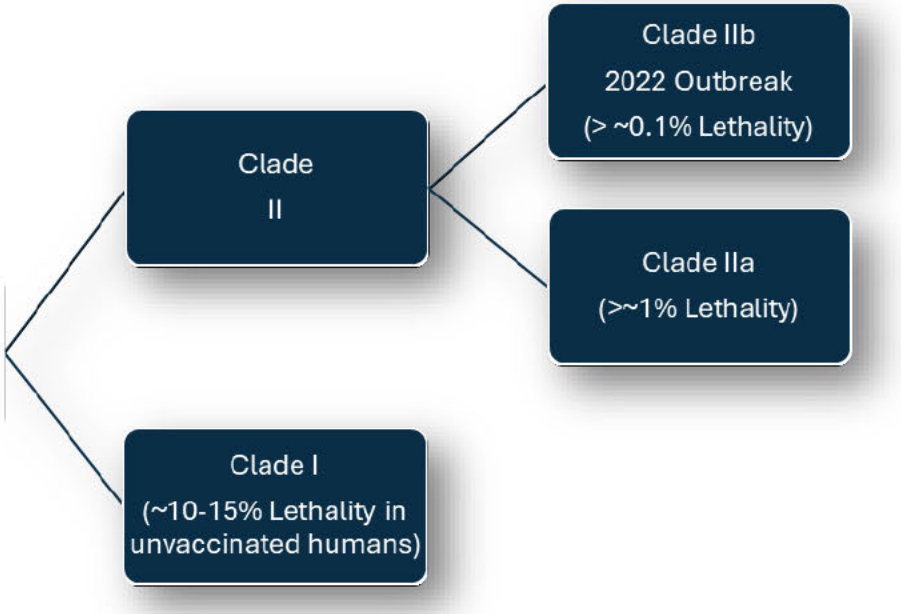

Figure 1: Outline of mpvx clades. Note that a 2017 mpox outbreak in Nigeria had a fatality rate of 9 percent, according to CDC experts who briefed Majority Committee staff. Years later, this mpox was classified as a clade IIb strain. However, other clade II outbreaks had low lethality rates.

HHS's repeated assertions that the risky transfer of clade I material into clade II virus experiment was never proposed or approved were false. Internal NIH documents show this experiment was formally proposed and received approval before the NIH's Institutional Biosafety Committee (IBC) on **June 30, 2015**—seven years before the Committee first asked about the MPXV experiment. With the IBC's approval, researchers could have conducted the proposed bidirectional experiment at any time after June 2015, until May 2023, when the approval was effectively revoked by the NIH (approximately seven months after the Committee's initial letter that raised concerns about conducting the experiment described by Dr. Moss). The only requirement imposed on the 2015 approved experiment was put in place after a 2018 IBC review, which required the scientists to notify—but not seek new

[7] The GOFROC experiment that would have inserted genes from the low transmissibility but highly pathogenic clade I version of the virus into a more transmissible but low pathogenic clade II version of the virus.
[8] Jocelyn Kaiser, *Making Trouble*, SCIENCE (Oct. 19, 2022, updated with clarification on Oct. 28, 2022, 4:25 p.m.), https://www.science.org/content/article/u-s-weighs-crackdown-experiments-could-make-viruses-more-dangerous.

approval from—the NIH's IBC when they wanted to begin inserting clade I genes into clade II virus.

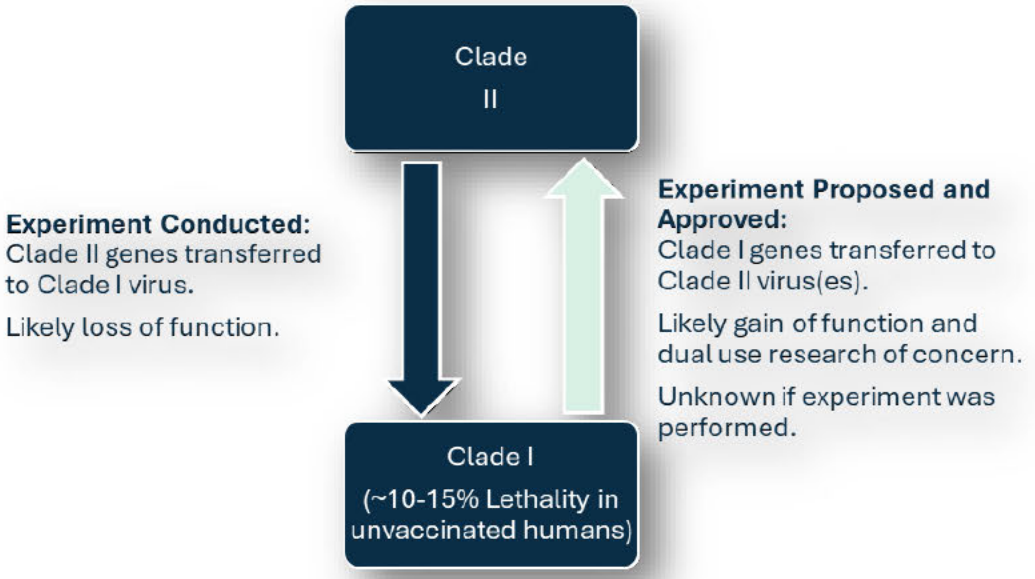

Figure 2: Overview of Proposed and Approved Experiment

The Committee only learned about the full extent of the proposed experiment and its approval after subpoena threats forced HHS and the NIH to make documents related to the risky experiment available *in camera*. In a March 19, 2024, letter to the Committee agreeing to the *in camera* review, HHS Assistant Secretary for Legislative Affairs Melanie Egorin admitted that "research involving bidirectional transfer of genes between clades I and II of the MPXV was considered and approved."[9]

This deliberate, prolonged effort to deceive the Committee is unacceptable and potentially criminal.[10] HHS, the NIH, and NIAID continue to insist the GOFROC experiment transferring material from clade I into clade II was never conducted, despite being approved for a period of over eight years. However, HHS has repeatedly refused to produce any documents that corroborate this claim.

In civil law, when one party refuses to produce evidence in its possession, a jury is permitted to draw an adverse inference that the information not produced was unfavorable.[11] Absent production of sufficient corroborating documentation, it is

[9] Letter from The Honorable Melanie Egorin, HHS ASL, to The Honorable Cathy McMorris Rodgers, Chair of the H. Comm. on Energy & Commerce, *et al.*, (March 19, 2024) (included in Appendix I).
[10] *See* 18 U.S.C § 1505 and 18 U.S.C § 1001.
[11] *International Union (UAW) v. NLRB*, 459 F.2d 1329 (D.C. Cir. 1972) ("When a party has relevant evidence within his control which he fails to produce, that failure gives rise to an inference that the evidence is unfavorable to him.")

reasonable for the Committee to infer that assertions that the experiment was never conducted are inaccurate in light of HHS's past misrepresentation that the risky experiment[12] was never formally proposed or approved.

The Committee needs additional evidence from HHS, the NIH, or NIAID to have confidence that the experiment did not occur. While it could have been by inadvertence or mistake, the deceptive conduct suggests that HHS, the NIH, and particularly NIAID, may have knowingly and deliberately misled the Committee regarding potentially dangerous intramural GOFROC/DURC research.[13] The obstruction and misrepresentations by the agencies involved is also concerning if the experiment, in fact, never occurred because it illustrates the lengths to which NIAID will go to evade outside oversight just for the sake of evasion.

Despite the obstructive behavior by HHS and the NIH, Committee staff believe that NIAID is the agency that bears the most responsibility for misleading the Committee. The NIH has a decentralized structure where the research institutes have a large degree of autonomy in setting research priorities and managing grants, including approval and oversight of biosafety measures.[14] Further, NIAID has the personnel with first-hand knowledge of events, subject matter expertise, and control of the documents related to the experiment.

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[12] The bidirectional gene transfer experiment raises the possibility of making the more transmissible clade gain the lethality of clade I. Under the 2017 HHS Potential Pandemic Pathogens Care and Oversight (P3CO) framework, there are legitimate concerns that this experiment could enhance a pathogen with pandemic potential by making the more transmissible mpox clade I more transmissible.

[13] "Gain-of-function (GOF) research is a broad area of scientific inquiry where an organism gains a new property or an existing property is altered." Congressional Research Service, *supra* note 5.

Gain-of-function research of concern is defined as "experiments that enhance a pathogen's transmissibility or virulence, or disrupt the effectiveness of pre-existing immunity, regardless of its progenitor agent, such that it may pose a significant threat to public health, the capacity of health systems to function, or national security." *See* The White House Office of Science and Technology Policy, *U.S. Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential*, Section3.J (May 6, 2024), https://www.whitehouse.gov/ostp/news-updates/2024/05/06/united-states-government-policy-for-oversight-of-dual-use-research-of-concern-and-pathogens-with-enhanced-pandemic-potential/.

"Dual use research of concern (DURC) is life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security." U.S. Health & Human Serv., *supra* note 6.

[14] JUDITH A. JOHNSON & KAVYA SEKAR, CONG. RESEARCH SERV., R41705, THE NATIONAL INSTITUTES OF HEALTH (NIH): BACKGROUND AND CONGRESSIONAL ISSUES (2019), https://www.crs.gov/Reports/R41705?source=search#ifn21.

Accordingly, HHS and NIH leadership would initially be reliant on NIAID to relay to them accurate information about the MPXV experiments. The documents reviewed by Committee staff, except for the Federal Select Agent Program documents held by the Centers for Disease Control and Prevention (CDC), belonged to NIAID. Such reliance does not excuse HHS and the NIH's conduct, but principal responsibility for misleading the Committee most likely lies within NIAID.

The primary conclusion drawn at this point in the investigation is that NIAID cannot be trusted to oversee its own research of pathogens responsibly. It cannot be trusted to determine whether an experiment on a potential pandemic pathogen or enhanced potential pandemic pathogen poses unacceptable biosafety risk or a serious public health threat. Lastly, NIAID cannot be trusted to honestly communicate with Congress and the public about controversial GOFROC experiments.[15]

This interim finding is particularly relevant given that the White House Office of Science and Technology Policy (OSTP) recently issued updated policy and related guidance on DURC and Gain-of-Function (GOF) research. This updated policy replaced the earlier OSTP Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight and the HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens (collectively hereinafter referred to as "P3CO") imposed in 2017.[16]

The new OSTP policy continues to give funding agencies, like NIAID, primary responsibility for oversight of GOFROC and DURC experiments involving potentially dangerous pathogens.[17] Under both the 2017 policy and the new 2024 policy, for the vast majority of experiments involving potentially dangerous pathogens—like MPXV, the agency conducting the experiment is also tasked with regulating and overseeing the experiment. In almost any other scientific field or industry, this arrangement would be immediately recognized as a conflict of interest, necessitating independent review and oversight.

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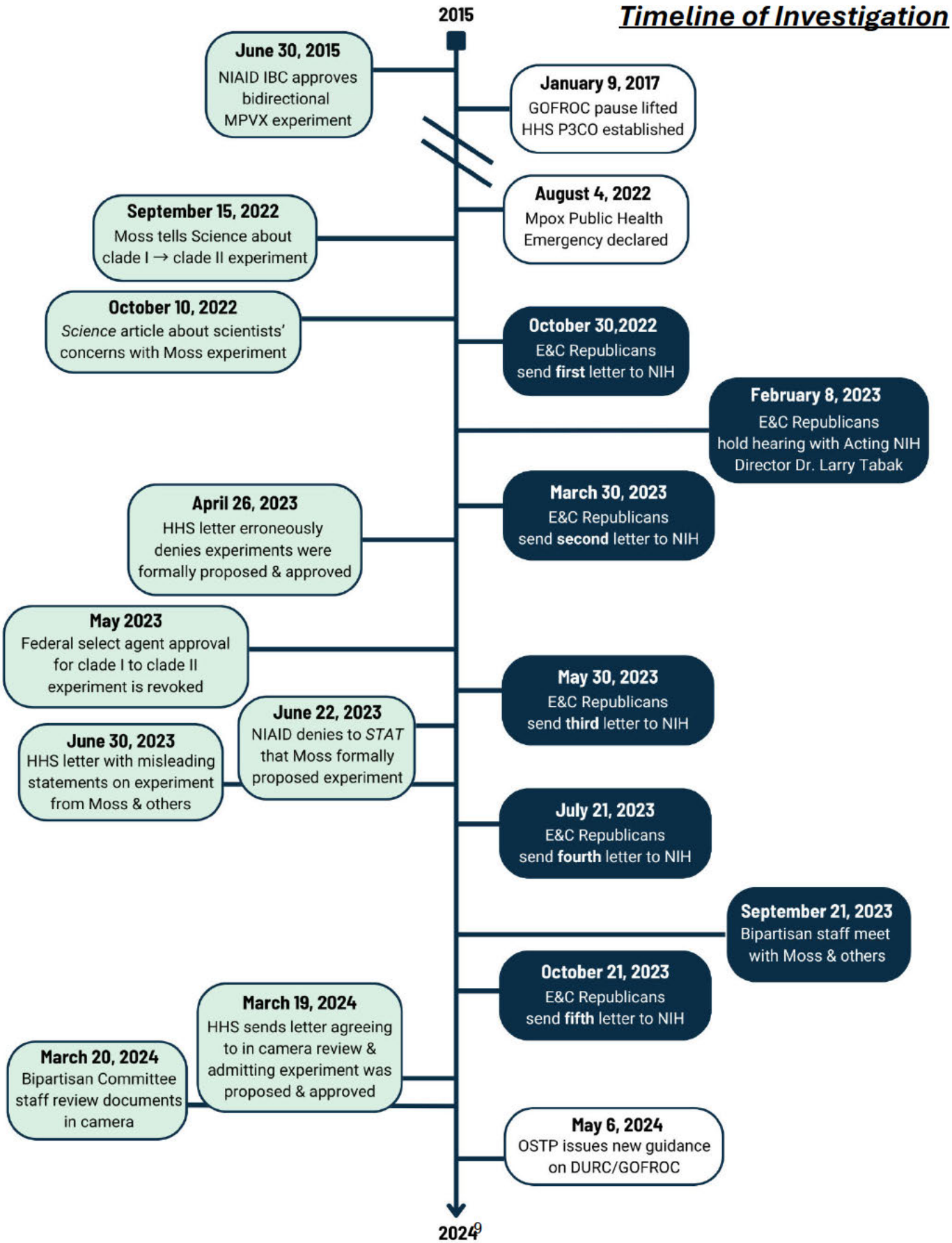
[15] U.S. HHS OFFICE OF INSPECTOR GENERAL, A-05-21-00025, THE NATIONAL INSTITUTES OF HEALTH AND ECOHEALTH ALLIANCE DID NOT EFFECTIVELY MONITOR AWARDS AND SUBAWARDS, RESULTING IN MISSED OPPORTUNITIES TO OVERSEE RESEARCH AND OTHER DEFICIENCIES (2023); U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-23-106119, NIH COULD TAKE ADDITIONAL ACTIONS TO MANAGE RISKS INVOLVING FOREIGN SUBRECIPIENTS (2023).

[16] The White House Office of Science and Technology Policy, *Recommended Policy Guidance for Potential Pandemic Pathogen Care and Oversight* (Jan. 9, 2017), https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/p3co-finalguidancestatement.pdf.

[17] The White House Office of Science and Technology Policy, *U.S. Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential* (May 6, 2024), https://www.whitehouse.gov/ostp/news-updates/2024/05/06/united-states-government-policy-for-oversight-of-dual-use-research-of-concern-and-pathogens-with-enhanced-pandemic-potential/.

Timeline of Investigation



The Virus

MPXV is an orthopoxvirus closely related to variola virus (VARV), a human virus that caused smallpox and was eradicated in 1980. MPXV is a zoonotic virus present in a natural animal reservoir in rodents in Africa, including squirrels, Gambian rats, and dormice, and can be transmitted to monkeys and humans. Two clades of MPXV have been identified.

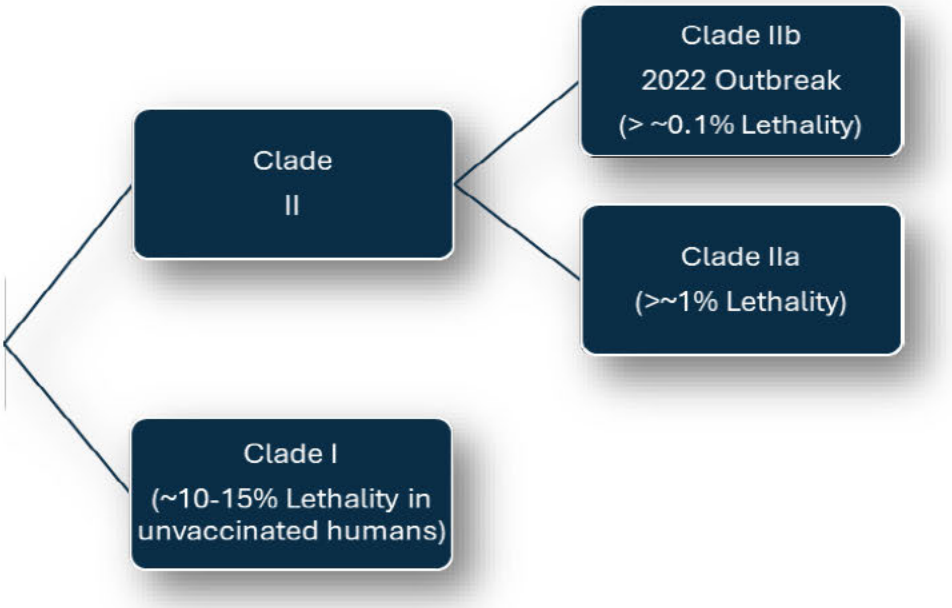


Figure 2:Outline of mpvx clades. Note that a 2017 mpox outbreak in Nigeria had a fatality rate of 9 percent, according to CDC experts who briefed Majority Committee staff. Years later, this mpox was classified as a clade IIb strain. However, other clade II outbreaks had low lethality rates.

Clade I (Central Africa or Congo Basin) is associated with a high mortality rate (~10-15 percent) and long chains of human-to-human transmission. By contrast, clade IIa (West Africa) is associated with a low mortality rate (~one percent) and is less transmissible between humans. The MPXV isolate-causing infections outside Africa are related to clade IIa and were designated as clade IIb. The MPXV genome consists of a double-stranded DNA molecule of ~200,000 base pairs encoding 190 proteins.[18]

[18] Fok-Moon Lum et al., *Monkeypox: Disease Epidemiology, Host Immunity and Clinical Interventions*, 22 NATURE REV. IMMUNOLOGY 597, 597–613 (2022), https://doi.org/10.1038/s41577-022-00775-4.

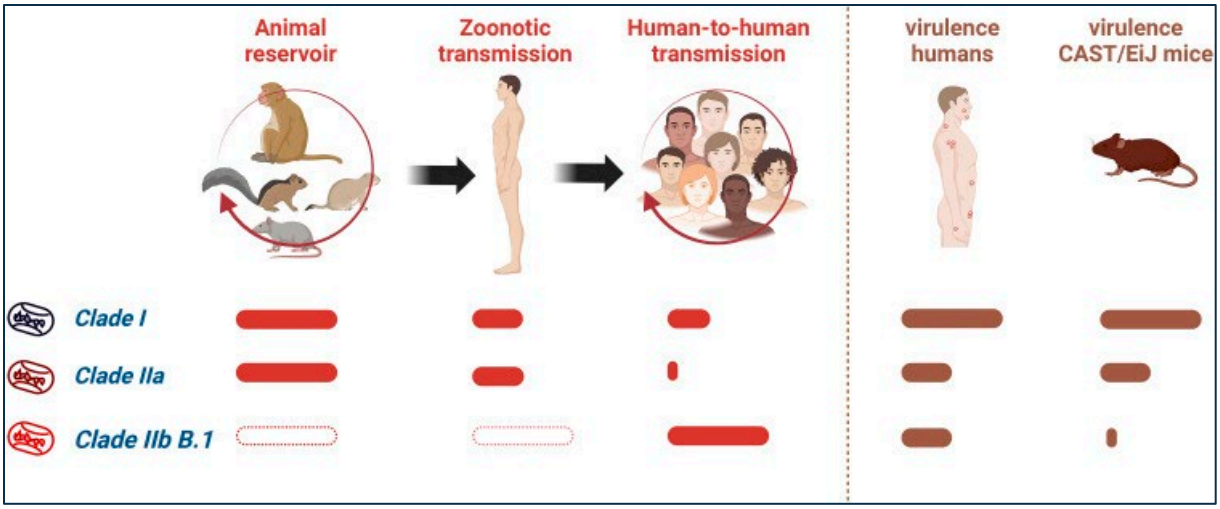


Figure 4: Transmission properties of different clades of MPXV and their virulence in humans and mice. Source: Alcamí A. Pathogenesis of the circulating MPXV virus and its adaptation to humans. Proc Natl Acad Sci U S A. 2023 Mar 28;120(13).

Mpox, the disease caused by infection with the MPVX, has become an increasing epidemic and pandemic threat. Of concern is the ongoing clade I mpox epidemic in Kamituga, Democratic Republic of Congo (DRC), and some of its neighboring countries which has infected almost 20,000 people and killed 975 (4.9 percent), both numbers almost certainly represent a significant undercounting of cases and deaths.[19]

The MPVX threat and its transmission dynamics are not yet fully understood. As noted by C. Raina MacIntyre, an Australian epidemiologist and Professor of Global Biosecurity, "the predominance of children in the DRC epidemic suggests transmission may be respiratory. In fact, smallpox and mpox are respiratory viruses, and mpox has been identified in ambient air [...]. If the more pathogenic clade I mpox becomes highly transmissible between humans, it may pose a greater pandemic threat than clade IIb."[20] MacIntyre later added, "If an emerging orthopoxvirus such as clade I mpox has an R0 of >1, it has epidemic and therefore pandemic potential."[21]

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[19] Stephanie Soucheray, *DR Congo Mpox Outbreak Poses Global Threat of Deadlier Clade*, Center for Infectious Disease Research and Policy (CIDRAP), University of Minnesota (May 20, 2024), https://www.cidrap.umn.edu/mpox/dr-congo-mpox-outbreak-poses-global-threat-deadlier-clade.

[20] C. Raina MacIntyre, *Mpox, Smallpox and the Increasing Threat of Orthopoxvirus Epidemics*, GLOBAL BIOSECURITY (Apr. 18, 2024). https://jglobalbiosecurity.com/articles/10.31646/gbio.268.
CDC subject matter experts in a May 3, 2024, briefing with Majority committee staff said they did not agree that mpox is established as primarily a respiratory virus and that mpox routes of transmission are being studied. *See* Lauren Vogel, *Is Monkeypox Airborne?* Can. Med. Ass'n J. (Aug. 22, 2022), https://doi.org/10.1503/cmaj.1096013 ("According to WHO, monkeypox is transmitted through close contact with an infected person or animal, or contaminated material like bedding. That includes contact with the respiratory droplets that people spray when they talk, cough, or sneeze – although scientists are still studying how commonly the virus spreads this way.").

[21] *Id.*

Figure 5: Map of countries where mpox clades are endemic.
Source: https://www.cdc.gov/poxvirus/mpox/about/index.html

MPXV, along with smallpox and other orthopoxviruses, also poses a significant threat to the United States and the world due to its potential for weaponization, accidental release, and the vulnerability of populations which stopped routinely vaccinating against smallpox in the 1970s.[22] The former Soviet Union extensively researched MPXV and used it as a model to weaponize smallpox, demonstrating the plausibility of bad actors using MPXV as a biological weapon.[23] The biological weapons potential of MPXV and other orthopoxviruses has only increased since the end of the Cold War.[24] On March 26, 2024, the National

[22] Bipartisan Comm'n on Biodefense, *Box the Pox: Reducing the Risk of Smallpox and Other Orthopoxviruses* 2 (Feb. 2024), https://biodefensecommission.org/reports/box-the-pox-reducing-the-risk-of-smallpox-and-other-orthopoxviruses/.

[23] *Id*. citing Steve Mitchell, *Monkeypox Could Be Used as a Bioweapon*, UNITED PRESS INT'L (June 9, 2002), https://www.upi.com/Science_News/2002/06/09/Monkeypox-could-be-used-as-bioweapon/19421023612300/.

[24] *See* Ryan S. Noyce & David H. Evans, *Synthetic Horsepox Viruses and the Continuing Debate about Dual Use Research*, PLOS PATHOGENS (Oct. 14, 2018): "At the heart of the discussion lies the fact that this is dual use research of concern (DURC) because any method that can be used to assemble horsepox virus could be used to construct variola, the virus that causes smallpox." The same argument could be made about similar research involving monkeypox. *See* Nicholas G. Evans, *Dual-use Decision Making: Relational and Positional Issues*, MONASH BIOETH. REV. 268 (2014): "Though the work [mousepox study] had potential application in controlling rodent plagues in Australia [ ] and better understanding poxviruses – of which cowpox, monkeypox, and smallpox are all transmissible in humans – the research also had a dark side. The genetic similarity of poxviruses left open the potential for using the research to modify a human-transmissible poxvirus; a recipe for a deadly pandemic [ ]." There is no evidence that the NIH IBC or any other NIH committee in 2015 reviewed the mpox gene transfer experiment for dual-use concerns. Since a different

Academies of Science, Medicine, and Engineering issued a consensus study report that noted the future risk posed by the proliferation of synthetic biology and gene editing technology:

> While construction of orthopoxvirus from scratch is now possible, the committee estimated that the number of labs capable of carrying out such work is limited to perhaps less than 100 globally. The committee expects this number to increase over the next two decades as DNA synthesis and genome construction techniques improve dramatically. Moreover, the modification of an existing orthopoxvirus to increase virulence has long been possible.[25]

The Experiment

According to the NIH, the experiment at issue is a project on MPXV virus enhancement planned and/or conducted at NIAID. The NIH project number that includes this experiment is *Poxvirus Host Interactions, pathogenesis and immunity*, 1ZIAAI000979. The Principal Investigator of this project is Dr. Bernard Moss of NIAID.[26]

The project involves transferring genes from clade I or Congo Basin clade MPXV (a rare version of MPXV that is 1,000 times more lethal in mice than the version currently circulating in the United States) into clade II or West African clade MPXV (the version currently circulating in the United States). Clade I MPXV is lethal to more than 10 percent of unvaccinated humans while clade II MPXV is much more transmissible.[27]

Moss team mpox study published in 2023 underwent NIH IBC review for dual-use, it is unclear what is NIH policy for reviewing mpox for DURC. Majority Committee staff requests to NIH on these issues remain unanswered.

[25] NAT'L ACADEMIES OF SCIENCES, ENGINEERING, & MEDICINE, FUTURE STATE OF SMALLPOX MEDICAL COUNTERMEASURES (2024), https://doi.org/10.17226/27652.

[26] NIH RePORTER, Project Details, *Poxvirus Host Interactions, Pathogenesis and Immunity*, https://reporter.nih.gov/search/Dm7t3Wqn0k-MLTGNZf3t2g/project-details/10482754. The specific experiments to transfer genes from clade 2 monkeypox to clade 1 monkeypox virus are not mentioned in the abstract, being one of many specific experiments being performed in a large project with a 30-line project summary.

[27] Christina L. Hutson, et al., *Dosage Comparison of Congo Basin and West African Strains of Monkeypox Virus using a Prairie Dog Animal Model of Systemic Orthopoxvirus Disease*, 402 VIROLOGY 72-82 (2010), https://www.sciencedirect.com/science/article/pii/S0042682210001650?via%3Dihub.

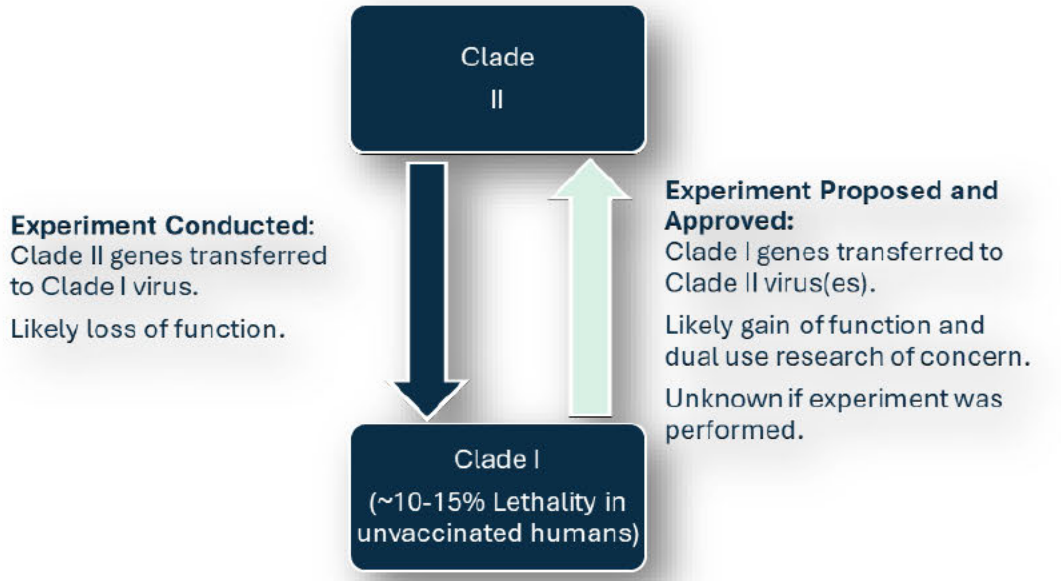

Figure 6: Overview of Proposed and Approved Experiment

Dr. Bernard Moss discussed this direction of gene transfer in a September 2022 *Science* article on NIAID work on MPXV (then referred to as "monkeypox").[28] In particular, the article detailed the following about the project:

> Evolutionary virologists have instead concentrated on the influenza virus, HIV, and other small viruses whose genomes consist of RNA. Poxviruses, by contrast, are made of DNA, and are much larger and more complex. With roughly 200,000 nucleotides and 200 genes, the monkeypox genome is more than 20 times the size of HIV's. It's not clear what many of those genes do, [Dr. Bernard] Moss says, let alone how they interact with each other or how changes in any of them might affect their impact on humans.
>
> Moss has been trying for years to figure out the crucial difference between two variants of monkeypox virus: clade 2, which until recently was found only in West Africa and is now causing the global outbreak, and clade 1, believed to be much deadlier, which has caused outbreaks in the Democratic

[28] Kai Kupferschmidt, *Moving Target: The Global Monkeypox Outbreak is the Virus an Unprecedented Opportunity to Adapt to Humans. Will it Change for the Worse?* SCIENCE (Sept. 16, 2022), https://www.science.org/content/article/will-monkeypox-virus-become-more-dangerous.

> Republic of Congo for many decades. He's found that clade 1 virus can kill a mouse at levels 1000 times lower than those needed with clade 2. To find out why, Moss and his colleagues swapped dozens of clade 2 genes, one at a time, into clade 1 virus, hoping to see it become less deadly, but with no luck so far. **Now, they are planning to try the opposite, endowing clade 2 virus with genes from its deadlier relative**. [Bold added for emphasis].[29]

As Members of the committee of jurisdiction responsible for the NIH and federal biomedical research, Republican Committee Leaders wrote to HHS to understand better the scope and potential risk of the proposed gene transfer experiment. As described above in the *Science* article, the experiment could result in a chimeric virus[30] with the increased transmissibility of clade II viruses while retaining the high levels of lethality found in the clade I virus.

If the experiment transferred genes from clade IIb MPXV—which caused the 2022–2023 mpox epidemic—into clade I virus, the resulting chimeric virus could have a reproductive number (R_0) of 1.10 to 2.40 coupled with a case fatality rate of 10 – 15 percent in the unvaccinated. The *Science* article did not specify which clade II virus the Moss team intended to use. However, the then ongoing 2022 – 2023 mpox outbreak would have given researchers an incentive to switch from studying clade IIa to clade IIb, both to assist in the response and for the chance to perform high-profile research in what had historically been a low priority pathogen for research funding.[31] Moreover, modifying ongoing research to study a pathogen causing an ongoing outbreak is a common practice and was done extensively in response to the emergence of SARS-CoV-2 and resulting COVID-19 pandemic.[32]

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[29] *Id*.

[30] A chimeric virus is a virus that contains genetic material from two or more separate viruses.

[31] *See* Jeffrey L. Americo, Patricia L. Earl, and Bernard Moss, *Virulence Differences of Mpox (monkeypox) Virus Clades I, IIa, and IIb.1 in a Small Animal Model*, PNAS (2023), https://www.pnas.org/doi/full/10.1073/pnas.2220415120: "We have started to investigate the genetic determinants responsible for virulence differences of clade I and IIa viruses and plan to extend this to clade IIb pending institutional approval." This statement suggests an intention of conducting the same gene transfer experiments with the clade IIb virus. In a September 2023 meeting with committee staff, Dr. Moss denied this statement was evidence of such intention but admitted that the statement could be interpreted as suggesting such an intention. Given the totality of the circumstances and the language of the statement, staff does not find Dr. Moss's interpretation persuasive or plausible.

[32] Diana Kwon, *Scientists Around the Globe Pivot Their Research to SARS-CoV-2*, THE SCIENTIST (Apr. 6, 2020), https://www.the-scientist.com/scientists-around-the-globe-pivot-their-research-to-sars-cov-2-67385.

Materially Misleading and Potentially False Representations to the Committee

HHS and the NIH misled the Committee in official written correspondence about the MPXV gene transfer experiment on no fewer than five occasions over the course of 17 months. This does not include additional instances of misleading verbal statements or email communications by HHS and NIH leadership and senior scientific officials to Committee staff.

HHS, the NIH, and NIAID told the Committee that a risky MPXV research proposal at NIAID had not been "formally proposed" or "planned".[33] These assertions simply were not true. The project was formally submitted to the NIH's IBC for approval, and the project received the approval from the IBC on June 30, 2015, as documented in written meeting minutes reviewed by Committee staff.[34]

The agencies' deception of Congress is unacceptable and potentially criminal.

Accordingly, the Committee has lost trust in the NIH and NIAID's ability to oversee its own research on potential pandemic pathogens or enhanced potential pandemic pathogens and to fairly determine whether an experiment poses an unacceptable biosafety or public health risk.

A March 19, 2024, letter from HHS and documents reviewed on March 20, 2024, *in camera* by bipartisan Committee staff confirmed what the agencies had been denying for over a year: that a research team led by Dr. Bernard Moss of NIAID submitted a proposal for a bidirectional MPXV approach at a meeting before the NIH IBC on June 30, 2015.[35] This bidirectional approach "was considered and approved by the IBC."[36] The research proposal involved bidirectional transfer of genes between clades I and II of the MPXV, **including a proposed transfer of genes from the more lethal clade I into the less lethal but much more transmissible clade II**.

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[33] Letter from The Honorable Melanie Egorin, HHS ASL, to The Honorable Cathy McMorris Rodgers, Chair, H. Comm. on Energy & Commerce, *et al*, (Apr. 26, 2023) (included in Appendix I).
[34] Letter, *supra* note 9.
[35] HHS and NIAID insisted on *in camera* review citing unspecified biosafety concerns if the documents were made public. This is a common basis for withholding information related to dual-use and gain-of-function research of concern from Congress and the public. Committee staff question the validity of these concerns, particularly in light of the fact the grant has resulted in multiple academic publications which publicly describe – in great detail – the dual-use and gain-of-function techniques utilized by the Moss team.
[36] Letter, *supra* note 33.

Prior to March 19, 2024, HHS and the NIH made numerous statements that such a gene transfer had not been formally proposed and omitted any mention that the IBC had, in fact, approved a gene transfer in the direction from clade I to clade II, not just in the direction of clade II to clade I. This deception appears to be part of a systematic effort by HHS and the NIH to delay and obstruct the Committee's lawful investigation into NIAID's risky research that could raise concerns about the agencies' management of GOFROC and DURC. HHS continues to maintain that, despite receiving approval, Dr. Moss decided not to conduct gene transfer research from clade I to clade II. The Committee continues to request documents from HHS that support this assertion.

To conduct effective oversight, it is imperative that Congress be able to gather facts. Deception and obstruction interfere with this constitutional responsibility.[37] Further, NIH employees swear an oath to support and defend the Constitution of the United States.[38] Their ultimate loyalty is to the Constitution, not the Executive Branch. Thus, to fulfill their oaths, NIH employees have an obligation to tell the truth to Congress, the representatives of the American people, which has the implied oversight responsibility attached to the explicit Article I Section 8 legislative authority in the Constitution.

The MPXV research proposal has become a case study about how the NIH, and particularly NIAID, oversees and accounts for the monitoring of potentially dangerous GOFROC research. It is particularly relevant as the Biden administration has just issued its new "policy for oversight of dual use research of concern and pathogens with enhanced pandemic potential" and related implementation guidance, which largely leave funding agencies, like NIAID, in charge of approval and oversight of potentially risky research they fund.[39]

The pattern of HHS and NIH misrepresentations to the Committee leaves open at least two possibilities: the officials at HHS who repeatedly denied that a MPXV experiment was ever formally submitted or approved were knowingly making material misrepresentations to Congress, or these officials were misled by the individuals who

[37] *Watkins v. United States*, 354 U.S. 178, 187 (1957).
[38] *See, e.g.*, U.S. Office of Personnel Management, Appointment Affidavits, Form SF-61 (revised August 2002) (on file with Committee).
[39] A research study similar to the Moss experiment as discussed in the September 15, 2022, *Science* article was featured as an example in the Implementation Guidance for the United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential 69 (May 6, 2024), https://www.whitehouse.gov/wp-content/uploads/2024/05/USG-DURC-PEPP-Implementation-Guidance.pdf.

initially relayed that information. In either case, it is clear that there is a need for transparency and additional, external oversight of potentially risky GOFROC experiments.

History of the Investigation

Clarification to the Science article on the Dr. Moss MPXV Experiments

On October 28, 2022, *Science* magazine made a clarification to its October 19, 2022, article based on information provided by the NIH. The clarification stated explicitly that the clade II virus in Dr. Moss' research discussion in the September 2022 *Science* magazine was clade IIa, not clade IIb, which had spread in the U.S.[40] The clarification did not refute that Dr. Moss had proposed or planned gene transfers from clade I to clade IIa. Further, Dr. Moss' team wrote in an early November 2022 preprint of an article in the Proceedings of the National Academy of Sciences of the United States of America (PNAS) that later appeared in February 2023 that they intended to extend their research to include clade IIb: "We have started to investigate the genetic determinants responsible for virulence differences of clade I and IIa viruses and plan to extend this to clade IIb pending institutional approval."[41]

No distinction was made about the directions of gene transfers in either of these statements, nor was the NIH explicit about the directions of the transfer either. There is no contemporaneous evidence in the fall of 2022 supporting the NIH contention that the gene transfer from clade I to clade II was not proposed or acted on in any way. It was not until

[40] However, in 2015, when the Moss team proposed the gene transfer study the sub-clades of clade II were not yet known. The sub-clades were not identified until 2022. The documents indicate that the Moss team was using the Clade II strain of monkeypox known as USA 2003. The monkeypox spread from a prairie dog to a human, but there was no documented human-to-human transmission. In 2017, monkeypox reemerged in Nigeria as an outbreak and was classified as Clade II. It was later determined that it was Clade IIb Between 2017 and 2021, 226 laboratory-confirmed cases and eight deaths (3.5 percent fatality rate) due to monkeypox were reported in Nigeria. Dimie Ogoina, *Science Speaks: A Brief History of Monkeypox in Nigeria*, Infectious Disease Soc'y of Am. (Sept. 20, 2022), https://www.idsociety.org/science-speaks-blog/2022/a-brief-history-of-monkeypox-in-nigeria/#/+/0/publishedDate_na_dt/desc/. It is unclear whether the IBC approval included permission for the Moss team to change Clade II viruses if it wanted to. Majority Committee staff has a pending informational request with NIH on this point. The Nigerian case data indicates a much higher lethality than the rates for other clade II(b) outbreaks. The Moss team's PNAS article in 2023 showed their interest in extending gene transfer studies to include Clade IIb. It is also interesting that clade IIb is more transmissible than clade IIa but with higher lethality. This seems contrary to the general understanding that as a virus gets more transmissible it gets less lethal. Given the lack of information about the immunological competency and nutritional status of the infected patients, more study and analysis are needed to account for this data.

[41] Jeffrey L. Americo, Patricia L. Earl, & Bernard Moss, *Virulence Differences of Mpox (Monkeypox) Virus Clades I, IIa, and IIb.1 in a Small Animal Model*, PNAS (2023), https://doi.org/10.1073/pnas.2220415120.

2023 that the NIH shifted from clarification on the clade II subclade in the transfer experiment to a denial that such a transfer was proposed or seriously pursued.

October 31, 2022, Letter from E&C Republicans

On October 31, 2022, Committee Republican Leaders, sent a letter to the NIH, raising basic oversight questions about this project, spurred on in-part by the MPXV discussion in the *Science* magazine article.[42] A few days earlier, Committee Republican Leaders had sent a similar request for information to Boston University about an experiment involving a hybrid of different Sars-CoV-2 strains that had received media attention.[43] Boston University cooperated with this request, and, in a matter of weeks, voluntarily provided background information, documents, and a staff briefing, assuaging many of the initial concerns about the safety of its MPXV experiments. In contrast, the NIH refused to respond to the initial letter and chose to continue to be non-responsive to follow-up efforts from staff through the end of 2022.

February 8, 2023, Hearing Titled " The Federal Response to COVID-19"

On February 8, 2023, the Subcommittees on Health and on Oversight and Investigations held a joint hearing.[44] Dr. Lawrence Tabak, then Acting NIH Director, testified on behalf of the NIH. During the hearing, Congresswoman Diana Harshbarger asked Dr. Tabak questions about the MPXV research. Dr. Tabak appeared poised to deliver a scripted response that had been prepared in writing before the hearing. Unfortunately, the Congresswoman's allotted time for questioning expired as he began to answer, so she asked him to submit the answer in writing. As of the date of this report, the NIH has refused to provide copies of Dr. Tabak's prepared statement despite the Congresswoman's request and subsequent requests from Committee staff. Questions for the record are routine

[42] Letter from The Honorable Cathy McMorris Rodgers, Republican Leader, et al, H. Comm. on Energy & Commerce to Lawrence A. Tabak, Acting Director, National Institutes of Health (Oct. 31, 2022), https://energycommerce.house.gov/posts/e-and-c-republicans-question-nih-over-experiment-using-more-lethal-monkeypox-virus-listed-as-federal-select-agent.31, 2022), https://energycommerce.house.gov/posts/e-and-c-republicans-question-nih-over-experiment-using-more-lethal-monkeypox-virus-listed-as-federal-select-agent.

[43] Letter from The Honorable Cathy McMorris Rodgers, Republican Leader, et al, H. Comm. on Energy & Commerce to Robert A. Brown, President, Boston University (Oct. 25, 2022), https://d1dth6e84htgma.cloudfront.net/10_25_22_Boston_U_ebbb7d1b25.pdf?updated_at=2022-12-05T15:47:22.524Z.

[44] *The Federal Response to COVID-19: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 118th Cong. (2023), https://docs.house.gov/meetings/IF/IF02/20230208/115351/HHRG-118-IF02-20230208-SD004.pdf.

requests of hearing witnesses given time constraints on Member questioning during congressional hearings.

A few days after the hearing, Committee staff indicated to the NIH it was doing due diligence regarding a potential investigation into the matter in the 118th Congress and asked the NIH to provide the information that was referenced in Dr. Tabak's prepared response to Congresswoman Harshbarger. The NIH refused and insisted on a formal request in a letter from the Committee Chair. As of the date of this report, the NIH has refused to provide copies of Dr. Tabak's prepared statement despite the Congresswoman's request and multiple requests from Committee staff.

Subsequent emails from the NIH staff imply that the information prepared for Dr. Tabak's response at the February 2023 hearing was consistent with HHS's factually incorrect response on April 26, 2023.

March 30, 2023, Letter[45]

On March 30, 2023, having not received a formal response to the October 31, 2022, letter, Committee Chair Cathy McMorris Rodgers, Health Subcommittee Chair Brett Guthrie, and O&I Subcommittee Chair Morgan Griffith sent a letter to the NIH launching an investigation into the MPXV research proposal, requesting documents and information.

April 26, 2023, Letter from HHS Assistant Secretary for Legislation[46]

On April 26, 2023, the HHS Assistant Secretary for Legislation sent a response letter to the Committee that only provided limited information about IBC consideration and approval of the 2015 proposal but also included the following erroneous and misleading statements:

- "**This study has not been formally proposed** […] This type of research would require formal proposal to be submitted for review, and the proposal would need to undergo

[45] Letter from The Honorable Cathy McMorris Rodgers, Republican Leader, et al, H. Comm. on Energy & Commerce to Lawrence A. Tabak, Acting Director, National Institutes of Health (Mar. 30, 2023), https://energycommerce.house.gov/posts/chairs-rodgers-guthrie-and-griffith-demand-answers-on-nih-planned-experiments-using-more-lethal-group-of-monkeypox-virus.30, 2023), https://energycommerce.house.gov/posts/chairs-rodgers-guthrie-and-griffith-demand-answers-on-nih-planned-experiments-using-more-lethal-group-of-monkeypox-virus.

[46] Letter, *supra* note 33.

the rigorous review process described in this letter before it could be initiated." [Bold added for emphasis].

Analysis of the accuracy of the HHS response: This statement is materially misleading.

The study in question was included in a submission to the NIH IBC in June 2015. In 2015, during the GOF research pause, the only pathogen research undergoing the rigorous review referenced in the April 26, 2023, response were projects involving influenza, SARS, and MERS. Dr. Moss's MPXV project was not subjected to rigorous review because it predated the HHS P3CO framework that was announced in December 2017. Finally, HHS's April 26, 2023, letter stated that "the NIH Institutional Biosafety Committee (IBC) ***formally reviews*** *any NIH intramural research [...]." [Bold added for emphasis]. This is an acknowledgement by HHS that an IBC review is a formal process. There was no evidence in the documents that there was any referral of the research project to be reviewed for dual-use research concerns.*

- "**One approach** to studying mpox clade differences was proposed and approved in 2015 and involves the generation of chimeric viruses—viruses that incorporate genes from two mpox strains. **This ongoing sub-project includes only chimeric viruses created by replacing genes in the more virulent clade 1 virus with genes from the less virulent clade IIa virus**." [Bold added for emphasis].

  Analysis of the accuracy of the HHS response: The statement makes a material omission.

  The letter omits the fact that the approved proposal to study MPXV clade differences was bidirectional, not just replacing genes in the clade I virus with genes from the clade II virus but also transferring genes from the clade I virus into the clade II virus. This is a material omission because, earlier in the letter, NIAID continued to deny that gene transfers from the clade I virus into the clade II virus had been formally proposed and approved. As written, the statement was clearly intended to leave the inaccurate impression that the only gene transfer experiments proposed and approved were replacing genes in the clade I virus with genes from the clade II virus, which would be expected to yield either no gain in function or a loss in function for the resulting chimeric virus.

- "As stated above, the September 2022 *Science* article noted in your letter referenced a potential sub-project, which your letter refers to as **the 'clade 1 study,' that has not been formally proposed**. This potential sub-project would include the generation of chimeric viruses by replacing genes in the less virulent Clade IIa virus with those in the more virulent Clade I virus [...].

  "As detailed above, **this type of research would require a formal proposal to be submitted for review**, and the proposal would need to undergo the rigorous review process described in this letter before it could be initiated. This review process would specifically include an assessment of whether the research may be subject to the HHS P3CO Framework."[47] [Bold added for emphasis].

  Analysis of the accuracy of the HHS response: As noted above, this statement is incorrect.

  The clade I study was included in the bidirectional MPXV gene transfer proposal presented to the NIH IBC in June 2015. There was no rigorous review process for such a project because the proposal predated the HHS P3CO framework, which was announced in December 2017. The review of research for GOF concerns during the 2014-2017 pause were only triggered if the experiments included influenza, SARS, or MERS. According to the October 19, 2022, Science article, a "safety panel" in 2018 determined that the Moss team gene transfer proposal was not subject to P3CO.[48]

[47] Prior to the HHS P3CO Framework, research proposals were reviewed to determine whether they were subject to the gain-of-function research pause if the experiments might be reasonably anticipated to confer attributes to influenza, SARS, and MERS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. U.S Dep't of Health & Human Serv., *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses* (Oct. 17, 2014), https://www.phe.gov/s3/dualuse/documents/gain-of-function.pdf. There was also review for dual use research of concern, but mpox was not on the list of 15 federal select agents that would trigger this additional scrutiny. However, per the 2023 PNAS article by the Moss team, apparently some mpox research was subject to DURC review even though mpox clade 1 is not one of the 15 federal select agents on the DURC list. Neither HHS nor NIH have explained the criteria for conducting a DURC review even if the experiment does not involve one of the listed 15 federal select agents. In a May 3, 2024, briefing with Majority committee staff, CDC subject matter experts mentioned mpox research projects at CDC were subject to DURC review. However, the Committee is concerned no system at NIH or HHS exists to ensure adequate DURC review.

[48] According to the March 19, 2024, HHS letter to the Committee, "the [Moss] research team stated during a 2018 IBC review that they would not conduct this experiment without further discussions with the IBC." Neither HHS nor NIH have provided any further context or explanation for why the Moss research team did not conduct the part of the gene transfer experiment moving genes from clade I to clade II. The timing of the Moss research team statement in 2018 leaves the impression that the Moss research team was worried that review of this part of the experiment would raise concerns with the IBC under the new P3CO framework

> *With respect to review for DURC, there was no indication from the documents that the IBC reviewed for DURC or referred for DURC review in 2015 and 2018. According to a 2023 PNAS article by the Moss team about other research on MPXV, all procedures and protocols were approved by the NIH IBC and judged not to have the potential for DURC. This suggests that there was DURC review for MPXV experiments, but there has not yet been any evidence showing that the MPXV gene transfer experiments were reviewed for DURC.*[49]

May 30, 2023, Committee Letter[50]

On May 30, 2023, Chair Rodgers, Health Subcommittee Chair Guthrie, and O&I Subcommittee Chair Griffith sent a letter to the HHS Assistant Secretary for Legislation as a follow up to HHS's April 26, 2023, letter, which did not respond directly to most of the questions in the Committee's March 2023 letter. Because HHS had not been forthcoming with documents and written responses, the Committee requested a videotaped, transcribed in-person interview with Dr. Moss by June 30, 2023.

June 22, 2023, STAT Article

In a June 22, 2023, *STAT* article, NIAID denied Dr. Moss had made any formal proposal for the MPXV experiment:

> But a spokesperson for NIAID told STAT in late May that there had been **no formal proposal from Moss** to do the research

issued in December 2017. Because of HHS and NIH lack of transparency and lack of detailed discussion for this course of conduct, the staff at this time makes the inference that the Moss research team itself lacked confidence that under the P3CO framework the IBC would find the benefits outweighed the risks of this direction of the experiment. The Moss research team may have also lacked confidence because they secretly conducted this part of the experiment and were dismayed by the results.

[49] In a May 3, 2024, briefing with Majority Committee staff, CDC experts stated that CDC mpox research proposals were subjected to DURC review. However, CDC has not yet responded to follow-up questions as to why CDC conducted such DURC reviews, and how this practice originated. The fact that both NIH and CDC conducted DURC reviews of mpox research suggests that these agencies were not confident that the lack of required DURC review for mpox research was adequate for protecting public safety.

[50] Letter from The Honorable Cathy McMorris Rodgers, Republican Leader, et al, H. Comm. on Energy & Commerce to The Honorable Melanie Egorin, HHS ASL, (May 30, 2023), https://energycommerce.house.gov/posts/e-and-c-leaders-request-top-nih-researcher-sit-for-videotaped-interview-after-admin-stalls-on-providing-lethal-mpox-experiment-documents.on Energy & Commerce to The Honorable Melanie Egorin, HHS ASL, (May 30, 2023), https://energycommerce.house.gov/posts/e-and-c-leaders-request-top-nih-researcher-sit-for-videotaped-interview-after-admin-stalls-on-providing-lethal-mpox-experiment-documents.

and the institution had no plan to proceed with the study. [Bold added for emphasis]. [51]

As explained above in detail, this was a materially misleading statement from NIAID as the experiment was formally proposed and approved in 2015. This again raises a question whether the NIAID official had knowingly made the misleading statement to *STAT* (and therefore the public) or had the NIAID official been misled by others at NIAID.

June 30, 2023, Letter from Dr. Moss[52]

On June 30, 2023, HHS forwarded a letter signed by Dr. Moss addressed to Chair Rodgers. This letter also included the following misleading statements:

- "We received approval from the Institutional Biosafety Committee to carry out related experiments in which genes from the more virulent mpox clade I were replaced with the corresponding genes from the less virulent clade IIa virus."

  Analysis of the accuracy of Dr. Moss's response: This statement contains a material omission of fact.

  Dr. Moss's team received approval from the IBC not just for replacing genes in clade I with genes from clade II, but also were simultaneously approved to conduct experiments replacing genes in clade II with genes from clade I.

  Of note: Dr. Moss also did not disclose that he received the approval in 2015, making it more difficult for the Committee to understand the timeframe of approval.

- "I will consider additional gene exchanges that might include transfers in the opposite direction or involve clade IIb. **I have not planned or proposed such experiments for approval** since we have not completed the current experiments." [Bold added for emphasis].

[51] Helen Branswell, *House GOP Inquiry over Gain-of-Function Research Targets a Scientific Giant*, STAT NEWS (June 22, 2023), https://www.statnews.com/2023/06/22/bernard-moss-niaid-gain-of-function-research-inquiry/.
[52] Letter from Dr. Bernard Moss to The Honorable Cathy McMorris Rodgers, Republican Leader, et al, H. Comm. on Energy & Commerce, (June 30, 2023) (included in Appendix I).

Analysis of the accuracy of Dr. Moss's response: This statement is materially misleading.

As written, the statement is clearly intended to give the impression that Dr. Moss's team did not consider transfers in the direction from clade I to clade IIa. It is also misleading because it suggests that the research approach was only linear and conditional (transfers from clade IIa to clade I, then the opposite direction) when, in fact, the Moss team presented an experimental proposal to the IBC that called for concurrent, bidirectional gene transfers.

September 21, 2023, Meeting with Dr. Moss and other NIH/NIAID Officials

The request for a transcribed interview was refused by HHS and the NIH, but led to a September 21, 2023, bipartisan Committee staff meeting with Dr. Moss and other HHS/NIH staff. Dr. Moss and other HHS/NIH staff gave lengthy, prepared opening remarks. Committee majority and minority staff were limited to about 22 minutes of questioning each. During the meeting, there were several problematic statements made.

In his written statement[53] for the September 21, 2023, meeting, Dr. Moss wrote:

- "Depending on the results of those experiments, I will consider additional gene exchanges that might include transfers in the opposite direction or involve clade IIb."

Analysis of the accuracy of the statement by Dr. Moss: This statement is materially misleading.

As with his June 30, 2023, letter, this statement implies that Dr. Moss's team did not consider transfers in the direction from clade I to clade IIa. In fact, such transfers were included in the 2015 submission to the IBC. It is also misleading because it suggests that the research approach was only linear and conditional (transfers from clade IIa to clade I first, then in a later potential experiment transfers would be made in the opposite direction, from clade I to clade IIa) when in fact the Moss team presented an experimental proposal to the IBC that called for concurrent, bidirectional gene transfers.

[53] Written Statement of Dr. Bernard Moss for E&C Committee Staff Interview, (Sept. 21, 2023) (included in Appendix II).

- "**I have not planned or proposed such experiments for approval** since we have not completed the current experiments and therefore do not yet know which genes might be best to transfer." [Bold added for emphasis].

  Analysis of the accuracy of the statement by Dr. Moss: This statement is materially misleading.

  While Dr. Moss personally did not propose such an experiment for approval, a researcher in his lab and under his supervision did include such an experiment in the 2015 submission before the IBC. The statement is also misleading for again suggesting the research approach was in only one direction, and that going in the direction of clade I to clade II was contingent on the results of experiments from the other direction. The research approach presented to the IBC was concurrent and bidirectional.

In his written statement[54] for the September 21, 2023, meeting, Dr. Steven Holland, Director of the Division of Intramural Research at NIAID, wrote:

- [Dr. Moss] "has **not at any point** pursued transferring genes from the more virulent strain into the less virulent strain, **nor has he made specific plans to do so**." [Bold added for emphasis].

  Analysis of the accuracy of the statement by Dr. Holland: This statement is materially misleading.

  It suggests that Dr. Moss and his team never pursued a research approach involving the direction of transferring genes from clade I into clade II. The 2015 IBC meeting minutes show that Dr. Moss' team sought approval that included this approach. The IBC meeting minutes indicated that the Moss team had taken preparatory steps for this research proposal by inserting reporter genes into the virus and by making certain deletions/mutations in five genes considered the most likely to be responsible for differences in virulence.

[54] Written Statement of Dr. Steven Holland for E&C Committee Staff Interview, (Sept. 21, 2023) (included in Appendix II).

In a written statement[55] for the September 21, 2023, meeting, Jeffrey Potts, MPH, CBSP, Chief of the Biorisk Management Branch within the NIH Division of Occupational Health and Safety, wrote:

- "Dr. Moss **does not have approval** to perform the specific experiments identified as the 'Clade 1 study.'" [Bold added for emphasis].

  Analysis of the accuracy of the statement by Mr. Potts: This statement contains a material omission of fact.

  This statement omits the fact that Dr. Moss and his team did get approval in 2015 to perform specific experiments identified as the clade I study. Documents viewed show that, in May 2023, the Moss team's Federal Select Agent Registration for MPXV was amended to exclude approval for gene transfers from clade I to clade II. This raises questions about what led to the revocation of the 2015 approval in May 2023. The May 2023 exclusion of approval was a recent change to the previous approval, and the NIH/NIAID should have been transparent about the history of this research project. Further, the statement that Dr. Moss "does not have approval" in the fall of 2023 omits that he did have approval from 2015 until May of 2023.

Dr. Moss was emphatic during this meeting that the MPXV experiment involving the transfer of genes from clade I to clade II as described in the September 2022 *Science* article was merely aspirational. At one point, he analogized his consideration of the gene transfer idea to discussing trips that one would want to take as in a "bucket list." He insisted that no steps had been taken to advance this idea, such as writing and/or planning the experiment, even if not conducted. All these assertions are contradicted by the 2015 application and subsequent approval by the IBC.

The Moss team's claims that the submission to the IBC in 2015 was not a formal proposal are unpersuasive. A submission of some kind was made to the NIH IBC, and the researcher had to respond to questions on the record in a meeting with recorded minutes. The IBC took a recorded vote to approve the experiment. It is reasonable to conclude a submission, a question-and-answer session, a meeting with recorded minutes, and a recorded vote constitutes a formal process. Furthermore, the NIH has produced no documentation that draws a distinction between an informal process and formal process before the IBC for approving intramural research experiments.

[55] Written Statement of Mr. Jeffery Potts for E&C Committee Staff Interview, (Sept. 21, 2023) (included in Appendix II).

Additional Observations

Inadequate IBC Review Process

The June 2015 IBC review of the bidirectional MPXV gene transfer experiment is troubling. The IBC approved this proposal, but the documents reviewed by Committee staff *in camera* at HHS did not reflect that the IBC acknowledged and considered the risks entailed with potentially making a much more transmissible MPXV clade with more lethality. Nor did the IBC examine whether a loss-of-function approach would be a viable and safer alternative.

The extent of the IBC's review was to acknowledge that the NIAID investigators should treat clade II MPXV as a select agent since there would be a gene transfer from MPXV clade I, which is classified as a federal select agent. There is no evidence in the record made available to Committee staff that shows the IBC assessed the risks of the bidirectional gene transfer experiment. Nor is there evidence in the record showing the IBC assessed the dual-use concerns.

While such reviews may not be apparently required, documents acquired by the Committee in its investigation of NIAID's management of the EcoHealth Alliance grant showed that during the 2014-2017 gain-of-function research pause, the NIAID DURC GOF committee reviewed projects for DURC and gain-of-function concerns, even though the projects were not covered by the funding pause. The June 2015 IBC review appears to have fallen short of these practices.

Lack of Ongoing NIAID Oversight

The MPXV research investigation has revealed other concerns. In addition to the flawed IBC review process, the annual progress reports[56] submitted by the Moss team for four consecutive years simply repeated the same generic summary paragraphs in each year to discuss their research activities. While publications were listed, there was no narrative discussion with updates on research activities.

The language in the "Goals and Objectives" and "Summary" sections were identical to the section language for four consecutive years. For the three years that followed, these sections were also identical but with an additional paragraph in the Summary section

[56] See Appendix III: Moss Annual Progress Reports.

describing some activities. Compared to the level of discussion and detail provided in extramural research annual reports, there is minimal information in the intramural research reports that would allow NIAID program officers to conduct meaningful oversight.

The summary information in the reports was not informative as to what was accomplished and how objectives were met. The NIH needs to reassess its requirements for annual intramural research reports in light of Principle 13 "Use Quality Information," in GAO's Standards for Internal Controls in the Federal Government (also known as "the Green Book").[57] In the alternative, if annual progress reports are not a useful oversight tool, the NIH should devise a more effective way to track the progress and accomplishments of its intramural research programs.

Conclusion & Next Steps

The Committee continues to seek information on this matter and will continue to request documents and answers about what research has been conducted and how it has been overseen. HHS, the NIH, and NIAID have not been forthcoming about the details of the MPXV gene transfer research efforts. In addition to refusing to produce relevant documents, HHS, the NIH, and NIAID made misrepresentations that misled the Committee and attempted to conceal the fact that transfers from clade I to clade II had been proposed and approved.

The obstructive behavior by HHS and the NIH is unacceptable. However, Committee staff believe that NIAID bears the most responsibility for misleading the Committee. The NIH's decentralized structure gives its institutes and centers a substantial level of autonomy in setting research priorities and managing grants, including approval and oversight of biosafety measures.[58] Further, the individuals with first-hand knowledge of events, subject matter expertise, and control of the documents related to the experiment are all employed by NIAID.

The Constitution assigns to Congress the power to legislate, including the implied authority to conduct oversight of federal government programs, including research impacting public health. Congress cannot discharge this duty of oversight if agencies, like NIAID, obstruct the collection of facts, analysis, and documents needed to assess policies to support critical research and to make sure it is conducted safely. The lack of transparency

[57] U.S GOV'T ACCOUNTABILITY OFFICE, GAO-14-704G, STANDARDS FOR INTERNAL CONTROLS IN THE FEDERAL GOVERNMENT 59 (2014), https://www.gao.gov/assets/gao-14-704g.pdf.
[58] CONG. RESEARCH SERV., *supra* note 14.

and lack of full cooperation undermines public trust in the NIH. The stubborn refusal to provide basic information about research of public concern warrants significant action by Congress to enhance oversight and control over NIH's risky activities.

Ultimately, this investigation and interim report underscore the importance of restoring public trust in our government health agencies as well as Congress reasserting its Article I authority. Transparency and accountability are the most pressing remedies.

Outstanding Questions

Two sets of major outstanding factual questions in this investigation remain.

The first set of outstanding questions relate to the MPXV experiments:

- Despite denials, did the Moss team, in fact, perform some or all of the proposed and approved experiments transferring genes from clade I to clade II (either clade IIa or IIb)?

- Does the NIH/NIAID leadership exercise sufficient oversight of its GOFROC/DURC research and researchers to be able to state with confidence whether or not such experiments were performed?

The second set of outstanding questions relate to the materially misleading and potentially false representations to the Committee by HHS, the NIH, and NIAID:

- If the experiments were not performed, why would HHS and the NIH/NIAID go to such great lengths to mislead the Committee about an approval for experiment that never occurred?

- Does this misleading and obstructive conduct merit holding the persons responsible in contempt of Congress or referral to the Department of Justice for violating 18 U.S.C. § 1001 and/or 31 U.S.C. § 3729?

Interim Findings and Recommendations

Despite these unresolved questions, the Committee can make the following interim findings and recommendations:

- **Finding:** Dr. Moss and his team at NIH formally proposed to IBC MPXV research involving gene transfers from clade I to clade II, and IBC approved this research.

- **Finding:** Mpox continues to evolve into a more significant public health threat. For the U.S. to be properly prepared, research is essential.

- **Finding:** Experiments involving pandemic or potential pandemic pathogens, including MPXV, pose a non-trivial risk to public health in the event of an accident leading to a breach of containment.

- **Finding:** NIAID has a culture of secrecy and obfuscation regarding experiments involving pandemic and potential pandemic pathogens. HHS and the NIH are complicit in enabling NIAID's culture of secrecy and obfuscation. This is incompatible with accountable, democratic governance and further erodes the public's trust in government health agencies.

- **Finding:** Congress and the American people must have a working relationship with the NIH and federal biomedical research enterprise that is built on trust and transparency.

- **Finding:** Principal investigators, research institutes, and funding agencies are poorly positioned to, and perhaps incapable of, conducting adequate risk/benefit analysis and oversight of experiments that—by virtue of having proposed them and approved their funding—they want to see conducted. This is an inescapable conflict of interest and misalignment of incentives that results in experiments being approved and conducted without sufficient scrutiny or ongoing oversight.

- **Recommendation:** Remove final review and approval for experiments involving GOFROC/DURC from the NIH/NIAID. Under the recently released *United States Government Policy for Oversight of Dual Use Research of Concern and Pathogens with Enhanced Pandemic Potential*, this would remove final approval for Category 1 Research from NIAID. Committee staff should evaluate whether removal of final review and approval authority should be limited to the NIH/NIAID or applied to all federal departments and agencies funding such research.[59]

[59] While outside the scope of this interim report, committee staff believe several of the definitions in the policy are too narrow to effectively achieve the policy's stated purpose. For example, the definition of pathogen with pandemic potential (PPP) is limited to those "likely capable of wide and uncontrollable spread

- **Recommendation:** Consider expanding the role of the HHS P3CO or its successor entity to include making determinations about whether a research project should be subject to its review framework. If HHS P3CO cannot or will not appropriately accomplish this charged duty, Congress should consider alternative entities. Such review authority must be wholly independent of the NIH/NIAID and should be empowered and charged with making a final determination as to whether a proposed experiment involving GOFROC/DURC in a grant that NIAID has selected for funding should be approved, modified, or rejected. Such entity should issue regular, detailed reports of its determination decisions. Any such leadership or board members should be free of conflicts of interest, and member composition and identity should be made publicly available. Congress could consider whether Senate confirmation of leadership or members is desirable. Congress should also examine what, if any, additional biosecurity or biosafety functions or policy responsibilities should be relocated to such reviewing entity or committee.

- **Recommendation:** Require institutions conducting NIAID-funded research involving potentially dangerous agents to establish community oversight boards, similar to those currently required for high-containment biosafety level four laboratories.

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in a human population and would likely cause moderate to severe disease in humans." *See Section 3.K*. Thus, many of the most likely pandemic pathogens such as Ebola, Mpox, SARS-like viruses that bind to hACE2, MERS-like viruses that bind to the DPP-4 receptor, Nipah, Hendra, and highly pathogenic avian influenza, among other, do not qualify as potential pandemic pathogens simply because they have yet to spillover and cause widespread human to human transmission even though scientific consensus is that these viruses pose a serious pandemic threat. As written, the definition is too backwards looking and inappropriately exempts viral discovery and characterization work (like that performed at the Wuhan Institute of Virology) from additional biosafety review.

Moreover, Category 2 Research – which is subject to department level review – is limited to experimental outcomes that are reasonably anticipated to enhance transmissibility, virulence, or immune evasion in humans. The publicly stated positions of NIH and NIAID leadership would exempt almost all gain-of-function experiments from Category 2 review. NIH and NIAID leadership take the position that experimentally infecting animal models, including those animal models used as a stand-in for humans such as humanized mice and ferrets, with PPP or enhanced PPP is irrelevant to determining whether it a pathogen is reasonably anticipated to be transmissible or cause disease in humans.

Committee staff believe a sounder approach would be to define potential pandemic pathogens as "a pathogen that is likely capable of wide and uncontrollable spread in mammals and would likely cause moderate to severe disease and or mortality in mammals." Similarly, Category II Research Experimental Outcomes or Actions (Section 4.2.2) should also be defined in the context of mammals instead of limited to humans. This would result in experiments involving potentially dangerous emerging viruses with pandemic potential, such as those listed above, receiving appropriate, additional biosafety and biosecurity reviews.

Congress should consider whether to give such community oversight boards veto authority over proposed experiments.

Appendix I

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

April 26, 2023

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Chair Rodgers:

Thank you for your March 30, 2023, letter regarding research on mpox, formerly known as monkeypox, and the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH). NIAID and NIH take the safe and secure conduct of research very seriously and have robust guidance, procedures, and protocols in place to ensure that intramural and extramural scientists, including those proposing research on mpox, maintain the highest possible standards for biosafety and biosecurity, as well as follow all applicable laws and regulations. I am pleased to respond on behalf of NIH.

At the outset, I want to respond specifically to the portion of your letter that described a September 2022 *Science* article that referenced a potential sub-project, which you called the "clade 1 study." This study has not been formally proposed, and NIAID has no plans to move forward with this research. This type of research would require a formal proposal to be submitted for review, and the proposal would need to undergo the rigorous review process described in this letter before it could be initiated.

By way of background, NIH intramural projects are required to follow all applicable NIH policies and procedures, including adherence to biosafety and biosecurity guidance as outlined in the current edition of the Biosafety in Microbiological and Biomedical Laboratories, the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines),[1] the Federal Select Agent Regulations,[2] and other applicable regulations as appropriate. All NIH intramural research is subject to a standard review process whenever new experimental procedures are scientifically necessary. This standard NIH intramural review process includes specific requirements based upon the proposed experiments and initiates upon submission of a research proposal to the relevant committees. Notably, the proposed research cannot begin until approved by all relevant entities.

[1] NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. https://osp.od.nih.gov/wp-content/uploads/2019_NIH_Guidelines.htm
[2] Federal Select Agent Program. Select Agents Regulations. https://www.selectagents.gov/regulations/index.htm

The NIH Institutional Biosafety Committee (IBC)[3] formally reviews any NIH intramural research proposing to use recombinant and/or synthetic nucleic acid molecules in accordance with the NIH Guidelines, in the context of research involving potentially infectious human, plant, or animal materials; human pathogens; and human and non-human primate blood, tissues, and body fluids, including primary human cell cultures. The NIH IBC also determines the required biosafety level and biocontainment measures for any proposed research during this review. Such proposed research then undergoes review by any other appropriate entities, including the Dual Use Research of Concern (DURC) Institutional Review Entity (IRE), if appropriate.

The DURC-IRE is the NIH authority for the oversight and evaluation for proposed research that may fall under the Department of Health and Human Services' (HHS) *Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* (HHS P3CO Framework).[4] As noted in the HHS P3CO Framework, proposed intramural and extramural life sciences research that is being considered for funding and that has been determined by the funding agency as reasonably anticipated to create, transfer, or use enhanced potential pandemic pathogens is subject to additional HHS department-level review.

NIH research involving select agent strains and recombinant work is always performed in close collaboration with the Federal Select Agent Program (FSAP)—which is managed jointly by the Centers for Diseases Control and Prevention and the Department of Agriculture[5]—and the entity Responsible Official to ensure compliance with applicable regulations and subjected to any reviews FSAP deems appropriate.

Your letter inquired about research involving the mpox virus. By way of background, the mpox virus is made up of two genetically distinct clades. Clade I mpox viruses, endemic in the Congo Basin, cause more severe disease than the Clade II mpox viruses, which are endemic to Western Africa. The Clade II mpox virus also consists of two subclades—Clade IIa and IIb. The current global mpox outbreak is driven by a Clade IIb virus, but circulation of both Clade I and Clade IIa in Africa presents an ongoing risk of future regional and global outbreaks of these viruses. The genetic basis for the variability in disease outcomes of the two clades is unknown. Additional research to identify the viral components that account for the observed differences in mpox disease severity between the two clades could help determine key targets within the mpox virus genome for the development of medical countermeasures.

Your letter also referenced a specific NIAID intramural project—*Poxvirus Host Interactions, pathogenesis and immunity*, 1ZIAAI000979. This project includes research on several orthopoxviruses including vaccinia virus, cowpox virus, and mpox virus. The mpox projects include development of a small animal model, investigation of the basis for mpox pathogenicity, assessment of mpox vaccines, and analysis of mpox clade differences. One approach to studying mpox clade differences was proposed and approved in 2015 and involves the generation of chimeric viruses—viruses that incorporate genes from two mpox strains. This ongoing sub-project includes only chimeric viruses created by replacing genes in the more virulent Clade I

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[3] NIH Policy Manual – Chapter 3035. https://policymanual.nih.gov/3035
[4] HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens. https://www.phe.gov/s3/dualuse/documents/p3co.pdf
[5] Federal Select Agent Program. https://www.selectagents.gov/

virus with genes from the less virulent Clade IIa virus. The project was conceived and approved years before the recent mpox outbreak, and it does not include any studies with the circulating Clade IIb virus.

When the sub-project was proposed in 2015, the proposed experiments were subject to a rigorous review process and were subsequently approved. Since 2009, mpox research within the NIAID intramural program has been registered with the FSAP. As required by the FSAP, the NIAID intramural program FSAP registration was updated to reflect the mpox research when the experiments were approved. During FSAP inspections, all NIH IBC-related documents and minutes are reviewed. This work would not meet the definition of a restricted experiment and was not reviewed by the Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC), all strains created were inventoried and treated as select agents, and the FSAP did not determine ISATTAC review was required based on the project description and detail included in our select agent registration.

After the approval of the proposed experiments in the mpox sub-project investigating clade differences, NIAID investigators generated chimeric viruses by replacing certain genes of Clade I mpox virus with the corresponding genes of Clade IIa virus and infecting an appropriate mouse model with them to determine if any of the genetic changes could decrease the severity of mpox disease caused by the Clade I virus. To date, these experiments have not identified the genetic underpinnings of the observed increased pathogenicity of the Clade I mpox viruses, indicating that further research is necessary to determine these critical genetic factors.

Throughout these experiments, all viruses—including the new chimeric viruses—were handled and inventoried as select agents, and all work with select agent strains was performed in compliance with the requirements in the Federal Select Agent Regulations and NIH policies regarding biological materials. For these experiments, all live viruses were handled at a Biosafety Level 3 (BSL-3) laboratory, in select agent registered facilities, by personnel with approved security risk assessments, and with approval through the NIH Biological Surety Program.[6] While the experiments were subject to the Federal Select Agent Regulations, including registration of planned recombinant work, none of the experiments meet the definition of a restricted experiment as outlined in Federal regulations.[7]

As stated above, the September 2022 *Science* article noted in your letter referenced a potential sub-project, which your letter refers to as the "clade 1 study," that has not been formally proposed. This potential sub-project would include the generation of chimeric viruses by replacing genes in the less virulent Clade IIa virus with those in the more virulent Clade I virus. To reiterate, NIAID has no plans to move forward with this research. As detailed above, this type of research would require a formal proposal to be submitted for review, and the proposal would need to undergo the rigorous review process described in this letter before it could be initiated. This review process would specifically include an assessment of whether the research may be subject to the HHS P3CO Framework.

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[6] NIH Policy Manual – Chapter 3037. https://policymanual.nih.gov/3037

[7] Code of Federal Regulations. 42 CFR Part 73.13. https://www.ecfr.gov/current/title-42/chapter-I/subchapter-F/part-73/section-73.13

The mpox virus causes significant disease and death in the regions in which it is endemic, with an increasing incidence of human infections. Even prior to the ongoing global outbreak of mpox in non-endemic countries, this virus was identified by NIAID and others as an important global health threat in light of sporadic outbreaks associated with international travel. NIAID is conducting and supporting research focused on developing and evaluating treatments and vaccines for mpox, understanding disease transmission and spillover, evaluating immunological characteristics of mpox, and bolstering support for the ongoing public health response. However, NIAID is not supporting research that would include experiments to replace genes in the less virulent Clade IIa virus with those in the more virulent Clade I virus, and there are currently no plans to do so.

Thank you for your interest in NIH's mpox virus research. NIAID and NIH prioritize robust biosafety and biosecurity in intramural research. If you or your staff have any questions, please feel free to contact the Office of the Assistant Secretary for Legislation at (202) 690-7627.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

June 30, 2023

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chair Rodgers:

Thank you for your March 30, 2023, and May 30, 2023, letters regarding research on mpox, formerly known as monkeypox, at the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH). The enclosed document is a letter from Dr. Bernard Moss, NIH Distinguished Investigator at the Laboratory of Viral Diseases at NIAID.

If you or your staff have any questions, please feel free to contact the Office of the Assistant Secretary for Legislation at (202) 690-7627.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

June 30, 2023

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Chair Rodgers:

As your letter of May 30 referred to my research, I thought it would be helpful if I replied directly to clarify my goals and clear up any misunderstandings. First, I would like to describe my education and research background. After receiving an M.D. from the New York University School of Medicine, I interned at Children's Hospital Medical Center in Boston, and then completed a Ph.D. in biochemistry at the Massachusetts Institute of Technology. I then enlisted in the U.S. Public Health Service in 1966 and was detailed to the National Institutes of Health (NIH), where I joined the Laboratory of Biology of Viruses in the National Institute of Allergy and Infectious Diseases (NIAID) as a Medical Officer. I was subsequently promoted to the dual positions of Chief of the Laboratory of Viral Diseases, a position that I held for about 35 years, and Chief of the Genetic Engineering Section, a position that I still hold that allows me to do research full-time.

For more than 50 years I have investigated the biology and host interactions of poxviruses and have published more than 800 original scientific papers on the subject, and several of my inventions have been patented by the U.S. Government. My contributions have been recognized by election to the National Academy of Sciences and the receipt of prestigious awards, the most recent being the Lifetime Achievement Award by the American Society for Microbiology.

My research on mpox began about 15 years ago when I moved my research into the newly constructed C.W "Bill" Young Center (building 33), named for the congressman who was a strong proponent of biomedical research during his more than three decades in the House of Representatives. This high containment facility allows NIH to safely carry out basic research on infectious diseases of global importance that occur naturally or may be caused by agents intentionally released through an act of bioterrorism. All my research on the mpox virus has been carried out under BSL-3 and ABSL-3 containment in building 33, using protocols that have been approved by a rigorous review process.

Mpox is a zoonosis that has been increasing in incidence in Africa since it was first recognized in 1970, but largely neglected by the outside world. Historically, there have been more cases of mpox in Central Africa than in West Africa and the severity of the disease is higher in the former. In that respect, it is fortunate that all cases of mpox outside of Africa have been caused by the less virulent clade II virus from West Africa rather than clade I from Central Africa. Nevertheless, we should be prepared for the possibility of the more virulent Central African

clade I virus escaping from Africa in the future. A goal of my mpox research is to determine the basis for the greater virulence of clade I compared to clade II viruses to better contain such a potential outbreak. A step toward this goal has been the development of a small animal model that mimics the severity of human disease caused by clade I and clade II mpox viruses. The work was published this year showing that the lethality of mpox virus in our model is clade I > clade IIa > clade IIb. The finding that the current clade IIb outbreak strain is less virulent than either clade I or clade IIa in our model is consistent with the self-limiting disease in immunocompetent adults, although mpox can be devastating in individuals with AIDS or other immunodeficiencies.

Our next step is to use this model to determine the basis for the differences in virulence of mpox virus clades I and II. Fortunately, we developed the tools to do this during our previous research. The virulence genes of vaccinia virus, the vaccine used to prevent smallpox, were identified by constructing recombinant viruses in which genes were deleted or modified and testing them in animal models. We received approval from the Institutional Biosafety Committee to carry out related experiments in which genes from the more virulent mpox clade I virus were replaced with the corresponding genes from the less virulent clade IIa virus. The expectation of such experiments is that chimeric clade I virus will be attenuated when the genes responsible for virulence are replaced. However, mpox virus contains about 200 genes, so this is an arduous task and is still ongoing. Depending on the results of these experiments, I will consider additional gene exchanges that might include transfers in the opposite direction or involve clade IIb. I have not planned or proposed such experiments for approval since we have not completed the current experiments and therefore do not yet know which genes might be best to transfer. However, should it appear in the future that such an experiment would greatly contribute to understanding the basis for mpox virus virulence, then I may make such a proposal and would abide by the decision of the Institutional Biosafety Committee.

Lastly, with respect to the *Science* magazine article referenced in your letter, it would have been more accurate for that reporter to use the word "considering" rather than "planning" to represent the stage of my thinking about potential future research on the mpox virus.

Sincerely yours,

Bernard Moss

Bernard Moss M.D., Ph.D.
NIH Distinguished Investigator
Laboratory of Viral Diseases, NIAID

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

July 25, 2023

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chair Rodgers:

We are in receipt of your July 21, 2023, letter to the Department of Health and Human Services (Department) regarding research on mpox, formerly known as monkeypox, and the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH).

In response to your March 30 letter regarding a *Science* magazine article on mpox virus research, the Department informed the committee on April 26 that the experiment on which your letter was premised had not been conducted. We also clearly stated that NIAID does not presently have any plans to move forward with such an experiment.[1] Despite this clear representation, on May 30 the committee sent another letter to the Department claiming it was "still unclear whether this research may have been conducted, or even how NIAID knows that this research was not conducted." In a June 30 letter that was drafted and personally signed by Dr. Bernard Moss, an NIH Distinguished Investigator with whom you requested a videotaped transcribed interview regarding the experiment that has not happened, Dr. Moss himself reiterated that the experiment at issue had not been conducted and there were currently no plans to do so.[2]

The Department believed—and continues to believe—these April 26 and June 30 letters reflect appropriate accommodations that addressed the committee's questions regarding this matter. Moreover, the insinuation in the committee's July 21 letter that the June 30 letter signed by Dr. Moss was not from Dr. Moss is entirely baseless. This unfounded questioning of the authenticity of Dr. Moss's letter is inappropriate and appears to be part of this committee's persistent refusal to accept the information provided in a good-faith effort to satisfy the committee's inquiry. This type of accusation is detrimental to the continuing relationship between co-equal branches of government and serves as another example of the committee engaging in groundless attacks that amount to intimidation simply because it is dissatisfied with the Department's response to its inquiries.

[1] April 26, 2023, letter to Committee on Energy and Commerce Chair Cathy McMorris Rodgers from Assistant Secretary for Legislation Melanie Anne Egorin.
[2] June 30, 2023, letter to Committee on Energy and Commerce Chair Cathy McMorris Rodgers from Dr. Bernard Moss, NIH Distinguished Investigator, Laboratory of Viral Diseases, NIAID.

Nevertheless, in yet a further effort to work with the committee in good faith consistent with the accommodation process, the Department is willing to coordinate a briefing with appropriate NIH officials, as well as Dr. Moss, so the committee can ask any further additional questions it may have relevant to its March 30 inquiry.

If you or your staff have any questions, please feel free to contact the Office of the Assistant Secretary for Legislation at (202) 690-7627.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

October 31, 2023

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chair Rodgers:

The Department of Health and Human Services (HHS or Department) is in receipt of your October 20, 2023, letter to the National Institutes of Health (NIH) regarding certain research on mpox, formerly known as monkeypox, and the National Institute of Allergy and Infectious Diseases (NIAID). I am pleased to respond on behalf of NIH.

NIH and the Department have made significant accommodations to address the committee's inquiry regarding a potential experiment the committee has referred to as the so-called "clade 1 study." As you know, when the committee began its inquiry, you raised questions regarding whether the "clade 1 study" "was reviewed under the HHS P3CO framework," in addition to the Federal Select Agent Program (FSAP) and the Centers for Disease Control and Prevention's Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC). In response, the Department informed the committee that the "clade 1 study" had not been conducted. We also explained that NIAID does not presently have any plans to move forward with such an experiment, and if it did in the future, any such research would need to undergo a rigorous review process, including an assessment of whether the research may be subject to the HHS P3CO Framework.[1]

Despite this clear response tailored to the committee's stated concerns, the committee subsequently claimed it was "still unclear whether this research may have been conducted." In an extraordinary accommodation, the Department conveyed to the committee a June 30 letter that was drafted and personally signed by Dr. Bernard Moss, an NIH Distinguished Investigator with whom you requested a transcribed interview regarding the "clade 1 study." In his letter, Dr. Moss reiterated that the experiment at issue had not been conducted and that there were currently no plans to do so.[2]

The committee then shifted to baselessly questioning the authenticity of Dr. Moss's June 30 letter. Once again, the Department offered the committee an extraordinary accommodation

[1] April 26, 2023, letter to Committee on Energy and Commerce Chair Cathy McMorris Rodgers from Assistant Secretary for Legislation Melanie Anne Egorin.
[2] June 30, 2023, letter to Committee on Energy and Commerce Chair Cathy McMorris Rodgers from Dr. Bernard Moss, NIH Distinguished Investigator, Laboratory of Viral Diseases, NIAID.

tailored to its newly stated concerns, arranging for a bipartisan briefing that allowed committee staff to hear directly from Dr. Moss and ask questions regarding his mpox research, as well as hear from senior NIH officials who oversee NIH's intramural research program and high containment laboratories.[3] During the briefing, majority staff used effectively all its time on one line of narrow questioning directed only at Dr. Moss regarding a September 2022 *Science* article—the same article that Dr. Moss already told the committee had mischaracterized his stage of thinking about potential future mpox research.[4]

The Department believes these accommodations appropriately addressed the committee's shifting slate of stated concerns regarding this matter. Your October 20 letter, however, appears to shift the premise of your inquiry yet again—inserting wholly new document requests and materially changing your scope, all while failing to give due consideration to the significant accommodations the Department has provided the committee to date. On top of that, the committee is now threatening to resort to compulsory process if the requested documents are not produced by the committee's dictated deadline—despite the fact that the Department has consistently engaged with the committee in good faith and provided appropriate accommodations tailored to your stated concerns.

Your current approach is particularly troubling given that the committee has now threatened to use compulsory process in at least six different matters involving the Department over the last month alone—materially frustrating the Department's ability to identify your priorities and continue to respond to your various requests, which currently include a significant number of requests for transcribed interviews with senior NIH officials and voluminous document requests, all of which the Department is actively working to address. This reflexive threat to issue compulsory process is inconsistent with the constitutionally mandated accommodation process and a disservice to both the committee and the Department.

NIH and the Department intend to continue cooperating with the committee voluntarily in this matter, in good faith, and consistent with the accommodation process. To that end, enclosed with this letter is an initial production of materials. As we have conveyed to your staff, we welcome a discussion regarding the prioritization of your various requests.

If you or your staff have any questions, please feel free to contact the Office of the Assistant Secretary for Legislation at (202) 690-7627.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

cc: The Honorable Frank Pallone, Jr., Ranking Member

[3] July 25, 2023, letter to Committee on Energy and Commerce Chair Cathy McMorris Rodgers from Assistant Secretary for Legislation Melanie Anne Egorin.
[4] *See* June 30, 2023, letter to Committee on Energy and Commerce Chair Cathy McMorris Rodgers from Dr. Bernard Moss, NIH Distinguished Investigator, Laboratory of Viral Diseases, NIAID.

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

October 31, 2023

VIA EMAIL DELIVERY

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chair Rodgers:

The enclosed documents are a production of materials in response to your March 30, 2023 and October 20, 2023, letters to the National Institutes of Health (NIH) regarding mpox research. Today's production bears documents in bates range: ECMPOX000001 to ECMPOX000015.

By producing these documents, the Department of Health and Human Services (HHS) is making an accommodation unique to the facts and circumstances of this particular matter in a good faith effort to assist the Committee in its inquiry. We respectfully request that the Committee not disseminate or otherwise disclose these documents outside of the Committee without prior consultation with HHS. The production of these materials does not waive any applicable privilege. Should you have any questions regarding this document production, please have your staff contact Daria Berstell at Daria.Berstell@hhs.gov.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

Enclosures

cc: The Honorable Frank Pallone, Jr., Ranking Member

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

March 19, 2024

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Chair Rodgers,

I write in further response to your March 30, 2023, and October 20, 2023, letters regarding certain research on mpox and the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH).

In your March 30, 2023, letter, you requested information pertaining to NIAID intramural project *Poxvirus Host Interactions, pathogenesis and immunity*, 1ZIAAI000979, including a potential sub-project your letter refers to as the "clade 1 study" to transfer genes from clade 1 mpox into the clade 2 mpox virus currently circulating in humans (now referred to as clade 2b). Since the Department of Health and Human Services' (HHS or Department) April 26, 2023, response, we have collected additional documentation pertaining to the NIH Institutional Biosafety Committee (IBC) review in 2015 and 2018 of experiments involving clade 1 and a clade 2 virus now known as clade 2a, which appeared years before the different clade 2b virus that was first identified in 2022.

The documentation, which is also being provided to the committee *in camera* on March 20, indicates that, during the 2015 IBC review, research involving bidirectional transfer of genes between clades 1 and 2 of the mpox virus was considered and approved by the IBC. However, as has been previously shared with the Committee, no such research involving the replacement of genes in either the clade 2a or clade 2b viruses with genes from clade 1 has been performed, nor are there currently any plans to do so. Additionally, as is reflected in the newest set of documents, the research team stated during a 2018 IBC review that they would not conduct this experiment without further discussions with the IBC. Should the research team want to conduct such an experiment in the future, it would first need to be reviewed and approved by the NIH IBC before proceeding. We appreciate the opportunity to provide this additional clarification.

HHS and NIH take the safe and secure conduct of research very seriously and have robust guidance, procedures, and protocols in place to ensure that intramural and extramural scientists, including those proposing research on mpox, maintain the highest possible standards for biosafety and biosecurity, as well as follow all applicable laws, regulations, and policies. If you

or your staff have any questions, please feel free to contact the Office of the Assistant Secretary for Legislation at (202) 690-7627.

Sincerely,

Melanie Anne Egorin

Melanie Anne Egorin, PhD
Assistant Secretary for Legislation

cc: The Honorable Frank Pallone, Jr., Ranking Member

Appendix II

As prepared

Briefing for the Committee on Energy and Commerce Opening Statements
September 21, 2023

Steven Holland, MD

My name is Dr. Steven Holland. I am an infectious disease physician and serve as the Director of the Division of Intramural Research of the National Institute of Allergy and Infectious Diseases (NIAID). I received my MD from Johns Hopkins in 1983 and stayed there to serve as a resident in internal medicine before becoming a chief resident and then a fellow in infectious disease. I came to the NIAID in 1989 and have remained here ever since. I have been Director of the Division of Intramural Research since 2016. Previously I served as Chief of the Laboratory of Clinical Infectious Diseases. The intramural program of NIAID consists of about 130 scientists and about 1500 total employees. Our portfolio includes basic and clinical investigation into viral, fungal, and bacterial diseases as well as the underlying immunologic defects that make these diseases severe. We are particularly lucky to have Dr. Bernard Moss as one of our most prestigious tenured faculty. Dr. Moss has been the preeminent pox virologist in the world for decades and his work has materially increased our understanding of pox viruses in general and mpox in particular. My goal today is to tell you about some of our work around mpox.

Just last year, in 2022, more than 86,000 people in more than 100 countries were infected with mpox. This constituted a true public health emergency of international concern. This was not entirely new, the incidence of mpox has been rising over the last 50 years in Africa and infected travelers have been identified in many countries. Mpox was first discovered in captive monkeys in 1958. Human infections derived from animals were identified first in the 1970s. Mpox as an incubation period of 5 to 21 days and is evidenced by fever, rash, and lymph node swelling. Although it looks a lot like smallpox, it is not: the mortality from mpox in Africa ranges from 4 to 10%, while that of smallpox is about 30%. Most cases of mpox have been in the Democratic Republic of the Congo. Mpox is less severe in West Africa than Central Africa but the West African incidence has been increasing. Importantly, this is a disease that can have outbreaks. After 39 years without any cases there was an outbreak in Nigeria in 2017, affecting 2635 people. Although the animal source of mpox is still somewhat unclear, it is apparent that many different rodents, primates and other animals can harbor and transmit it.

Let me spend a moment on nomenclature. There are different strains of mpox that are typically referred to as clades. Currently three clades are identified: clade I is in Central Africa, whereas clades IIa and IIb are in West Africa. Only about 5% of the genomes of clades I and II differ, while the differences between clades IIa and IIb are even less. Clade IIb has a particular activity (APOBEC3B cytosine deaminase activity) that may be relevant to human transmission.

While the occurrence of mpox outside of Africa has been uncommon until recently, the outbreak beginning in 2022 has been dramatic and severe. Luckily, the mortality from this outbreak has been relatively low except in those with underlying immune deficiencies. Sequencing of these viruses has indicated that they arise from clade IIb and likely arose from Nigeria.

We are lucky to have Dr. Bernard Moss as a member of our institute. Dr. Moss has devoted his career to studying pox viruses and has pioneered this area. In fact, it was his brilliant insight to

study mpox, even when it was not an epidemic infection, in order to generate the kind of information that we have today. That information serves as the foundation for the development of a whole variety of strategies, including the vaccine that is now used to prevent mpox (Jynneos). Dr. Moss's critical insight was to recognize that the different strains or clades of mpox had different levels of virulence. Clade I was very virulent, while clade II was not. Therefore, since only about 5% of the DNA differed between these two strains, there must be specific DNA differences that determined why one strain was highly virulent and fatal in up to 10% and the other less so. These molecular changes are critical to identify if we are going to understand viral pathophysiology and human disease. Dr. Moss's innovation, using the molecular tools his laboratory developed, the building infrastructure and the extensive safety support of the NIH, was to replace specific genes of the more virulent clade I with genes from the less virulent clade IIa to see if he could diminish the virulence of the more severe virus in a rodent model. This is the most cautious approach, trying to attenuate the virulent strain, and this was the approach that Dr. Moss has taken. He has not at any point pursued transferring genes from the more virulent strain (clade I) into the less virulent strain (clade II), nor has he made specific plans to do so. If the latter strategy were to be pursued in the future, it would be preceded extensive consultation and rigorous evaluation and review by the committees that Jeff Potts will discuss shortly, which exist to ensure in-depth safety assessments.

Let me speak for a moment about the imperative of performing this kind of research. It remains a deep concern to all of us thinking about pandemic preparedness that we may be only a plane flight away from transmission of a more virulent strain of mpox, clade I. The fact that the epidemic strain of 2022 was from the less virulent clade II is a wake up call that we need higher vigilance and much more research in order to identify and create appropriate countermeasures. In fact, it was Dr. Moss's work in particular that proved that Jynneos was effective against mpox in nonhuman primates, which indicated that this would likely be successful for preventing mpox in humans.

I genuinely appreciate and share the concern of this committee, as do my colleagues, to understand, anticipate and prevent pandemic disease. We are all in agreement that viral infections are a concern for the entire human family. I believe we are also in agreement that it is only through careful, insightful scientific research that we will be able to anticipate, understand, prevent, and treat these deadly diseases.

As prepared

Bernard Moss, MD, PhD

Good afternoon. My name is Bernard Moss. I am an Investigator and Section Chief in the National Institute of Allergy and Infectious Diseases. I joined NIAID as a Medical Officer in 1966. For more than 50 years I have investigated the biology and host interactions of poxviruses including mpox for the last 15 years.

My current mpox research has two major goals.

The first, which has taken precedence since the 2022 outbreak of mpox, is to develop improved vaccines using mRNA and protein lipid nanoparticles. I am happy to say that the mRNA vaccine is now recruiting subjects for a clinical trial.

The second and longer-term goal is to determine the genetic basis for the difference in virulence of mpox virus clades. Such information could open new opportunities for managing and treating mpox and predicting the impact of new strains should they arise.

To achieve both goals, we developed a small animal model that mimics the severity of disease caused by mpox virus in humans (clade I>IIa>II2b). My laboratory previously developed ways of deleting and replacing genes of vaccinia virus, the prototype poxvirus used as the smallpox vaccine. Such studies had allowed us to determine the roles of genes involved in virus replication and host interactions using a mouse model.

Similarly, I am now investigating the genetic basis for differences in the virulence of clade I and clade IIa mpox virus by replacing genes of the clade I virus with genes of a clade IIa virus. I want to emphasize that clade IIa viruses have caused few human mpox cases in Africa and human-to-human transmission has never been reported anywhere, in contrast to the clade I and clade IIb current outbreak strain.

Following institutional approval, we began to replace genes of the virulent clade I with the corresponding genes of clade IIa, with the expectation that virulence of the chimeric virus would be less than that of clade I. Since there is evidence for human-to-human transmission of clade I, but none for clade IIa, the expectation is that the chimeric virus would also be less transmissible.

To date, we have exchanged approximately 50 of the 200 genes but have seen no effect on virulence. We are considering three main possibilities: (1) we have not yet exchanged the individual genes most important for the difference in virulence, (2) virulence is due to multiple genes acting together, or (3) two or more genes have redundant functions.
Replacement of additional clade I genes will be necessary to evaluate these possibilities.

Depending on the results of those experiments, I will consider additional gene exchanges that might include transfers in the opposite direction or involve clade Ilb. I have not planned or proposed such experiments for approval since we have not completed the current experiments and therefore do not yet know which genes might be best to transfer. However, should it appear in the future that such an experiment would greatly contribute to understanding the basis for

mpox virus virulence, then I may make such a proposal and would abide by the decision of the Institutional Biosafety Committee.

Research on mpox virus has been neglected since its discovery in the late 1950's. However, the 2022 mpox outbreak provided a wakeup call that the disease is not exclusively an African problem. We need to be prepared for greater adaptation of mpox virus to humans and prevent the importation of the more virulent clade I virus. Although the mpox virus clades I, IIa and IIb have been geographically segregated, climate change may alter the distribution of animal hosts and greater human travel within Africa may cause a mixing of clades. By developing a small animal model that mimics the severity of mpox disease, we are now able to safely carry out experiments to determine the genetic basis for the virulence of current mpox virus clades, anticipate changes that could lead to greater virulence, and develop new therapeutics that target virulence genes.

As prepared

Jeffrey Potts, MPH, CBSP

My name is Jeff Potts, and I am currently the Chief of the Biorisk Management Branch within the NIH Division of Occupational Health and Safety. The DOHS, which resides within the Office of the Director, provides leadership in the development and implementation of occupational health policies, standards, and procedures applicable to biomedical research that is conducted throughout our intramural program. Specifically, the Biorisk Management Branch is responsible for providing regulatory compliance oversight and expert guidance to the NIH community for matters involving research with high-consequence pathogens. Among other activities, the Biorisk Management branch is responsible for implementing the NIH Select Agent Program and administering the NIH Institutional Biosafety Committee and Institutional Review Entity.

Compliance with, and constant oversight over, the implementation of biosafety standards is extremely important to our mission. At NIH, all research involving human, plant, or animal pathogens as well as experiments involving recombinant or synthetic nucleic acid molecules, are reviewed and assessed by the IBC and if applicable, the IRE. Together, these committees review submitted proposals to ensure compliance with the NIH Guidelines, the BMBL, USG Policies involving Dual Use Research of Concern and the USG P3CO framework. The NIH has been a leader in this effort starting back in 2009 and most recently, evaluating our review process against the proposed recommendations of the NSABB.

Dr. Moss does not have approval to perform the specific experiments identified as the "Clade I study". If Dr. Moss formally proposes this line of research in the future, it would be subject to a rigorous evaluation and review by the committees which I have already mentioned. This process would be true of any formally proposed research at NIH. Our office is fully committed to ensuring compliance with all applicable regulations and policies. We will continue to monitor this research and future regulatory changes for any impact that it might have on our internal review processes.

Appendix III

NIH Annual Intramural Research Report

ZIA AI000979-10

Report Title
Poxvirus pathogenesis and immunity

2015 Fiscal Year
October 01, 2014 - September 30, 2015

Principal Investigator
Bernard Moss, MD, PhD

Research Organization
Genetic Engineering Section

Lab Staff and Collaborators within the *Genetic Engineering Section*
Patricia Earl, PhD
Jeffrey L Americo, MS
Gilad Silvan
Ruikang Liu, PhD
Debasis Panda
Jorge David Mendez Rios
Sara E Reynolds
Catherine Griffin

Collaborators from other NIAID organizations
There were 1 collaborators within NIAID

Timothy G Myers, PhD	Research Technologies Branch

Collaborators from other NIH organizations
There were 3 NIH collaborators from other Institutes/Centers

Eugen Christian Buehler, PhD	NHGRI
Scott E Martin, PhD	NCATS
Pinar Tuzmen	NHGRI

Keywords
monkeypox virus pathogenesis, orthopoxvirus pathogenesis, poxvirus pathogenesis, vaccinia virus pathogenesis, cowpox virus pathogenesis, poxvirus immunity, smallpox vaccine, cell mediated immunity, cytokines, monoclonal antibodies

Goals and Objectives
The goals of this project are to increase our understanding of poxvirus pathogenesis and the basis for immunity to poxviruses. We are particularly interested in the members of the orthopoxvirus genus, which include variola virus (the causal agent of smallpox), vaccinia virus (used as the smallpox vaccine), cowpox virus (causes zoonotic infections) and monkeypox virus (causes of human monkeypox in parts of Africa).

Summary
Poxviruses comprise a large family of complex DNA viruses that have vertebrate and invertebrate hosts. Two poxviruses, variola virus and molluscum contagiosum virus, are specific human pathogens. Variola virus was the cause of smallpox until the latter was eradicated but is still feared because of potential use a biological weapon. Molluscum contagiosum virus causes benign skin lesions in immunocompetent infants and a more severe and widespread disease in immunodeficient adults. In addition, several animal poxviruses can be transmitted to humans as zoonosis. The most serious of these is monkeypox, which has an estimated human mortality of 1 to 10%. The poxviruses express a large number of host immune evasion genes that contribute to virulence. The purpose of this project is to increase our understanding of poxvirus pathogenesis and the basis for immunity to poxviruses.A human genome-wide RNAi screen was conducted to determine host factors that impact poxvirus replication.

Publications Generated during the 2015 Reporting Period
Ordered by publication type and then author name.

1. Earl PL, Americo JL, Cotter CA, Moss B (2015). Comparative live bioluminescence imaging of monkeypox virus dissemination in a wild-derived inbred mouse (Mus musculus castaneus) and outbred African dormouse (Graphiurus kelleni). Virology 475, 150-8. https://doi.org/10.1016/j.virol.2014.11.015

PubMed ID 25462355 Pubmed Central ID 4280325

2. Earl PL, Americo JL, Moss B (2015). Genetic studies of the susceptibility of classical and wild-derived inbred mouse strains to monkeypox virus. Virology 481, 161-5. https://doi.org/10.1016/j.virol.2015.02.048

PubMed ID 25791934 Pubmed Central ID 4437815

3. Gjessing MC, Yutin N, Tengs T, Senkevich T, Koonin E, Rønning HP, Alarcon M, Ylving S, Lie KI, Saure B, Tran L, Moss B, Dale OB (2015). Salmon Gill Poxvirus, the Deepest Representative of the Chordopoxvirinae. J Virol 89, 9348-67. https://doi.org/10.1128/JVI.01174-15

PubMed ID 26136578 Pubmed Central ID 4542343

4. Liu SW, Katsafanas GC, Liu R, Wyatt LS, Moss B (2015). Poxvirus decapping enzymes enhance virulence by preventing the accumulation of dsRNA and the induction of innate antiviral responses. Cell Host Microbe 17, 320-331. https://doi.org/10.1016/j.chom.2015.02.002

PubMed ID 25766293 Pubmed Central ID 4359750

5. Reynolds SE, Moss B (2015). Characterization of a large, proteolytically processed cowpox virus membrane glycoprotein conserved in most chordopoxviruses. Virology 483, 209-17. https://doi.org/10.1016/j.virol.2015.04.014

PubMed ID 25980741 Pubmed Central ID 4516581

6. Sivan G, Ormanoglu P, Buehler EC, Martin SE, Moss B (2015). Identification of Restriction Factors by Human Genome-Wide RNA Interference Screening of Viral Host Range Mutants Exemplified by Discovery of SAMD9 and WDR6 as Inhibitors of the Vaccinia Virus K1L-C7L- Mutant. MBio 6, e01122. https://doi.org/10.1128/mBio.01122-15

PubMed ID 26242627 Pubmed Central ID 4526713

NIH Annual Intramural Research Report

ZIA AI000979-11

Report Title
Poxvirus pathogenesis and immunity

2016 Fiscal Year
October 01, 2015 - September 30, 2016

Principal Investigator
Bernard Moss, MD, PhD

Research Organization
Genetic Engineering Section

Lab Staff and Collaborators within the *Genetic Engineering Section*
Patricia Earl, PhD
Ruikang Liu, PhD
Gilad Silvan
Debasis Panda
Jeffrey L Americo, MS
Sara E Reynolds
Baoming Liu
Catherine Griffin

Collaborators from other NIAID organizations
There were 1 collaborators within NIAID

Timothy G Myers, PhD	Research Technologies Branch

Collaborators from other NIH organizations
There were 3 NIH collaborators from other Institutes/Centers

Eugen Christian Buehler, PhD	NHGRI
Madhu A Lal	NCATS
Pinar Tuzmen	NHGRI

Keywords
cowpox virus pathogenesis, poxvirus immunity, smallpox vaccine, monkeypox virus pathogenesis, orthopoxvirus pathogenesis, poxvirus pathogenesis, vaccinia virus pathogenesis, cell mediated immunity, cytokines, monoclonal antibodies

Goals and Objectives
The goals of this project are to increase our understanding of poxvirus pathogenesis and the basis for immunity to poxviruses. We are particularly interested in the members of the orthopoxvirus genus, which include variola virus (the causal agent of smallpox), vaccinia virus (used as the smallpox vaccine), cowpox virus (causes zoonotic infections) and monkeypox virus (causes of human monkeypox in parts of Africa).

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Publications Generated during the 2016 Reporting Period
Ordered by publication type and then author name.

1. Liu R, Moss B (2016). Opposing Roles of Double-Stranded RNA Effector Pathways and Viral Defense Proteins Revealed with CRISPR-Cas9 Knockout Cell Lines and Vaccinia Virus Mutants. J Virol 90, 7864-79. https://doi.org/10.1128/JVI.00869-16

PubMed ID 27334583 Pubmed Central ID 4988158

NIH Annual Intramural Research Report

ZIA AI000979-12

Report Title
Poxvirus host interactions, pathogenesis and immunity

2017 Fiscal Year
October 01, 2016 - September 30, 2017

Principal Investigator
Bernard Moss, MD, PhD

Research Organization
Genetic Engineering Section

Lab Staff and Collaborators within the *Genetic Engineering Section*
Patricia Earl, PhD
Ruikang Liu, PhD
Gilad Silvan
Baoming Liu
Jeffrey L Americo, MS
Shira Gabriella Glushakow-Smith
Catherine Griffin

Collaborators from other NIH organizations
There were 3 NIH collaborators from other Institutes/Centers

Eugen Christian Buehler, PhD	NHGRI
Madhu A Lal	NCATS
Pinar Tuzmen	NHGRI

Keywords
cowpox virus pathogenesis, poxvirus immunity, smallpox vaccine, monkeypox virus pathogenesis, orthopoxvirus pathogenesis, poxvirus pathogenesis, vaccinia virus pathogenesis, cell mediated immunity, cytokines, monoclonal antibodies

Goals and Objectives
The goals of this project are to increase our understanding of poxvirus pathogenesis and the basis for immunity to poxviruses. We are particularly interested in the members of the orthopoxvirus genus, which include variola virus (the causal agent of smallpox), vaccinia virus (used as the smallpox vaccine), cowpox virus (causes zoonotic infections) and monkeypox virus (causes of human monkeypox in parts of Africa).

Summary
Poxviruses comprise a large family of complex DNA viruses that have vertebrate and invertebrate hosts. Two poxviruses, variola virus and molluscum contagiosum virus, are specific human pathogens. Variola virus was the cause of smallpox until the latter was eradicated but is still feared because of potential use a biological weapon. Molluscum contagiosum virus causes benign skin lesions in immunocompetent infants and a more severe and widespread disease in immunodeficient adults. In addition, several animal poxviruses can be transmitted to humans as zoonosis. The most serious of these is monkeypox, which has an estimated human mortality of 1 to 10%. The poxviruses express a large number of host immune evasion genes that contribute to virulence. The purpose of this project is to increase our understanding of poxvirus pathogenesis and the basis for immunity to poxviruses. Human genome-wide RNAi screens were conducted to determine host factors that impact poxvirus replication.

Publications Generated during the 2017 Reporting Period
Ordered by publication type and then author name.

1. Americo JL, Earl PL, Moss B (2017). Droplet digital PCR for rapid enumeration of viral genomes and particles from cells and animals infected with orthopoxviruses. Virology 511, 19-22. https://doi.org/10.1016/j.virol.2017.08.005

PubMed ID 28802157 Pubmed Central ID 5623639

2. Earl PL, Americo JL, Moss B (2017). Insufficient Innate Immunity Contributes to the Susceptibility of the Castaneous Mouse to Orthopoxvirus Infection. J Virol 91. https://doi.org/10.1128/JVI.01042-17

PubMed ID 28747505 Pubmed Central ID 5599762

3. Reynolds SE, Earl PL, Minai M, Moore I, Moss B (2017). A homolog of the variola virus B22 membrane protein contributes to ectromelia virus pathogenicity in the mouse footpad model. Virology 501, 107-114. https://doi.org/10.1016/j.virol.2016.11.010

PubMed ID 27898336 Pubmed Central ID 5201442

NIH Annual Intramural Research Report

ZIA AI000979-13

Report Title

Poxvirus host interactions, pathogenesis and immunity

2018 Fiscal Year

October 01, 2017 - September 30, 2018

Principal Investigator

Bernard Moss, MD, PhD

Research Organization

Genetic Engineering Section

Lab Staff and Collaborators within the *Genetic Engineering Section*

Patricia Earl, PhD
Ruikang Liu, PhD
Chen Peng, PhD
Jeffrey L Americo, MS
Gilad Silvan
Shira Gabriella Glushakow-Smith
Catherine Griffin

Collaborators from other NIH organizations

There were 3 NIH collaborators from other Institutes/Centers

Eugen Christian Buehler, PhD	NHGRI
Madhu A Lal	NCATS
Pinar Tuzmen	NHGRI

Keywords

cowpox virus pathogenesis, poxvirus immunity, smallpox vaccine, monkeypox virus pathogenesis, orthopoxvirus pathogenesis, poxvirus pathogenesis, vaccinia virus pathogenesis, cell mediated immunity, cytokines, monoclonal antibodies

Goals and Objectives

The goals of this project are to increase our understanding of poxvirus pathogenesis and the basis for immunity to poxviruses. We are particularly interested in the members of the orthopoxvirus genus, which include variola virus (the causal agent of smallpox), vaccinia virus (used as the smallpox vaccine), cowpox virus (causes zoonotic infections) and monkeypox virus (causes of human monkeypox in parts of Africa).

Summary

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Publications Generated during the 2018 Reporting Period

Ordered by reference within the summary, then by publication type and author name.

1. Liu R, Moss B (2018). Vaccinia Virus C9 Ankyrin Repeat/F-Box Protein Is a Newly Identified Antagonist of the Type I Interferon-Induced Antiviral State. J Virol 92. https://doi.org/10.1128/JVI.00053-18

2. Sivan G, Ormanoglu P, Buehler EC, Martin SE, Moss B (2017). Erratum for Sivan et al, "Identification of Restriction Factors by Human Genome-Wide RNA Interference Screening of Viral Host Range Mutants Exemplified by Discovery of SAMD9 and WDR6 as Inhibitors of the Vaccinia Virus K1L⁻C7L⁻ Mutant". MBio 8. https://doi.org/10.1128/mBio.01735-17

NIH Annual Intramural Research Report

ZIA AI000979-14

Report Title
Poxvirus host interactions, pathogenesis and immunity

2019 Fiscal Year
October 01, 2018 - September 30, 2019

Principal Investigator
Bernard Moss, MD, PhD

Research Organization
Genetic Engineering Section

Lab Staff and Collaborators within the *Genetic Engineering Section*
Patricia Earl, PhD
Jeffrey L Americo, MS
Ruikang Liu, PhD
Chen Peng, PhD
David John Villani
Wei Xiao
Catherine Griffin

Collaborators from other NIH organizations
There were 3 NIH collaborators from other Institutes/Centers

Eugen Christian Buehler, PhD	NHGRI
Madhu A Lal	NCATS
Pinar Tuzmen	NHGRI

External Collaborator
There was one External Collaborator
Paul Gershon, PhD — University of California, Irvine, Molecular Biology and Biochemistry

Keywords
cowpox virus pathogenesis, poxvirus immunity, smallpox vaccine, monkeypox virus pathogenesis, orthopoxvirus pathogenesis, poxvirus pathogenesis, vaccinia virus pathogenesis, cell mediated immunity, cytokines, monoclonal antibodies

Goals and Objectives
The goals of this project are to increase our understanding of poxvirus pathogenesis and the basis for immunity to poxviruses. We are particularly interested in the members of the orthopoxvirus genus, which include variola virus (the causal agent of smallpox), vaccinia virus (used as the smallpox vaccine), cowpox virus (causes zoonotic infections) and monkeypox virus (causes of human monkeypox in parts of Africa).

Summary
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Publications Generated during the 2019 Reporting Period
Ordered by publication type and then author name.

1. Liu R, Mendez-Rios JD, Peng C, Xiao W, Weisberg AS, Wyatt LS, Moss B (2019). SPI-1 is a missing host-range factor required for replication of the attenuated modified vaccinia Ankara

(MVA) vaccine vector in human cells. PLoS Pathog 15, e1007710. https://doi.org/10.1371/journal.ppat.1007710

PubMed ID 31145755 Pubmed Central ID 6542542

NIH Annual Intramural Research Report

ZIA AI000979-15

Report Title
Poxvirus host interactions, pathogenesis and immunity

2020 Fiscal Year
October 01, 2019 - September 30, 2020

Principal Investigator
Bernard Moss, MD, PhD

Research Organization
Genetic Engineering Section

Lab Staff and Collaborators within the *Genetic Engineering Section*
Tatiana Georgia Koonin, PhD
Ruikang Liu, PhD
Patricia Earl, PhD
Jeffrey L Americo, MS
Catherine Griffin
Andrea S Weisberg, MS
Wei Xiao

External Collaborator
There was one External Collaborator
Paul Gershon — University of California, Irvine, Molecular Biology and Biochemistry

Keywords
cowpox virus pathogenesis, poxvirus immunity, smallpox vaccine, monkeypox virus pathogenesis, orthopoxvirus pathogenesis, poxvirus pathogenesis, vaccinia virus pathogenesis, cell mediated immunity, cytokines, monoclonal antibodies

Goals and Objectives
The goals of this project are to increase our understanding of poxvirus host interactions, pathogenesis and the basis for immunity to poxviruses. We are particularly interested in the members of the orthopoxvirus genus, which include variola virus (the causal agent of smallpox), vaccinia virus (used as the smallpox vaccine), cowpox virus (causes zoonotic infections) and monkeypox virus (causes of human monkeypox in parts of Africa).

Summary
Poxviruses comprise a large family of complex DNA viruses that have vertebrate and invertebrate hosts. Two poxviruses, variola virus and molluscum contagiosum virus, are specific human pathogens. Variola virus was the cause of smallpox until the latter was eradicated but is still feared because of potential use a biological weapon. Molluscum contagiosum virus causes benign skin lesions in immunocompetent infants and a more severe and widespread disease in immunodeficient adults. In addition, several animal poxviruses can be transmitted to humans as zoonosis. The most serious of these is monkeypox, which has an estimated human mortality of 1 to 10%. The poxviruses express a large number of host immune evasion genes that contribute to virulence. The purpose of this project is to increase our understanding of poxvirus host interactions, pathogenesis and the basis for immunity to poxviruses. Human genome-wide RNAi screens were conducted to determine host factors that impact poxvirus replication.

The followin advances were made in the current year. The wild-derived CAST mouse is an excellent small animal model for studying the pathogenicity of MPXV and related orthopoxviruses including vaccinia virus (VACV) and for evaluating therapeutics. We previously found that the susceptibility of CAST mice is correlated with low numbers of natural killer (NK) cells and a delayed interferon-gamma response. Here we showed that in vivo administration of the cytokine IL-15 transiently raised NK cell numbers and protected CAST mice from systemic infections with VACV and MPXV. CAST mouse NK cells that were purified and expanded in vitro with IL-15 also provided protection, further demonstrating the important role of NK cells. The rapid decline in NK cell numbers following cessation of IL-15 administration or NK cell transfer suggests that a low level of NK cell

homeostasis contributes to the susceptibility of CAST mice to virus infection.

Gene inactivation is an important driver of orthopoxirus evolution. Whereas cowpox virus contains intact orthologs of genes present in each orthopoxvirus species, numerous genes are inactivated in all other members of the genus. Inactivation of additional genes can occur upon extensive passaging of orthopoxviruses in cell culture leading to attenuation in vivo, a strategy for making vaccines. Whether inactivation of multiple viral genes enhances replication in the host cells or has a neutral effect is unknown in most cases. Using an experimental evolution protocol involving serial passages of an attenuated vaccinia virus, rapid acquisition of inactivating frameshift mutations occurred. After only 10 passage rounds, the starting attenuated vaccinia virus was displaced by viruses with one fixed mutation and one or more additional mutations. The frequency of multiple inactivating mutations during experimental evolution simulates their acquisition during normal evolution and extensive virus passaging to make vaccine strains.

Publications Generated during the 2020 Reporting Period

Ordered by publication type and then author name.

1. Earl PL, Americo JL, Moss B (2020). Natural killer cells expanded in vivo or ex vivo with IL-15 overcomes the inherent susceptibility of CAST mice to lethal infection with orthopoxviruses. PLoS Pathog 16, e1008505. https://doi.org/10.1371/journal.ppat.1008505

   PubMed ID 32320436 Pubmed Central ID 7197867

2. Liu R, Olano LR, Mirzakhanyan Y, Gershon PD, Moss B (2019). Vaccinia Virus Ankyrin-Repeat/F-Box Protein Targets Interferon-Induced IFITs for Proteasomal Degradation. Cell Rep 29, 816-828.e6. https://doi.org/10.1016/j.celrep.2019.09.039

   PubMed ID 31644906 Pubmed Central ID 6876622

3. Senkevich TG, Zhivkoplias EK, Weisberg AS, Moss B (2020). Inactivation of Genes by Frameshift Mutations Provides Rapid Adaptation of an Attenuated Vaccinia Virus. J Virol 94. https://doi.org/10.1128/JVI.01053-20

   PubMed ID 32669330 Pubmed Central ID 7459559

NIH Annual Intramural Research Report

ZIA AI000979-16

Report Title
Poxvirus host interactions, pathogenesis and immunity

2021 Fiscal Year
October 01, 2020 - September 30, 2021

Principal Investigator
Bernard Moss, MD, PhD

Research Organization
Genetic Engineering Section

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Collaborators from other NIH organizations
There were 3 NIH collaborators from other Institutes/Centers

Eugene Victor Koonin, PhD	NLM
Yuri Igorevich Wolf, PhD	NLM
Nataliya Yutin, PhD	NLM

External Collaborator
There was one External Collaborator

Paul Gershon	University of California, Irvine, Molecular Biology and Biochemistry

Keywords
cowpox virus pathogenesis, poxvirus immunity, smallpox vaccine, monkeypox virus pathogenesis, orthopoxvirus pathogenesis, poxvirus pathogenesis, vaccinia virus pathogenesis, cell mediated immunity, cytokines, monoclonal antibodies

Goals and Objectives
The goals of this project are to increase our understanding of poxvirus host interactions, pathogenesis and the basis for immunity to poxviruses. We are particularly interested in the members of the orthopoxvirus genus, which include variola virus (the causal agent of smallpox), vaccinia virus (used as the smallpox vaccine), cowpox virus (causes zoonotic infections) and monkeypox virus (causes of human monkeypox in parts of Africa).

Summary
Poxviruses comprise a large family of complex DNA viruses that have vertebrate and invertebrate hosts. Two poxviruses, variola virus and molluscum contagiosum virus, are specific human pathogens. Variola virus was the cause of smallpox until the latter was eradicated but is still feared because of potential use a biological weapon. Molluscum contagiosum virus causes benign skin lesions in immunocompetent infants and a more severe and widespread disease in immunodeficient adults. In addition, several animal poxviruses can be transmitted to humans as zoonosis. The most serious of these is monkeypox, which has an estimated human mortality of 1 to 10%. The poxviruses express a large number of host immune evasion genes that contribute to virulence. The purpose of this project is to increase our understanding of poxvirus host interactions, pathogenesis and the basis for immunity to poxviruses. Human genome-wide RNAi screens were conducted to determine host factors that impact poxvirus replication.

During the past year we took advantage of the 235 available unique complete genome sequences of Orthopoxviruses (ORPV) and reannotated the approximately 200 genes of each to provide the first uniform gene nomenclature. We focused on the approximately 100 accessory genes, predicting the functions of uncharacterized genes, and reconstructed the history of their gain and loss during

the evolution of ORPV. Most of the accessory genes were acquired in three major waves antedating the origin of ORPV from chordopoxviruses. The evolution of ORPV themselves was dominated by gene loss, with numerous genes lost at the base of each major group of ORPV. Examination of pairs of ORPV accessory genes that were either often or rarely lost concurrently during ORPV evolution allowed prediction of different types of functional interactions.

The MVA host range restriction is exceptional in that synthesis of the abundant viral proteins appears unaffected, but morphogenesis of virus particles is abortive. Despite the importance of the host range restriction for vaccine safety, the basis for this antiviral effect has remained an enigma. We demonstrated that the zinc finger antiviral protein (ZAP) is a specific host restriction factor for replication of MVA in human cells. Moreover, the intact vaccinia virus C16 protein, which was disrupted during the attenuation of MVA, sequesters ZAP in cytoplasmic punctae, and effectively counteracts the inhibitory effects of ZAP.

Publications Generated during the 2021 Reporting Period

Ordered by reference within the summary, then by publication type and author name.

1. Senkevich TG, Yutin N, Wolf YI, Koonin EV, Moss B (2021). Ancient Gene Capture and Recent Gene Loss Shape the Evolution of Orthopoxvirus-Host Interaction Genes. mBio 12, e0149521. https://doi.org/10.1128/mBio.01495-21

2. Peng C, Wyatt LS, Glushakow-Smith SG, Lal-Nag M, Weisberg AS, Moss B (2020). Zinc-finger antiviral protein (ZAP) is a restriction factor for replication of modified vaccinia virus Ankara (MVA) in human cells. PLoS Pathog 16, e1008845. https://doi.org/10.1371/journal.ppat.1008845

NIH Annual Intramural Research Report

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Report Title
Poxvirus host interactions, pathogenesis and immunity

2022 Fiscal Year
October 01, 2021 - September 30, 2022

Principal Investigator
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Collaborators from other NIH organizations
There were 2 NIH collaborators from other Institutes/Centers
Eugene Victor Koonin, PhD — NLM
Wolfgang Resch, PhD — CIT

Keywords
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during ORPV evolution allowed prediction of different types of functional interactions.

Publications Generated during the 2022 Reporting Period

Ordered by publication type and then author name.

1. Liu R, Americo JL, Earl PL, Villani J, Cotter CA, Moss B (2022). Interferon α/β Decoy Receptor Encoded by a Variant in the Dryvax Smallpox Vaccine Contributes to Virulence and Correlates with Severe Vaccine Side Effects. mBio 13, e0010222. https://doi.org/10.1128/mbio.00102-22

   PubMed ID 35189701 Pubmed Central ID 8903894

2. Moss B, Smith GL (2021). Research with variola virus after smallpox eradication: Development of a mouse model for variola virus infection. PLoS Pathog 17, e1009911. https://doi.org/10.1371/journal.ppat.1009911

   PubMed ID 34547026 Pubmed Central ID 8454959

3. Senkevich TG, Yutin N, Wolf YI, Koonin EV, Moss B (2021). Ancient Gene Capture and Recent Gene Loss Shape the Evolution of Orthopoxvirus-Host Interaction Genes. mBio 12, e0149521. https://doi.org/10.1128/mBio.01495-21

   PubMed ID 34253028 Pubmed Central ID 8406176