



July 28, 2021

The Honorable Charles Grassley
United States Senate
Washington, DC 20510

Dear Senator Grassley:

Thank you for your May 26, 2021, letter regarding the National Institute of Allergy and Infectious Diseases (NIAID) and gain-of-function (GOF) research of concern. You have raised multiple important topics. Those which relate to research funded by the National Institutes of Health (NIH) and published scientific literature are addressed below.

What is Known About the Origins of the SARS-CoV-2 Coronavirus

On May 26, 2021, the President called for a report within 90 days from the U.S. Intelligence Community regarding the origins of COVID-19, including whether it emerged from human contact with an infected animal or from a laboratory accident.¹ In addition to supporting and cooperating with the President's call for a U.S. Intelligence Community investigation, the NIH has previously stated that further objective, scientific assessments of data by technical experts into the circumstances regarding the origins and global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) would be beneficial.

We do not yet know the origin of the SARS-CoV-2 coronavirus and the U.S. Intelligence Community has not issued its report. NIH's view, based on the scientific literature, is that SARS-CoV-2 infection in people most likely resulted from zoonotic transmission from animals to humans, based on what occurred with Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and many other emerging diseases, as well as what is known about the molecular makeup of SARS-CoV-2. NIH has previously indicated that the available scientific evidence, including information about the sequence of the virus, does not support the assertion that SARS-CoV-2 was engineered. This view is consistent with an emerging consensus from world-renowned experts in virology, genetics, and evolutionary biology based on currently available data.² However, NIH has previously stated that the possibility of a laboratory accident should also be considered, including scenarios where a naturally occurring virus was unintentionally released during research activities such as collection of animal samples or examination of viruses in a laboratory. NIH is in favor of a full investigation and we defer to the investigators to determine the information they deem necessary to conduct a full and independent assessment and develop their findings.

¹ <https://www.whitehouse.gov/briefing-room/statements-releases/2021/05/26/statement-by-president-joe-biden-on-the-investigation-into-the-origins-of-covid-19/>

² <https://zenodo.org/record/5075888#.YOh4uXpKg2z>

How NIAID Evaluates the Science of Grant Applications

Research grant applications submitted to NIH, including to NIAID, are subject to NIH's two-stage review process in which both scientific review (i.e., rigorous peer review to evaluate and rate the scientific and technical merit of each application) and NIH Advisory Council review are conducted to inform funding decisions.

Peer review takes place in multiple steps. The initial step of the peer review process is undertaken in Scientific Review Groups (SRGs), which are composed primarily of non-federal scientists with expertise in relevant scientific disciplines and current research areas. SRGs assess grant applications and score several key criteria regarding the proposed research: significance, investigator(s) suitability, innovation, approach, and appropriateness of the environment for the research. If applicable, SRGs also evaluate whether grant applications contain appropriate plans for human subjects research, use of vertebrate animals, involvement of select agents or potential biohazards, and other aspects of specialized research.

The second level of peer review is carried out by the NIH National Advisory Councils, which are composed of expert scientists from the research community and public representatives. Only applications recommended for approval through both levels of peer review are considered for funding by NIAID and other NIH Institutes and Centers.

The grant issued to EcoHealth Alliance that included a sub-award to the Wuhan Institute of Virology (WIV) underwent the standard NIH peer review process and was recommended for funding by the NIAID National Advisory Allergy and Infectious Diseases Council prior to receiving the award.

How the United States Government (USG) Conducts Oversight of Research Involving Enhanced Potential Pandemic Pathogens

The USG remains committed to ensuring that research with infectious agents is conducted responsibly and considers the potential biosafety and biosecurity risks associated with such research. From 2014 to 2017, the USG paused funding for research that might be reasonably anticipated to confer to influenza, MERS, or SARS viruses' attributes that would enhance pathogenicity and/or transmissibility of these viruses in mammals via the respiratory route, that is, a form of gain-of-function (GOF) research. The USG research funding pause did not apply to the characterization or testing of naturally occurring influenza viruses, MERS coronavirus (MERS-CoV), and SARS coronavirus (SARS-CoV-1), unless the research was reasonably anticipated to increase transmissibility and/or pathogenicity in mammals via the respiratory route.

The GOF research pause allowed the USG, in partnership with the life sciences community and additional stakeholders, to conduct a comprehensive and prolonged public, deliberative process with the explicit goal of developing a new federal policy framework to guide future investments in this area of research. The deliberative process included multiple public meetings and two commissioned independent studies, including a comprehensive assessment of the risks and benefits of GOF research. The process defined a subset of GOF research that entails risks that are potentially significant enough to warrant additional oversight, specifically research likely to result in an enhanced potential pandemic pathogen (ePPP). A potential pandemic pathogen

(PPP) is a pathogen that is likely to be highly transmissible and capable of wide and uncontrollable spread in human populations; and likely to be highly virulent and cause significant morbidity and/or mortality in humans. An ePPP is a PPP resulting from the enhancement of the transmissibility and/or virulence of a pathogen. Following this deliberative process, the Office of Science and Technology Policy released the *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight (P3CO)* document outlining the USG policy guidance for federal agency review and reporting processes for the oversight of federally-funded research that is anticipated to create, transfer, or use ePPPs. The Department of Health and Human Services (HHS) implemented this guidance with the issuance of the *HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* (HHS P3CO Framework).³

As outlined in the HHS P3CO Framework, the responsibilities of the funding agency include conducting standard scientific merit reviews to identify and refer proposed research that is reasonably anticipated to create, transfer, or use ePPPs for Departmental-level review.⁴ At NIH, following the completion of peer review by an SRG, if an SRG identifies research that may create, transfer, or use ePPPs as described above, the Scientific Review Officer records this as an administrative note. NIH Institute or Center program officials with scientific expertise in infectious diseases then review all proposed research found to be scientifically meritorious that is being considered for funding to determine if the research meets the scope of the HHS P3CO Framework. In the case of NIAID, if NIAID program officials determine that the proposed research may meet the scope of the HHS P3CO Framework, the proposed research is further evaluated by a group within NIAID, including members of NIAID leadership, with broader infectious diseases expertise. When evaluating proposed research to determine if it meets the scope of the HHS P3CO Framework, details of the experiment(s) and pathogen(s) are considered in the context of the state of the science in that field. All proposed research determined by this group to fall within the scope of the HHS P3CO Framework is referred by NIAID to HHS. Throughout NIH, all proposals determined by NIH program officials to fall within the scope outlined in the HHS P3CO Framework as requiring additional Departmental-level review are referred by the relevant NIH Institute or Center to HHS.

The Role of NIAID in Oversight of Research Involving Enhanced Potential Pandemic Pathogens

As described above, NIH and NIAID follow the HHS P3CO Framework when assessing proposed research involving ePPPs. An important aspect of the HHS P3CO Framework is that it requires a deliberative process on whether funding such research is warranted given the assessed risks and benefits. If this HHS assessment finds that the likely risks of the proposed research outweigh the potential benefits, or that the risks cannot be appropriately mitigated, NIAID does not fund the research.

Biosafety and biosecurity risks, including the potential for laboratory accidents, are specifically addressed in the HHS P3CO Framework. One of the criteria guiding HHS funding decisions on proposed research that involves the use of ePPPs is whether the investigator and the institution

³ <https://www.phe.gov/s3/dualuse/Documents/P3CO.pdf>

⁴ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-071.html>

where the research would be carried out have the demonstrated capacity and commitment to conduct it safely and securely. The factors include access to facilities of appropriate biosafety level and the ability to respond rapidly, mitigate potential risks, and take corrective actions in response to laboratory accidents, lapses in protocol and procedures, and potential security breaches. The HHS P3CO Framework requires appropriate management of risks and ongoing federal and institutional oversight of all aspects of the research throughout the course of the award, such that risks would be monitored by NIAID, working with the funded institution, on an ongoing basis. NIAID and NIH are committed to the careful consideration of the risks and benefits of proposed research on ePPPs as outlined in the HHS P3CO Framework. NIAID and NIH also are committed to appropriate oversight of this research and mitigation of risks as recommended by Department-level review via the HHS P3CO Review Committee.

Since the implementation of the HHS P3CO Framework, NIAID has referred three influenza research proposals to the HHS P3CO Review Committee. One project identified for review pending funding decisions will be modified to remove activities that would be applicable to the HHS P3CO Framework. NIH has funded two projects involving ePPP research subsequent to review by the HHS P3CO Review Committee. Both projects have since ended. The HHS P3CO Review Committee determined that, in the case of both research proposals, the research was acceptable for HHS funding with recommended changes to increase the potential benefits while decreasing risks. The funded institutions were required to comply with the terms of the award as recommended by the HHS P3CO Review Committee. These terms required the funded institution to:

- Comply with applicable dual use research of concern and P3CO policies and the risk mitigation plan(s) developed for the research;⁵
- Consult with NIAID regarding whether to test protective efficacy of candidate vaccine viruses against transmissible (H5N1) influenza viruses;
- Notify NIAID if there are unanticipated results from the research, in the event of an enhanced potential pandemic pathogen exposure or illness, or if the pathogens are found to be resistant to antimicrobial drugs;
- Report to NIAID whether there are any technical, biosecurity, or biosafety updates related to the research;
- Submit to NIAID all materials to be published prior to submission to the publishing agency; and
- Review the risk mitigation plan(s) at least annually and notify and submit for NIH approval any modifications within 30 calendar days of review by the Institutional Review Entity.

The Scientific Aims, Approach, and Findings of the EcoHealth Alliance Grant

The research that NIH approved under the EcoHealth Alliance grant sought to understand how animal coronaviruses, especially bat coronaviruses, evolve naturally in the environment to become transmissible to the human population. This research included studying viral diversity in bat reservoirs, surveying people who work in live animal markets or other jobs with high exposure to wildlife for evidence of bat coronavirus infection, and analyzing data to predict

⁵ <https://www.phe.gov/s3/dualuse/Documents/durc-policy.pdf>

which newly discovered viruses pose the greatest threat to human health. Under the grant, EcoHealth Alliance proposed research that involved sampling animals, especially bats, for previously unidentified coronaviruses and placing a small portion of newly identified bat coronaviruses into a larger portion of a well-characterized bat coronavirus that had never been demonstrated to infect humans. Additionally, during the course of the grant, the grantee proposed to place a small portion of the newly identified bat coronaviruses into a larger portion of MERS-CoV to understand the potential origins of MERS-CoV in bats. The purpose of these experiments, to be conducted at WIV, was to understand how differences between the coronaviruses affected how the viruses grew in the laboratory or behaved in mice infected with the viruses. Such information could be used to identify naturally occurring bat coronaviruses that might have the potential to infect other species including humans, and to determine any common features among them that could be utilized in surveillance of wild bats for coronaviruses with pandemic potential.

Viruses generated by combining portions of different viruses (referred to as “chimeric” viruses) are commonly used molecular biology tools to better understand viruses and to facilitate development of therapeutics and vaccines against these viruses. Combining parts of the bat coronaviruses into well-characterized viral model systems is not expected to generate viruses that would be more transmissible or more virulent in humans; in fact, the laboratory-generated viruses are often weaker than the viruses used to create them. However, this type of research must be conducted in appropriate laboratory settings to ensure precautions are taken to protect the safety of researchers and the public at all times. As with all NIH grants, NIH provided oversight of this award via NIH officials who review grant materials on a regular basis to identify any concerns with the data generated by the research or any other issues that may emerge after the award is made.

Results of the WIV experiments under the EcoHealth Alliance grant were reported to NIAID and published contemporaneously in peer-reviewed scientific literature to inform the global scientific community of these findings. The body of science produced under the grant, including the bat coronavirus sequences identified by the researchers and published in the scientific literature, showed that the viruses studied were evolutionarily quite distant from SARS-CoV-2 and could not have been the source of SARS-CoV-2.

It is important to note that studies such as the ones conducted at WIV provided us with critical knowledge about the emergence and behavior of coronaviruses. Understanding coronaviruses thought to have emerged from animal reservoirs, particularly SARS-CoV-1 and MERS-CoV, was instrumental to the unprecedented rapid development of vaccines, therapeutics, and diagnostics to address the COVID-19 pandemic.

Was the Research that NIAID Approved for Funding Determined to Be “Gain-of-Function” Research

NIAID reviewed this grant under the *U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause of Selected Gain-of-Function Research Involving Influenza, MERS and SARS Viruses* and determined that the research proposed under the grant to generate SARS-like or MERS-like chimeric coronaviruses did not meet the criteria for GOF research described in this policy. This determination was based upon the following:

- The chimeric viruses created would contain only small portions of evolutionarily distant bat coronaviruses; and
- Research published in peer-reviewed scientific journals demonstrated that similar chimeric viruses exhibited reduced pathogenicity.

For these reasons, it was not reasonably anticipated that the chimeric viruses developed under the grant would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. NIAID's determination that the USG research funding pause did not apply to this grant included a requirement that if any of the chimeric viruses generated under the grant showed evidence of enhanced virus growth greater than ten times that of the original virus from which they were created, the grantee must immediately stop all experiments with these viruses and provide NIAID and the WIV Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

Subsequently, NIAID also reviewed this grant under the HHS P3CO Framework and determined that the experiments to generate SARS-like or MERS-like chimeric coronaviruses were not subject to the HHS P3CO Framework because they were not reasonably expected to increase transmissibility or virulence of these viruses in humans. At the time of this determination, NIAID revised the terms and conditions of the award to indicate that should experiments proposed in this award result in a virus with enhanced growth by more than ten times compared to strains found in nature, the grantee must notify NIAID immediately and that further research involving the resulting virus(es) may require review by HHS in accordance with the HHS P3CO Framework.

It is important to note that none of the studies proposed under this grant were designed to manipulate the viruses in a way that would increase their transmissibility or pathogenicity, and no NIAID funding was approved to support GOF research at WIV as defined by USG criteria. Further, it is critical to emphasize that the body of science reported under the grant, including the bat coronavirus sequences published in the scientific literature, showed that the viruses studied were evolutionarily quite distant from SARS-CoV-2 and could not have been the source of SARS-CoV-2.

Thank you for your interest in NIH's research programs. I hope this information is helpful to you.

Sincerely yours,



Francis S. Collins, M.D., Ph.D.
Director